New Horizons in Osteoporosis Management

Yasser El Miedany
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Preface

Advances in the understanding of bone health and osteoporosis management in the last three decades have exceeded that of most other chronic diseases of aging. Clinicians treating osteoporosis have witnessed significant change in the disease management, from being a debilitating chronic illness with few treatment options and small chance of real improvement to a disease amenable to therapy, particularly with the introduction of new management modalities such as biologic therapy, with a consequent improvement in the bone mineral content and reduction in the fracture rates.

Osteoporosis can be considered of as an equation. Simply, the equation states that osteoporosis is the net outcome of deducting the ongoing losses related to age and menopause from the peak bone mass achieved by the age of 30. Osteoporosis is a complex disorder, which occurs as the consequence of the interactions between genetic and acquired factors. However, not all patients respond properly or equally to the same therapeutic modality, and some of them even suffer fragility fractures despite taking anti-osteoporotic pharmacotherapies. Furthermore, though no genetic markers for either low peak bone mass or high later losses are yet being measured routinely in clinical settings, genome-wide association studies have pointed to several genes as determinants of the osteoporosis risk. This paved the way for applying pharmacogenetic approaches to osteoporosis research.

The rationale for this book is the note that musculoskeletal health knowledge has focussed mainly on basic sciences, results of pharmaceutical drug research outcomes or specific medication-related side effects. Consequently, it has been felt there is a gap that need filling between basic skeletal health science and new developments in the field of bone health both in terms of concepts and management. So, this book has been set aiming at discussing the new horizons in bone health and osteoporosis management. The book starts with an introductory part including six chapters on the fundamentals of bone health, the skeletal structure and nature of osteoporosis, as well as the purposes of bone remodelling. This expands to discuss muscle health, and bone health in men and women as well as transgenders. The next part is on diagnosis, which includes six chapters and represents a clinician's guide to risk assessment tools, current imaging techniques, the challenges and limitations of osteoporosis diagnosis, best practice recommendations for DXA scans and reports, pitfalls in DXA scanning, and, lastly, best approach to mind the gap in osteopenia diagnosis and management. The next part deals with recent advances in prevention of osteoporosis. This includes four

chapters discussing the new concept of imminent fracture risk, fracture liaison service, and the unmet needs and challenges in osteoporosis as well as an osteoporosis update for primary care physicians. The fourth part includes new treatment concepts. The part contains four chapters discussing bone modulation therapy, the concept of Treat to Target in osteoporosis management, geroscience and management of osteoporosis in older adults as well as treatment strategies concerning fracture healing. In concordance, the fifth part is composed of four chapters discussing approaches towards optimized practice. This includes discussion of gaps in the patients' care and treatment, pharmacogenetics and pharmacogenomics of osteoporosis, optimizing the anabolic window, as well as optimizing sequential and combined osteoporosis therapy. The next set of chapters comes under a separate part discussing disparities of bone health. This includes four chapters handling osteoporosis in men, paediatric osteoporosis, atypical femur fractures as well as pregnancy, lactation and bone Health.

The last set of chapters deals with bone health as a comorbidity. This includes four chapters discussing bone health and cancer therapy, chronic kidney disease, glucocorticoids as well as osteonecrosis of the jaw. The final chapter brings together novel thoughts on recent advances in osteoporosis and bone care.

The main theme of this book is to deliver a very practical and reader-friendly guide. On the one hand, it delivers the science-based evidence and advanced knowledge of bone health and osteoporosis management; on the other hand, it provides the most recent in this field and examples of recent tools which the readers/researchers can use for their standard practice/clinical trials. With its 32 key chapters, this book is expected to fill an important void in the current literature. It represents what can be considered the best current thinking on bone health. Therefore, *New Horizons in Osteoporosis Management* can serve as both an excellent introductory book and a very good reference as well as a resource for implementation in standard clinical practice and future reading. Special thanks to my colleagues and family for their support throughout the whole project which helped to make this book complete.

Personally, I feel privileged to have compiled this work and am enthusiastic about all that it offers our readers. I hope you too will find this edition a uniquely valuable educational resource.

London, UK
1 August 2020

Yasser El Miedany

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Part I

Bone Health: Towards Better Bones

1 Bone Health: Basic and Applied Bone Biology

Yasser El Miedany

Introduction

Recently, bone biology and its role in maintaining the bone health integrity has got in focus and has become a vastly growing area of research. Given its intricate systemic and local connections, bone biology merges the traditional fields of anatomy, physiology, and biomechanics together with the increasingly complex fields of developmental biology and molecular genetics. Therefore, it is essential for clinicians who treat bone disorders such as osteoporosis, as well as other metabolic bone disorders to keep themselves updated and develop a working knowledge of this topic. Such studies of the bone biology revealed how the bone structure can be optimized so that it gets strong but, in the meantime, remains relatively light weight. In depth analysis of the bone biology and its fundamental role in preserving bone health revealed how the integrity of the skeleton is maintained through the balanced activities of its constituent cell types. Furthermore, molecular dissection of genetic disorders of highly increased or reduced bone mass has identified many of the crucial proteins controlling the activity of these bone cell types [1]. This information has resulted in both novel ways to treat or diagnose more common bone disorders and a better understanding of the common genetic variants that lead to differences in bone density in the general population.

The skeletal architecture is remarkably adapted to provide adequate strength and mobility without negative impact on the bones themselves; meaning that bones do not break when subjected to substantial impact, or heavy loads are placed on them during vigorous physical activity. Therefore, the bone shape and structure are considered, at least, as important as its mass in providing this strength. In addition, the skeleton act also as a storehouse for two important minerals, namely, calcium and phosphorus. These are essential for the functioning of other body systems, and this storehouse is called upon in times of need. To be able to carry out its dual roles of support and mineral homeostasis, as well as to repair any damage to the skeleton, bones are constantly changing. Old bone breaks down and new bone is formed on a regular basis, subsequently, the skeletal tissue is replaced several times during life. This requires a perfectly controlled regulatory system that involves specialized cells able to communicate with each other. These cells are expected also to respond to several different signals, both internal and external, mechanical, hormonal, systemic (affecting the whole skeleton) as well as local (affecting only a small region of the skeleton) [2]. It is not surprising that with so many different tasks to perform and so many different factors regulating how the

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skeleton grows, adapts, and responds to changing demands; there are many ways that these processes can go astray.

This chapter discusses bone biology, providing the reader with the background required to understand the basis of bone biology including bone structure, cells, and extracellular matrix, the mechanical and chemical stimulants versus inhibitors of bone activity, as well as the interaction among these components both in physiologic situations and in response to injury. It also expands to discuss applied bone biology and its implementation in the prevention, diagnosis, and principles of treatment approaches related to bone disease that are discussed in detail later in this book.

Basic Bone Biology

Bone is a specialized form of connective tissue that serves as both a tissue and an organ system within higher vertebrates. As such, its basic functions include locomotion, protection, and mineral homeostasis.

Cellular Composition

The cellular makeup of bones includes osteoblasts, osteocytes, bone lining cells, and osteoclasts, as well as its matrix which contains an organic and an inorganic component [3, 4]. Another cellular classification has also been developed stratifying the cells into bone forming and bone resorbing cells [5]. Further differentiation of bone cells is based on their origin. Osteoblasts, osteocytes, and bone lining cells originate from mesenchymal stem cells known as osteoprogenitor cells, whereas osteoclasts originate from hemopoietic stem cells. The location of these cells also varies. Bone cells found along the surface of bone include osteoblasts, osteoclasts, and bone lining cells, whereas osteocytes are located in the interior of bone [6, 7]. Downey and Siegel (2006) [6] as well as Rachner and colleagues (2011) [7] provided detailed reports on bone biology.

Osteoblasts

Osteoblasts are cuboidal cells that are located along the bone surface comprising 4–6% of the total resident bone cells and are largely known for their bone forming function. Osteoblasts are derived from undifferentiated mesenchymal cells that are located in the marrow, endosteum, periosteum, and bone canals. These cells, also referred to as "preosteoblasts," can migrate from surrounding tissue or through the vascular system. Mesenchymal cells are stellate in shape, contain relatively small amounts of cytoplasm and organelles, and possess a single nucleus. Differentiation and proliferation of mesenchymal cells into osteoblasts occurs during both intramembranous and endochondral bone formation (Fig. 1.1) [3, 4].

The commitment of mesenchymal cells towards the osteoprogenitor lineage requires the expression of specific genes, following timely programmed steps, including the synthesis of bone morphogenetic proteins (BMPs) and members of the Wingless (Wnt) pathways [8]. The expressions of Runt-related transcription factors 2, Distal-less homeobox 5 (Dlx5), and osterix (Osx) are crucial for osteoblast differentiation [9]. Additionally, Runx2 is a master gene of osteoblast differentiation, as demonstrated by the fact that Runx2-null mice are devoid of osteoblasts [9, 10]. Runx2 has demonstrated to upregulate osteoblast-related genes such as ColIA1, ALP, BSP, BGLAP, and OCN [11]. Once a pool of osteoblast progenitors expressing Runx2 and ColIA1 has been established during osteoblast differentiation, there is a proliferation phase. In this phase, osteoblast progenitors show alkaline phosphatase (ALP) activity, and are considered preosteoblasts [12]. The transition of preosteoblasts to mature osteoblasts is characterized by an increase in the expression of Osx and in the secretion of bone matrix proteins such as osteocalcin (OCN), bone sialoprotein (BSP) I/II, and collagen type I. Moreover, the osteoblasts undergo morphological changes, becoming large and cuboidal cells [13–17].

With the advent of electron microscopy, the structure of the osteoblast has become more

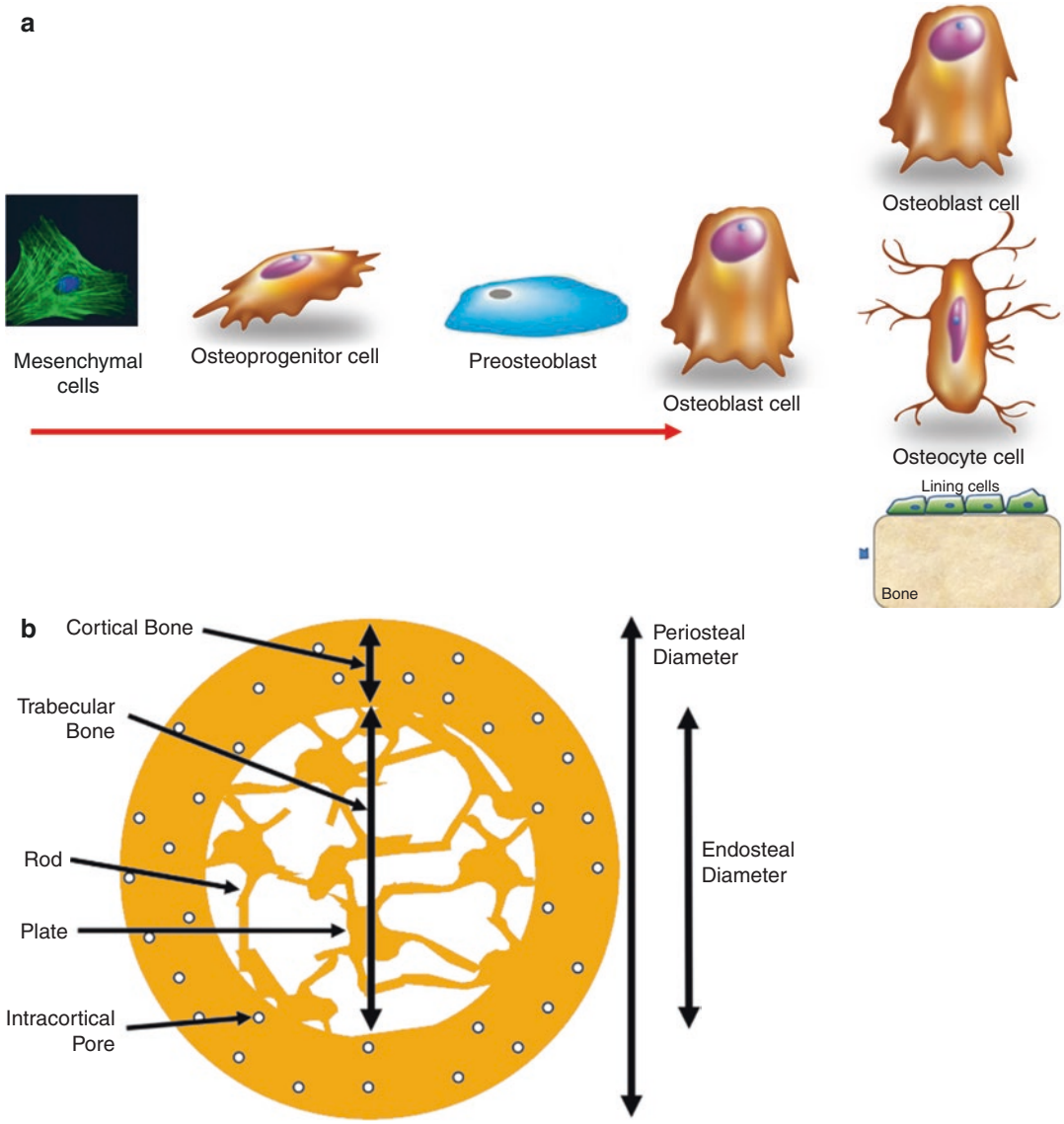


Fig. 1.1 (**a**) Development schema of mesenchymal cell differentiation into mature osteoblasts and its fate. Mesenchymal refers to cells which were deep within the embryo during early development; some of them remain in the bone marrow but do not form blood cells. (**b**) Structural characteristics of bone. Bone is comprised of a dense cortical shell that surrounds a spongy trabecular bone network. The periosteal diameter combined with the endosteal diameter determines cortical thickness. The size of bone along with cortical thickness and porosity significantly contribute to bone strength. The inner trabecular compartment contains a network of plates and rods that also contribute to bone strength. (Quoted under open access scheme from: Choksi et al. [286])

defined. These robust cells are tightly packed along the surface linings of bone. When active, osteoblasts are oval and contain large quantities of rough endoplasmic reticula (RER), mitochondria, and Golgi apparatus. Their single nucleus is found within the center of the cell. Other microscopic components found within these cells include mitochondria, microtubules, microfilaments, lysosomes, glycogen, and lipids. Functionally, the osteoblast is responsible for production of the organic matrix, which is composed of proteins and polysaccharides. Evidence

exists that osteoblasts, under the influence of parathyroid hormone and local cytokines, release mediators that activate osteoclasts [3].

Bone Lining Cells

Eventually, osteoblasts follow 1 of 3 pathways. These cells may (1) remain active osteoblasts, (2) become surrounded by matrix and become osteocytes, or (3) become relatively inactive and form bone lining cells. Bone lining cells are thin, elongated cells that cover most bone surfaces in the mature skeleton. Cytoplasmic extensions or gap junctions often link them to each other or to osteocytes. Because they are metabolically inactive, bone lining cells contain fewer organelles and less cytoplasm than osteoblasts. At times, they are referred to as "resting osteoblasts" or "surface osteocytes." [3–6].

Bone lining cells cover the bone surfaces, where neither bone resorption nor bone formation occurs [18]. The secretory activity of bone lining cells depends on the bone physiological status, whereby these cells can reacquire their secretory activity, enhancing their size and adopting a cuboidal appearance [19]. Several suggestions have been raised regarding the function of these cells. It has been shown that these cells prevent the direct interaction between osteoclasts and bone matrix, when bone resorption should not occur. They also participate in osteoclast differentiation, producing osteoprotegerin (OPG) and the receptor activator of nuclear factor kappa-B ligand (RANKL) [20]. Moreover, the bone lining cells, together with other bone cells, are an important component of the Bone Modeling Unit (BMU), an anatomical structure that is present during the bone remodeling cycle [21]. Buckwalter et al. [3] indicated that, in the presence of parathyroid hormone, these cells secrete enzymes that remove the osteoid covering of the bone matrix in preparation for osteoclastic removal of bone. Other authors [4, 6] reported that bone lining cells may be precursors for osteoblasts, regulate the crystal growth in bone, or function as a barrier between extracellular fluid and bone.

Osteocytes

It is estimated that osteocytes make up more than 90% of the bone cells in an adult skeleton. Osteocytes are derived from mesenchymal stem cells lineage through osteoblast differentiation. In this process, four recognizable stages have been proposed: osteoid-osteocyte, pre-osteocyte, young osteocyte, and mature osteocyte [22]. As immature osteocytes, recently surrounded in bone matrix, they closely resemble osteoblasts. Thus, the cytoplasm contains large amounts of rough endoplasmic reticula (RER) and large Golgi apparatus and mitochondria, with lesser amounts of microtubules, microfilaments, and lysosomes. As these cells mature and more matrix is laid down, osteocytes become located deeper within the bone tissue and eventually become smaller as they lose cytoplasm and get incorporated into the bone matrix. This process is accompanied by conspicuous morphological and ultrastructural changes, including the reduction of the round osteoblast size and the nucleus-to-cytoplasm ratio increases, which correspond to a decrease in the protein synthesis and secretion [23]. This accounts for the enlarged appearance of their nucleus. Furthermore, they are located within a space or lacuna and have long cytoplasmic processes that project through canaliculi within the matrix and facilitate the contact process among the adjacent cells. These connecting processes are thought to be extremely important in cellular communication and nutrition within a mineralized matrix [4–7]. Moreover, this important cellular network is thought to allow cell-mediated exchanges of minerals between the fluids in the bone and the vascular supply. It also is believed that the cellular network senses the mechanical deformation within bone that leads to the coordinated formation and resorption of bone [3].

Once the stage of mature osteocyte totally entrapped within mineralized bone matrix is accomplished, several of the previously expressed osteoblast markers such as OCN, BSPII, collagen type I, and ALP are downregulated. On the other hand, osteocyte markers including dentine matrix protein 1 (DMP1) and sclerostin are highly expressed [24–26]. While the osteocyte cell body

is located inside the lacuna, its cytoplasmic processes (up to 50 per each cell) cross tiny tunnels that originate from the lacuna space called canaliculi, forming the osteocyte lacuna-canalicular system [27] (Figs. 1.2). These cytoplasmic processes are connected, through gap junctions, to other neighboring osteocytes processes, as well as to cytoplasmic processes of osteoblasts and bone lining cells on the bone surface, facilitating the intercellular transport of small signaling molecules such as prostaglandins and nitric oxide among these cells [28]. In addition, the osteocyte lacuna-canalicular system is in close proximity to the vascular supply, whereby osteocytes have access to oxygen and nutrients [17].

It has been estimated that osteocyte surface is 400-fold larger than that of the all Haversian and Volkmann systems and more than 100-fold larger than the trabecular bone surface [29, 30]. The cell–cell communication is also achieved by interstitial fluid that flows between the osteocytes processes and canaliculi [30]. By the lacuna-canalicular system (Fig. 1.6), the osteocytes act as mechanosensors as their interconnected network has the capacity to detect mechanical pressures and loads, thereby helping the adaptation of bone to daily mechanical forces [31]. By this way, the osteocytes seem to act as orchestrators of bone remodeling, through regulation of osteoblast and osteoclast activities [32]. Moreover, osteocyte apoptosis has been recognized as a chemotactic signal to osteoclastic bone resorption [33, 35]. In agreement, it has been shown that during bone resorption, apoptotic osteocytes are engulfed by osteoclasts [36–38].

The mechanosensitive function of osteocytes (Fig. 1.3) is accomplished due to the strategic location of these cells within bone matrix. Thus, the shape and spatial arrangement of the osteocytes are in agreement with their sensing and signal transport functions, promoting the translation of mechanical stimuli into biochemical signals, a phenomenon that is called piezoelectric effect [39] (Fig. 1.7). The mechanisms and components by which osteocytes convert mechanical stimuli to biochemical signals are not well known. However, two mechanisms have been proposed. One of them is through a protein complex formed by a cilium, and its associated proteins PolyCystins 1 and 2, which has been suggested to be crucial for osteocyte mechanosensing and for osteoblast/ osteocyte-mediated bone formation [40]. The second mechanism involves osteocyte cytoskeleton components, including focal adhesion protein complex and its multiple actin-associated proteins such as paxillin, vinculin, talin, and zyxin [41]. Upon mechanical stimulation, osteocytes produce several secondary messengers, for example, ATP, nitric oxide (NO), Ca2+, and prostaglandins (PGE2 and PGI2,) which influence bone physiology [42]. Independently of the mechanism involved, it is important to mention that the mechanosensitive function of osteocytes is possible due to the intricate canalicular network, which allows the communication among bone cells.

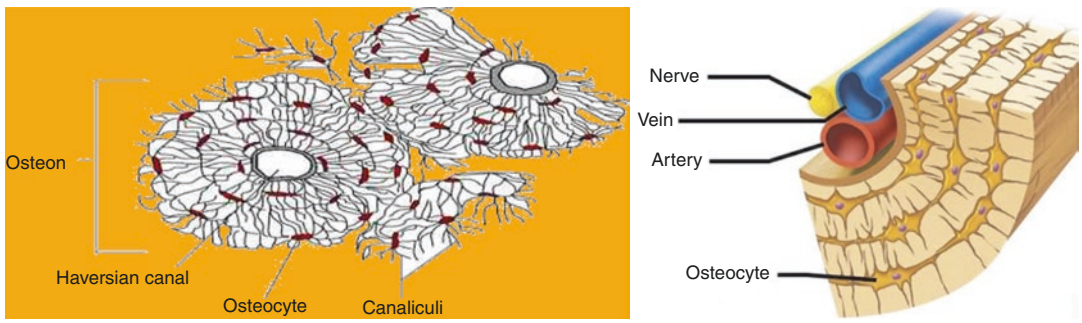


Fig. 1.2 The Haversian system. Bone can be thought of as a skyscraper with an elevator: The entire skyscraper is the osteon. The elevator of the building is like the Haversian Canal of the bone. Each floor of a building is like the Volkmann's Canal. Each office of the building represents an osteocyte

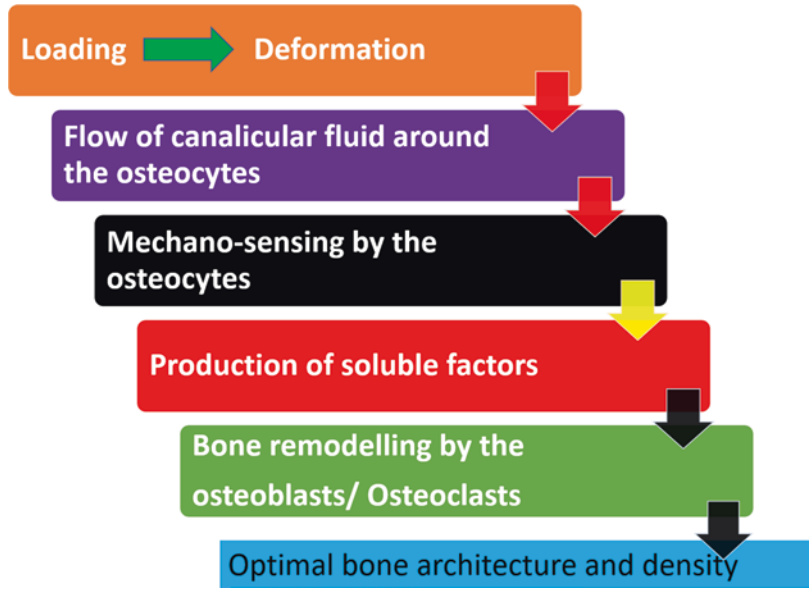


Fig. 1.3 The mechanosensitive function of osteocytes promoting the translation of mechanical stimuli into biochemical signals

Osteoclasts

Osteoclasts are terminally differentiated, multinucleated, giant cells that are responsible for bone resorption under both normal and pathological conditions, such as osteoporosis. Morphologically, osteoclasts tend to be much larger than other bone cells and are generally located on the surface of bones. They are known to be very mobile, moving from various sites and along the bone surface, and this motility is thought to account for the varied appearance of these cells [43]. In bone, osteoclasts are found in pits in the bone surface which are called resorption bays, or Howship's lacunae (Fig. 1.4).

Osteoclasts originate from mononuclear cells of the hematopoietic stem cell lineage, under the influence of several factors. Among these factors are the macrophage-colony stimulating factor (M-CSF), secreted by osteoprogenitor mesenchymal cells and osteoblasts [44]; and RANK ligand, secreted by osteoblasts, osteocytes, and stromal cells (Fig. 1.5) [45]. Together, these factors promote the activation of transcription factors [44, 46] and gene expression in osteoclasts [47, 48].

Macrophage-colony stimulating factor (M-CSF) binds to its receptor (cFMS) present in osteoclast precursors, which stimulates their proliferation and inhibits their apoptosis [46, 49]. RANKL is a crucial factor for osteoclastogenesis and is expressed by osteoblasts, osteocytes, and stromal cells. When it binds to its receptor RANK in osteoclast precursors, osteoclast formation is induced [50]. On the other hand, another factor called osteoprotegerin (OPG), which is produced by a wide range of cells including osteoblasts, stromal cells, and gingival and periodontal fibroblasts [51–53], binds to RANKL, preventing the RANK/RANKL interaction and, consequently, inhibiting the osteoclastogenesis [51] (Fig. 1.8). Thus, the RANKL/RANK/OPG system is a key mediator of osteoclastogenesis [50, 53].

Despite these osteoclastogenic factors having been well defined, it has recently been demonstrated that the osteoclastogenic potential may differ depending on the bone site considered. It has been reported that osteoclasts from long bone marrow are formed faster than in the jaw. This different dynamic of osteoclastogenesis possibly could be due to the cellular composition of the bone-site specific marrow [54].

Osteoclasts are characterized by having multiple nuclei, which average between 3 and 20, tend to be oval and concentrated mid-cell. There is less RER present than in osteoblasts, which is consistent with decreased production and secretion of proteins. Mitochondria are more numerous within osteoclasts than any other cell type within

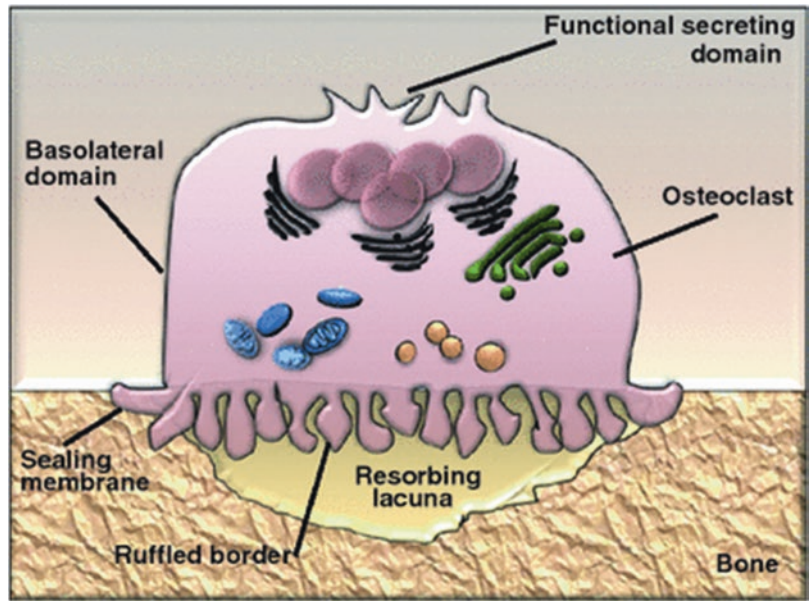


Fig. 1.4 Schema showing the resorption lacuna (Howship's lacuna): osteoclasts are found in pits in the bone surface which are called resorption bays, or Howship's lacunae

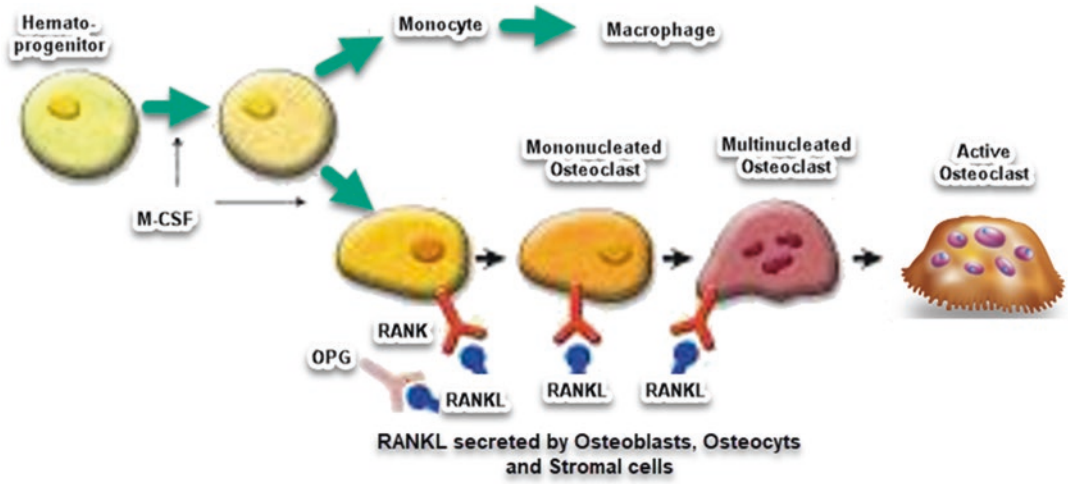


Fig. 1.5 Osteoclastogenesis: Development schema of hematopoietic precursor cell differentiation into mature osteoclasts. The hematopoietic cells form the liquid part of the bone marrow, and some of them circulate with the blood

the body. Between the nuclei are vesicles of Golgi material, which are relatively small in number. Many lysosomal types of vacuoles are present, leading to the common description of the cytoplasm as being "foamy." [55, 56]. The plasma membrane of the active osteoclast has an infolded appearance known as a ruffled border. The deep infolds of this border result in appendage-like projections of the cell that can wrap around bony prominences or lie along the surface. The large membrane surface area potentially permits extensive exchange between the intracellular and extracellular environments [3, 55].

During bone remodeling osteoclasts polarize; then, four types of osteoclast membrane domains can be observed: the sealing zone and ruffled border that are in contact with the bone matrix as well as the basolateral and functional secretory domains, which are not in contact with the bone matrix [57, 58]. These domains are only formed

when osteoclasts are in contact with extracellular mineralized matrix, in a process which $\alpha v\beta 3$-integrin, as well as the CD44, mediates the attachment of the osteoclast podosomes to the bone surface [59–62]. Ultrastructurally, the ruffled border is a membrane domain formed by microvilli, which is isolated from the surrounded tissue by the sealing zone, also known as clear zone. The sealing zone is an area devoid of organelles located in the periphery of the osteoclast adjacent to the bone matrix [61]. This sealing zone is formed by an actin ring as well as several other proteins [58]. The $\alpha v\beta 3$-integrin binds to noncollagenous bone matrix containing-RGD sequence such as bone sialoprotein, osteopontin, and vitronectin, establishing a peripheric sealing that delimits the central region, where the ruffled border is located [61].

The maintenance of the ruffled border is also essential for osteoclast activity; this structure is formed due to intense trafficking of lysosomal and endosomal components. In the ruffled border, there is a vacuolar-type H^+-ATPase (V-ATPase), which helps to acidify the resorption lacuna and hence to enable dissolution of hydroxyapatite crystals (Fig. 1.6) [45, 63, 64]. In this region, protons and enzymes, such as tartrate-resistant acid phosphatase (TRAP), cathepsin K, and matrix metalloproteinase-9 (MMP-9), are transported into a compartment called Howship lacuna leading to bone degradation [57, 64–67] (Fig. 1.3). The products of this degradation are then endocytosed across the ruffled border and transcytosed to the functional secretory domain at the plasma membrane [68].

Abnormal increase in osteoclast formation and activity leads to some bone diseases such as osteoporosis, where resorption exceeds formation causing decreased bone density and increased bone fractures [68]. In some pathologic conditions including bone metastases and inflammatory arthritis, abnormal osteoclast activation results in periarticular erosions and painful osteolytic lesions, respectively [47, 68, 69]. On the other hand, in osteopetrosis, which is a rare bone disease, genetic mutations that affect formation and resorption functions in osteoclasts lead to decreased bone resorption, resulting in a disproportionate accumulation of bone mass [70]. These diseases demonstrate the importance of the normal bone remodeling process for the maintenance of bone homeostasis.

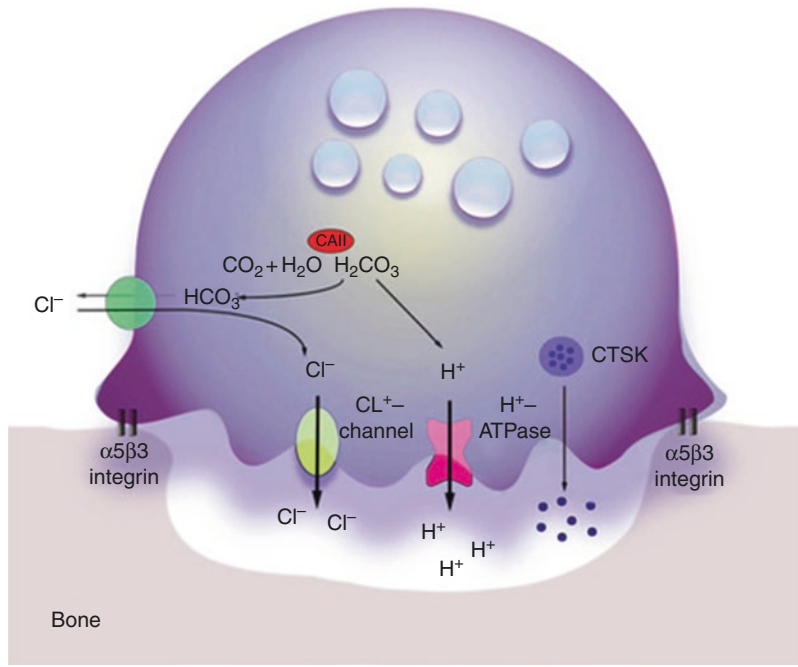


Fig. 1.6 Osteoclast bone resorption site: In the ruffled border, there is a vacuolar-type H + -ATPase (V-ATPase), which helps to acidify the resorption lacuna and hence to enable dissolution of hydroxyapatite crystals

Furthermore, there is evidence that osteoclasts display several other functions. For example, it has been shown that osteoclasts produce factors called clastokines that control osteoblast during the bone remodeling cycle. Furthermore, earlier studies revealed that osteoclasts may also directly regulate the hematopoietic stem cell niche [71]. These findings indicate that osteoclasts are not only bone resorbing cells but also a source of cytokines that influence the activity of other cells.

Bone Structure

Bone is a combination of osteoid matrix and hydroxyapatite [$Ca^{10}(PO4)^6(OH)^2$] crystal but bone also contains water, noncollagenous proteins, lipids, and specialized bone cells [72].

The type 1 collagen bone matrix gives bone elasticity, flexibility, and tensile strength. The collagen fibers are made up of three helical chains and combine together to form fibrils. Fibrils are then interwoven and bound by crosslinks [73]. Noncollagenous proteins, adsorbed from the serum, also make up the matrix. The role of such proteins is becoming increasingly clear and their major functions include strengthening the collagen structure and regulating its mineralization. Bone mineral, in the form of hydroxyapatite crystals, is an essential store of calcium and phosphate required for mineral homeostasis and provides the skeleton with mechanical rigidity and compressive strength. Recently, Nuclear Magnetic Resonance (NMR) spectroscopy has given new insights into the detailed composition of bone matrix and mineral [74].

Bones fulfill a protective and supportive role, but are also essential for locomotion; they are therefore required to be strong yet light. Consequently, bones are made up of two, structurally distinct, types– cortical and trabecular (cancellous) (Fig. 1.7). Cortical bone is solid with penetrating vascular canals and makes up the outer dense shell. It has an outer periosteal surface containing blood vessels, nerve endings, osteoblasts and osteoclasts and an inner, endosteal surface adjacent to the marrow [75]. On the endosteal surface of cortical bone is the honeycomb-like trabecular bone, which is made up of a fine network of connecting plates and rods [76].

The structural differences between cortical and trabecular bone underlie their diverse functions. The majority of the mature skeleton (80%)

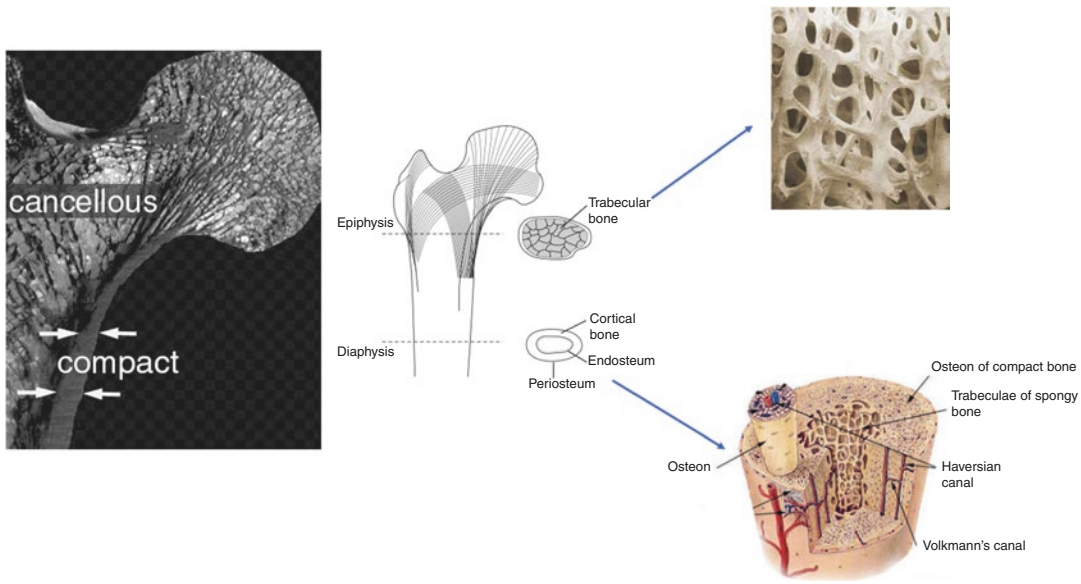


Fig. 1.7 Structural arrangement of cortical Bone and cancellous bone

is dense cortical bone that has a high torsional resistance and a lower rate of turnover. Nevertheless, it can release mineral in response to a significant or long-lasting deficiency. By contrast, trabecular bone, which is less dense, more elastic, has a higher turnover rate, and high resistance to compression makes up the rest of the skeleton. It serves to provide mechanical support, helping to maintain skeletal strength and integrity with its rods and plates aligned in a pattern that provides maximal strength. Trabecular bone has a large surface area for mineral exchange and is more metabolically active than cortical bone, rapidly liberating minerals in acute insufficiency [77]. Consequently, trabecular bone is also preferentially affected by osteoporosis [78].

The proportions of cortical and trabecular bone present are dependent on the individual bone's function. In vertebrae, trabecular bone predominates to resist compressive forces. By contrast, long bones, which principally act as levers, are mostly composed of cortical bone to allow them to resist both compressive and torsional forces [78, 79].

Although bone exhibits significant mechanical strength at a minimum weight, its biomechanical properties allow for significant flexibility without compromising this mechanical strength. Within these classifications, cortical and cancellous bone can consist of either woven (primary) or lamellar (secondary) bone. Comparison of cortical and cancellous bone demonstrates a similar matrix structure and composition, but vastly different masses, with cortical bone having a greater mass-to-volume ratio [3].

Cortical bone surrounds the marrow cavity and the trabecular plates of the cancellous bone. It accounts for 80% of the mature skeleton and forms the diaphysis, or shaft, of long bones. The metaphysis and epiphysis of long bones have thinner cortical walls, with the epiphysis forming a bulbous end surrounding the inner cancellous bone. Short bones (e.g. the tarsals and carpals), the vertebrae, skull, and pelvic bones also tend to have thinner cortical walls but contain a greater percentage of cancellous bone compared with long bones [17].

The differences in mechanical properties between cortical and cancellous bone are due to the differences in architecture, even though the composition and materials are the same. The thick, dense arrangement of the diaphysis of long bones allows cortical bone to have a much higher resistance to torsional and bending forces, whereas cancellous bone provides greater resilience and shock absorption, such as in the epiphyseal region of long bones. Cancellous bone generally has a higher metabolic rate and appears to respond quicker to changes in mechanical loading and unloading, such as seen with prolonged immobilization. This may be due, in part, to the greater exposure of bone cells within cancellous bone to the adjacent bone marrow cells and vascular supply, whereas cells within cortical bone tend to be embedded deeper within the bone matrix [3].

Woven and lamellar bone are the terms based on the microscopic differentiation of the bone. Lamellar bone represents the main type of bone in a mature skeleton. Woven bone is composed of loosely and randomly arranged collagen bundles containing numerous osteocytes which lie in lacunar that vary in size and shape, whereas lamellar bone is characterized by an orderly arrangement of collagen bundles and their cells. Lamellar bone is secondary bone created by remodeling of woven bone. Cortical and cancellous bone can be made up of either woven or lamellar bone. Woven bone, sometimes referred to as primary bone, is seen in embryonic bone that is later resorbed and replaced by lamellar, or secondary, bone by 4 to 5 years of age. Woven bone, however, also is seen during the initial stages of fracture healing, within cranial sutures, ear ossicles, and epiphyseal plates. Exemplified by the relatively quick turnover rate during deposition and resorption, woven bone has a greater rate of metabolic activity compared with lamellar bone. Due to its composition, woven bone has a scattered, irregular appearance, whereas lamellar bone has a very orderly arrangement [17].

Histologically, the osteocytes seen in woven bone also are more randomly scattered than those in lamellar bone, where the osteocytes are uniform in size and shape and are oriented in line

with the other cells and structures within the bone [80]. When lamellar bone is viewed microscopically in cross-section, the organization of the layers appears in parallel units or sheets with densely packed collagen fibrils. Concentric rings of lamellae form osteons, which are also known as haversian systems. Osteons surround central canals (haversian canals), which contain blood, lymph vessels, and, occasionally, nerves. Between the central canals and the surrounding cells are the cell processes of osteocytes, which travel within tunnel-like structures known as canaliculi. They extend out in a radial manner between the central canals and surrounding osteocytes (Fig. 1.4). This allows for diffusion of nutrients in a system that is surrounded by a hard, mineralized matrix. The central canals also branch and anastomose with obliquely oriented vascular branches known as Volkmann canals. These structures allow for extended communication from the periosteum to the endosteum [81].

Primary osteons undergo resorption and new osteons form, leaving behind boundaries known as cement lines. The constant resorption and deposition of new bone is the basis for the dynamic process of bone turnover. Histologically, it is possible to see areas within a cross-section of bone where remnants of primary osteons exist along with secondary osteons [81, 82].

The complex and dynamic network of lacunae and canals within bony tissue form an extravascular space where, adjacent to a mineralized matrix, fluids and ions can flow relatively unrestricted, and mechanical bone deformations can be converted to electrical signals and transmitted to other areas of the tissue. Some authors [83, 84] have hypothesized the role of electrical signals in the regulation of bone function based on this interdependent network.

Cells Gaps

The normal development and maintenance of skeletal tissue is dependent on the tightly coordinated activity of osteoblasts, osteoclasts, and osteocytes. This coordination balances the bone forming function of the osteoblasts, the bone resorption led by the osteoclasts, and the osteocytes which seem to coordinate the activation of these two cell types. In order for the bone embedded osteocytes (Fig. 1.8) to control and facilitate the bone formation and resorption on the bone surfaces, there is an obvious need for these cells

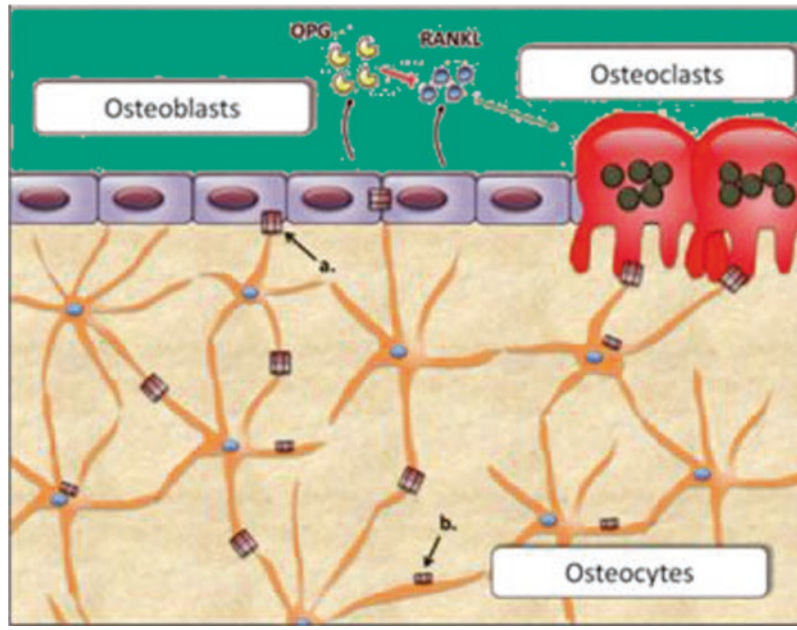
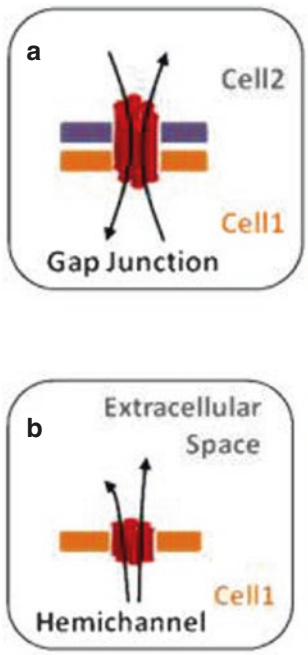


Fig. 1.8 Illustration of osteocytes embedded in bone. Long dendritic-like processes, enable contact between osteocytes and surface osteoblasts

to signal over a substantial distance, impeded by the presence of a mineralized matrix. This is accomplished both by the release of soluble signals (e.g., RANKL, osteoprotegerin and sclerostin) and by direct cell-to-cell communication through gap junctions. Osteocytes have an extensive network of long, dendritic-like cell processes that extend through the bone canaliculi, where they physically interconnect with adjacent osteocytes and with osteogenic cells on the bone surface via connexin-containing gap junctions [85] .

Gap junctional communication has been hypothesized to play a critical role in the coordination of bone remodeling. Osteoblasts and osteocytes have been shown to express three major gap junction proteins, connexin43 (Cx43), connexin45 (Cx45), and connexin46 (Cx46). Likewise, surface osteoblasts, osteoprogenitors, and bone lining cells express Cx43 and form functional gap junctions among each other as with osteocytes. Chondrocytes, the cells that form cartilage, have also been shown to express Cx43; as do the bone resorbing osteoclasts. Gap junctions are aqueous conduits that are formed by the docking of two hemichannels on juxtaposed cells (Fig. 1.9). They permit diffusion of ions, metabolites, and small signaling molecules (e.g., cyclic nucleotides and inositol derivatives). The result is a functional syncytium of interconnected cells throughout bone that acts in concert to orchestrate the formation and turnover of bone [86]. In addition to classic gap junctional intercellular communication, unopposed gap junction hemichannels exist at the membrane, where they function as direct conduits between the cytosol and extracellular milieu [87].

Depending upon the expressed connexin genes, the resultant gap junction channels will exhibit specific charge and size permeability. For example, Cx43 permits the diffusion of relatively large signal molecules <1.2 kDa molecular mass, with a preference for negatively charged molecules.



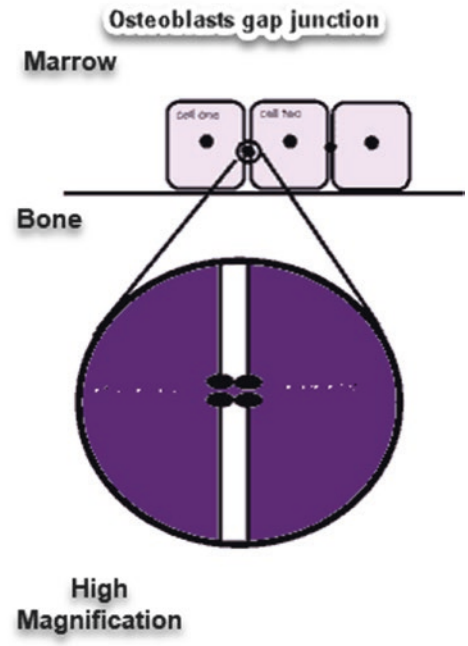


Fig. 1.9 Gap junctions with neighboring osteoblasts allow cells to communicate with each other or to extracellular space. Cx43 containing gap junctions form between the osteocytes and osteoblasts, (**a**) which allows the exchange of molecules between the cells. Osteocytes are also known to express gap junction hemichannels (**b**), that allow for the release of factors into the extracellular space. The regulation of bone resorption by osteoclasts is mediated by osteoblast/osteocyte produced RankL and OPG. The balance of these factors in the control of osteoclast formation is a target of Cx43

Inositol derivatives [88–93] and cADP-ribose [89, 94] are capable of diffusion through gap junctions and can elicit a $Ca2^{+}$ response in coupled cells. In contrast, Cx45 forms a smaller pore, permitting diffusion of molecules <0.3 kDa, with a preference for positively charged molecules. Interestingly, connexins can be present as a homomeric or heteromeric hemichannel, and the connexin isotypes that forms the gap junction hemichannels dictate the molecular size and permeability of the resulting gap junction channel [95–99]. For example, Cx43 and Cx45 are two such connexins that can assemble into a single hemichannel composed of both monomeric units. In the resultant Cx43/Cx45 heteromeric channel, the biochemical properties of Cx45 dominate and chemical and electrical coupling among cells is markedly reduced [95, 100, 101]. In addition, some connexin (hemichannel) pairs can form heterotypic interactions dependent upon the compatibility of the extracellular loops of the opposing hemichannels (e.g., one cell expressing monomeric Cx43 hemichannels may dock with an adjacent cell expressing monomeric Cx45 hemichannels).

These properties provide the gap junction great plasticity in dictating the size permeability and selectivity of the resultant communicative channel, restricting or allowing signaling only to coupled cells. Further, gap junction channels are regulated in a similar fashion as other membrane channels, with open/closed states sensitive to transmembrane voltage and posttranslational modification of the connexin subunits. Activation of extracellular signal regulated kinase (ERK) and protein kinase C has been shown to dynamically regulate Cx43 channel open/ closed state by phosphorylation of the C-terminal tail of the connexin monomers [102–104].

Accumulating evidence from many model systems consistently suggests that the unique profile of connexins expressed by a particular cell type can dictate the types of signals, second messengers, and metabolites that are propagated among cells. In this way, the cells can form a "functional syncytium" within which the cells communicate, with the advantage that the type of signals that can be diffused can be regulated. Thus, not all cells in the network share every signal; while some signals that diffuse through the gap junctions are rapidly distributed, propagation of others may be limited to serve specific functions [86].

Gap Junctions and Skeletal Development

The involvement of Cx43 in the processes that control bone cell function and ultimately bone quality is conspicuously complex, with differential responses based on the context of the effect. For example, loss of Cx43 differentially modulates the response of bone cells on the periosteal and endosteal surface of bone in response to mechanical loading [105]. Somewhat paradoxically, loss of Cx43 reduces the anabolic effect of mechanical load and yet also blunts the effects of mechanical unloading or perhaps even aging induced bone loss [106, 107]. This implies that Cx43 transmits signals that can be either osteoanabolic or osteo-catabolic, depending on the context such as aging, mechanical loading or unloading, or even location (i.e., differential effects on the periosteal and endosteal surfaces of bone) [108]. This complexity underscores the need to understand the specific details of how Cx43 affects bone cells and bone remodeling and raises several important questions. What are the second messengers and effectors of the osteoanabolic effects of Cx43 on bone? How do these differ from the effectors of the osteo-catabolic actions? Can we selectively regulate the ability to communicate and/or respond to some signals passed through gap junctions but not others? Understanding the molecular mechanisms by which Cx43 can modulate bone cell function in a context-dependent manner is critical to the development of treatments that modulate these connexin-regulated pathways to enhance or maintain bone quality.

Bone Remodeling

While the skeleton may seem an inert structure, in fact, it is a dynamic organ, comprised of tissue and cells in a continual state of activity through-

out a lifetime. The skeleton regulates its own maintenance and repair by remodeling. This process also provides a mechanism for rapid access to calcium and phosphate to maintain mineral homeostasis [109, 110]. Bone remodeling was recently reviewed by Kendre and Basset (2018) [110].

First defined by Frost, the bone remodeling cycle is a tightly regulated process that replaces old and damaged bone with new [111]. Anatomically, the cycle takes place within a Basic Multicellular Unit (BMU), which is composed of osteoclasts, osteoblasts, and a capillary blood supply [112]. The BMU lasts longer than the lifespan of the osteoblasts and osteoclasts within it and so requires constant replenishment of these cells, and is critically controlled by the osteocyte. The structure and composition of the BMU vary depending on whether it is located within trabecular or cortical bone. In trabecular bone, the BMU is located on the surface such that a "trench" of bone, called Howship's lacunae, is resorbed and then refilled. By contrast, in cortical bone, the osteoclasts within the BMU form a cutting cone that "tunnels" into the cortex (osteoclastic tunneling), removing damaged bone. Behind the cutting cone, new bone is then laid down concentrically on the tunnel walls by differentiated osteoblasts to leave a vascular supply within the Haversian canal of the new osteon [113]. In both instances, the BMU is covered by a canopy of cells which delineate the bone remodeling compartment (BRC).

The Bone Remodeling Compartment

Although macroscopically the skeleton seems to be a static organ, it is an extremely dynamic tissue at the microscopic level. Its ability to sustain the tremendous loads placed on it in everyday life depend on, among other factors, being able to remodel and repair the constant microcracks that develop both in cancellous bone — the "spongy" bone present in the vertebrae, pelvis, and ends (metaphyses) of long bones — and in cortical bone — the compact bone present in the shafts (diaphyses) of the long bones and surrounding cancellous bone in the vertebrae and pelvis. Since remodeling sites in cancellous bone in the vertebrae and pelvis are close to red marrow, which is known to contain osteoprogenitor cells (4), whereas remodeling sites in cortical bone are distant from red marrow, it had been assumed that the mechanisms of bone remodeling were likely to be different in cancellous versus cortical bone. Specifically, the assumption was that the cells needed for bone remodeling traveled directly from the red marrow to bone surfaces in cancellous bone, whereas they accessed cortical bone via the vasculature. However, it now seems that the fundamental mechanisms of bone remodeling might be very similar in both bone compartments, occurring in what has been termed the basic multicellular unit (BMU), which comprises the osteoclasts, osteoblasts, and osteocytes within the bone-remodeling cavity. Although the existence of the BMU has been established for a long time, the intimate relationship between the BMU and the vasculature, particularly in cancellous bone, was less well appreciated. This intimate relationship was initially described by Burkhardt et al. [114] more than 20 years ago and analyzed in detail in subsequent studies by Hauge and colleagues [115]. These investigators demonstrated that the cells in the BMU, even in cancellous bone, were not directly contiguous to the bone marrow, but rather they were covered by a "canopy" of cells (most probably bone-lining cells) that seem to be connected to bone-lining cells on the quiescent bone surface. In turn, these bone-lining cells on the quiescent bone surface are in communication with osteocytes embedded within the bone matrix. Penetrating the canopy of bone-lining cells, and presumably serving as a conduit for the cells needed in the BMU, are capillaries. Hauge et al. [115] introduced a new concept where he placed the BMU (consisting of osteoclasts, osteoblasts, and osteocytes), both in cancellous and in cortical bone, within the bone remodeling compartment (BRC), which comprises the BMU, the canopy of bone-lining cells, and the associated capillaries.

Therefore, the bone remodeling compartment (BRC) provides a defined area of remodeling

with close anatomical coupling of osteoclasts and osteoblasts [116, 117]. Hauge et al. [115] demonstrated that the cells in the BRC, are covered by a "canopy" of cells forming the outer lining of a specialized vascular structure with the denuded bone surface as the other delineation (Fig. 1.10). The cells of this canopy display all classical markers of the osteoblastic phenotype, and are therefore most probably bone-lining cells, which seem to be connected to bone-lining cells on the quiescent bone surface. The structure has been demonstrated in cortical as well as trabecular bones. In turn, these bone-lining cells on the quiescent bone surface are in communication with osteocytes embedded within the bone matrix. Penetrating the canopy of bone-lining cells, and presumably serving as a conduit for the cells needed in the BRC, are capillaries.

Cells may enter the remodeling space either via diapedesis through the lining cell dome covering the BRC or via the circulation. It is still debatable whether all cells involved in remodeling arrive via the circulation. Circulating osteoclast precursors have been demonstrated several years ago, there is a growing evidence that osteoblast lineage cells are also present in the circulation strengthening the involvement of circulating precursor cells in the process [118, 119].

The BRC is the most probable structure at which coupling between osteoclasts and osteo-

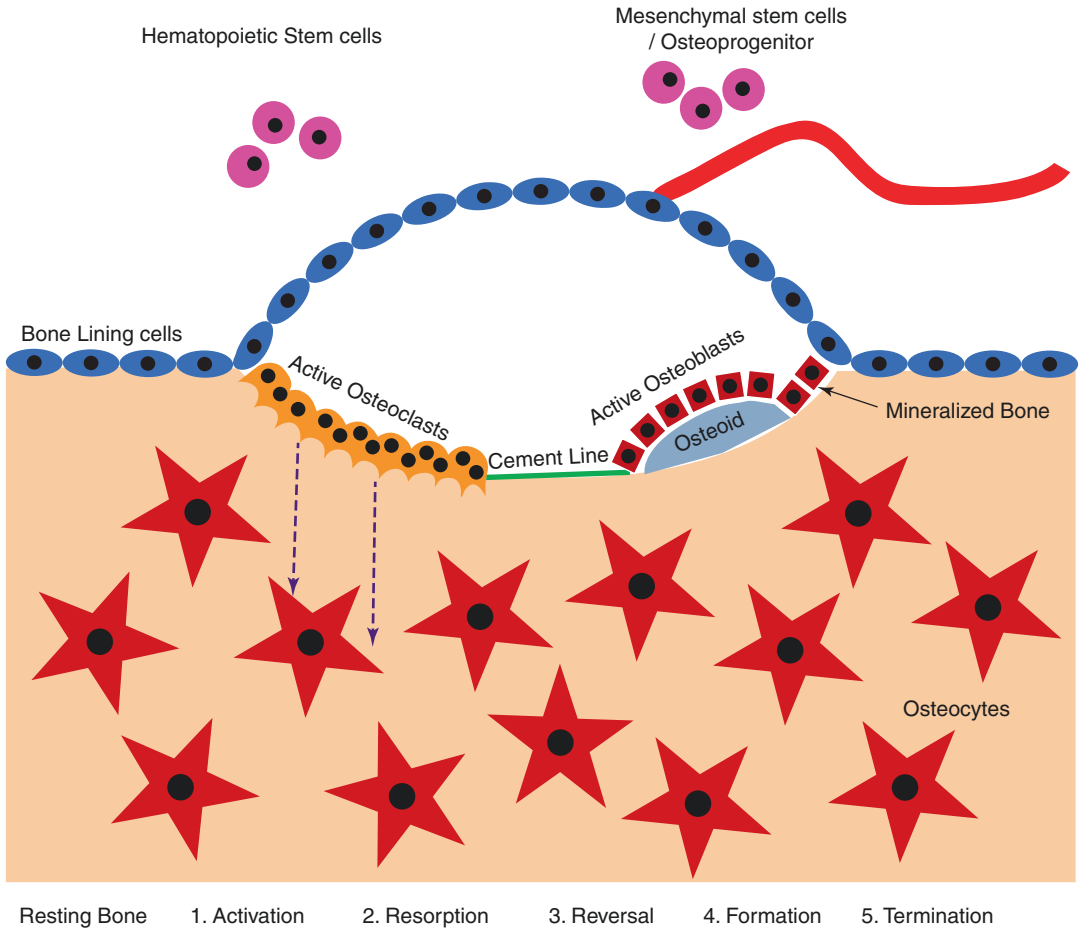


Fig. 1.10 The bone remodeling compartment (BRC) at different phases of the bone remodeling cycle. Schematic diagram of the bone remodeling cycle illustrating the phases of: activation, resorption, reversal, formation and termination. Hemopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). (Quoted with permission from Kendre and Bassett [110])

blasts occurs. It also obviates the need for a "postal code" system ensuring that resorptive and formative cells adhere to areas on the bone surface, where they are needed. Bone surfaces are generally covered by lining cells, which would prevent direct contact between bone cells and integrins or other adhesion molecules known to modulate cell activity. The BRC would be the only place where circulating osteoclasts as well as circulating osteoblast precursors would be in contact with these matrix constituents, because the formation of the BRC involves detachment of lining cells from the bone surface [117].

The Remodeling Cycle – Cellular and Molecular Mechanisms

The remodeling cycle occurs in a highly regulated and stereotyped fashion with five overlapping steps of activation, resorption, reversal, formation, and termination occurring over the course of 120–200 days in cortical and trabecular bone, respectively [120]. The remodeling cycle can be as short as 100 days in thyrotoxicosis and primary hyperparathyroidism and exceed 1000 days in low turnover states like myxedema and after bisphosphonate treatment [121]. Osteocytes orchestrate the bone remodeling by regulating osteoclast and osteoblast differentiation and consequently bone resorption and formation.

Activation

The first stage of bone remodeling involves detection of an initiating remodeling signal. This signal can take several forms, e.g. direct mechanical strain on the bone that results in structural damage or hormone (e.g. estrogen or parathyroid hormone [PTH]) action on bone cells in response to more systemic changes in homeostasis.

Daily activity places ongoing mechanical strain on the skeleton, and it is thought that osteocytes sense changes in these physical forces and translate them into biological signals that initiate bone remodeling (Fig. 1.11) [122]. Damage to the bone matrix [123] or limb immobilization [72] results in osteocyte apoptosis and increased osteoclastogenesis. Under basal conditions, osteocytes secrete transforming growth factor β (TGF-β), which inhibits osteoclastogenesis. Focal osteocyte apoptosis lowers local TGF-β levels, removing the inhibitory osteoclastogenesis signals and allowing osteoclast formation to proceed [73].

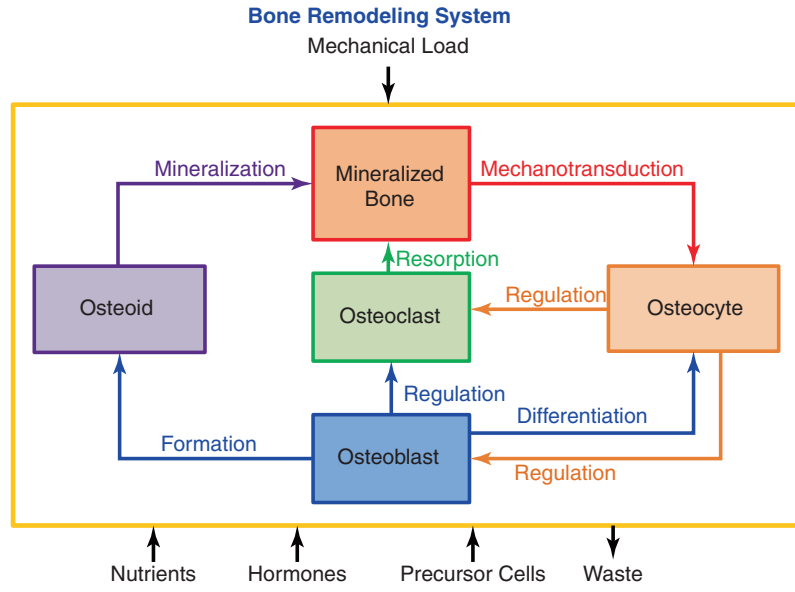


Fig. 1.11 Bone remodeling system in response to mechanical stimuli. In addition to the local factors, other systemic factors play a role in the remodeling process

Osteoclast precursor cells are recruited from the circulation and activated; the bone surface is exposed as the lining cells separate from underlying bone and form a raised canopy over the site to be resorbed [116]. Multiple mononuclear cells fuse to form multinucleated preosteoclasts which bind to the bone matrix to form sealing zones around bone-resorbing compartments, thus isolating the resorption pit from surrounding bone. Initiation of bone remodeling is the first important step ensuring that, in health, remodeling only takes place when it is required. In "*targeted remodeling,*" which refers to removal of a specific area of damaged or old bone, the initiating signal originates from the osteocytes that use their extensive network of dendritic processes to signal to other cells [109, 124–127]. Osteocyte apoptosis, induced for example by the disruption of osteocyte canaliculi caused by bone matrix microdamage, leads to release of paracrine factors that increase local angiogenesis and recruitment of osteoclast and osteoblast precursors [128–130]. In contrast, "*nontargeted remodeling*" refers to remodeling in response to systemic changes in hormones such as parathyroid hormone (PTH), thus allowing access to bone calcium stores and is not directed towards a specific site.

Resorption (Approximately Two Weeks in Duration)

Differentiation and activation of osteoclasts are also regulated by osteocytes. Rearrangement of the osteoclast cytoskeleton results in adherence to the bone surface, formation of a sealing zone and generation of a ruffled border that provides a greatly enhanced secretory surface area. Initially, osteoclasts pump protons, generated by Carbonic Anhydrase II, into the resorbing compartment to dissolve the bone mineral. Specifically, the H^+-ATPase pumps H^+ into resorption lacunae; this is coupled to Cl^- transported via a chloride channel thus maintaining electroneutrality [131]. Subsequently, the collagen-rich bone matrix is degraded by proteases such as cathepsin K and matrix metalloproteinases [132, 133]. The resorption phase is terminated by osteoclasts programmed cell death, ensuring that excess resorption does not occur (Fig. 1.12) [134].

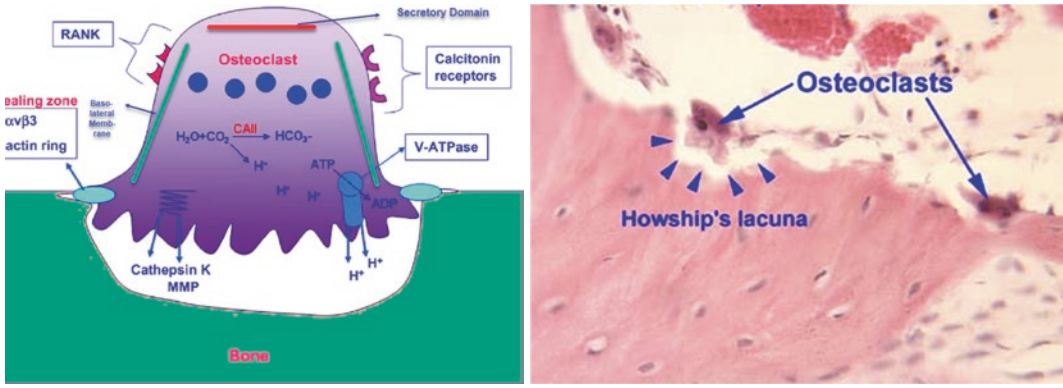


Fig. 1.12 Rearrangement of the osteoclast cytoskeleton results in adherence to the bone surface, formation of a sealing zone and generation of a ruffled border that provides a greatly enhanced secretory surface area. Consequently, four types of osteoclast membrane domains are observed: the sealing zone and ruffled border that are in contact with the bone matrix as well as the basolateral and functional secretory domains, which are not in contact with the bone matrix. In the ruffled border, there is a vacuolar-type H + -ATPase (V-ATPase), which helps to acidify the resorption lacuna and hence to enable dissolution of hydroxyapatite crystals. In this region, protons and enzymes, such as tartrate-resistant acid phosphatase (TRAP), cathepsin K, and matrix metalloproteinase-9 (MMP-9) are transported into a compartment called Howship lacuna leading to bone degradation. The products of this degradation are then endocytosed across the ruffled border and transcytosed to the functional secretory domain at the plasma membrane

Reversal (Approximately Four to Five Weeks in Duration)

The reversal phase, where bone resorption switches to formation. There are two key events occurring. Firstly, the freshly resorbed bone surface is prepared for deposition of new bone matrix and further signaling occurs that couples resorption to formation, ensuring that there is no net bone loss [135, 136]. Preparation of the bone surface is carried out by cells of an osteoblastic lineage which remove unmineralized collagen matrix, and a noncollagenous mineralized matrix "cement-line" is then deposited to enhance osteoblastic adherence [137].

The exact signal that couples bone resorption to subsequent formation is not yet fully understood. However, it is likely that the cells of the reversal phase are involved in sending or receiving these signals [138–140]. It has been postulated that osteoclasts may be the source of the coupling factor, either secreting cytokines such as interleukin 6 (IL-6), or via a regulatory receptor on their surface such as the Ephrin receptor family and their membrane bound ligand, Ephrins, present on osteoblasts [141]. Other signaling pathways may include matrix-derived factors such as BMP-2, transforming growth factor ßb and insulin-like growth factor [142, 143].

Formation (Approximately Four Months in Duration)

New bone formation can be divided into two parts. Firstly, osteoblasts synthesize and secrete a type-1 collagen-rich osteoid matrix. Secondly, osteoblasts play a part in regulating osteoid mineralization [125, 144].

The process of bone mineralization, whereby hydroxyapatite crystals are deposited among collagen fibrils, is complex and its regulation is incompletely understood. Control is exerted by systemic regulation of calcium and phosphate concentrations, local concentration of calcium and phosphate within extracellular matrix vesicles and by local inhibitors of mineralization, including pyrophosphate and noncollagenous proteins such as osteopontin. The ratio of inorganic pyrophosphate to phosphate is a critical regulator of mineralization, and the relative activities of tissue nonspecific alkaline phosphatase and ectonucleotide pyrophosphatase are the key determinants of this ratio [145–147].

Termination

Once mineralization is complete, osteoblasts undergo apoptosis, change into bone-lining cells or become entombed within the bone matrix and terminally differentiate into osteocytes. Osteocytes play a key role in signaling the end of remodeling via secretion of antagonists to osteogenesis, specifically antagonists of the Wnt signaling pathway such as SOST [76].

The Remodeling Cycle – Major Signaling Pathways

The remodeling cycle is tightly regulated to achieve balanced resorption and formation. While systemically released factors play a regulatory role, the fact that remodeling occurs at multiple, anatomically distinct sites at the same time indicates that local regulation is critical to achieving this fine balance. Accordingly, two key pathways, RANKL/RANK/OPG and Wnt, transduce systemically and locally produced signals. Their regulatory role in determining the balance and timing of bone resorption and formation within the remodeling cycle makes them potentially important targets for pharmacological interventions in disease states such as osteoporosis.

Receptor Activator of Nuclear Factor Kappa-B Ligand Signaling Pathway (RANKL/RANK/OPG Signaling)

Identification of the receptor activator of Nf-κb ligand (RANKL/RANK/OPG) Signaling Pathway in the 1990s was a crucial breakthrough in understanding the regulation of osteoclasto-

genesis in the remodeling cycle and provided the pharmacological target for the novel anti-resorptive denosumab [148].

A permissive concentration of macrophage-colony stimulating factor (M-CSF), which is expressed by osteocytes and osteoblasts and stimulates RANK expression, is required prior to the action of RANKL [149, 150].

RANKL binding to its receptor, RANK, on osteoclastic precursor cells, drives further osteoclast differentiation and facilitates fusion, activation, and survival. RANKL/RANK binding induces downstream signaling molecules including mitogen-activated protein kinase, tumor necrosis factor (TNF)-receptor-associated factor 6, NF-κB, and c-fos and ultimately activation of key transcription factors, including nuclear factor-activated T cell cytoplasmic 1 (NFATc1), a master transcription factor of osteoclast differentiation as it regulates the expression of osteoclast genes [151–154].

While RANKL can be produced by osteoblasts, osteocytes, and chondrocytes, it is the osteocytes, within the bone matrix, able to sense changes in load and microdamage that are thought to stimulate osteoclastogenesis via production of RANKL at the initiation of the bone remodeling cycle [155, 156].

Osteoprotegerin (OPG), a decoy receptor for RANKL, was identified prior to the discovery of RANK/RANKL. It is secreted by osteoblasts and osteocytes and is able to inhibit osteoclastic bone resorption by binding to RANKL and preventing its binding to RANK [156, 157]. Thus, the RANKL:OPG ratio is key in the regulation of bone resorption, bone mass, and skeletal integrity and is modulated by a number of systemic factors; RANKL expression is induced by bone-resorbing factors such as 1α,25-dihydroxy vitamin D3, interleukin 6, and parathyroid hormone (Fig. 1.13).

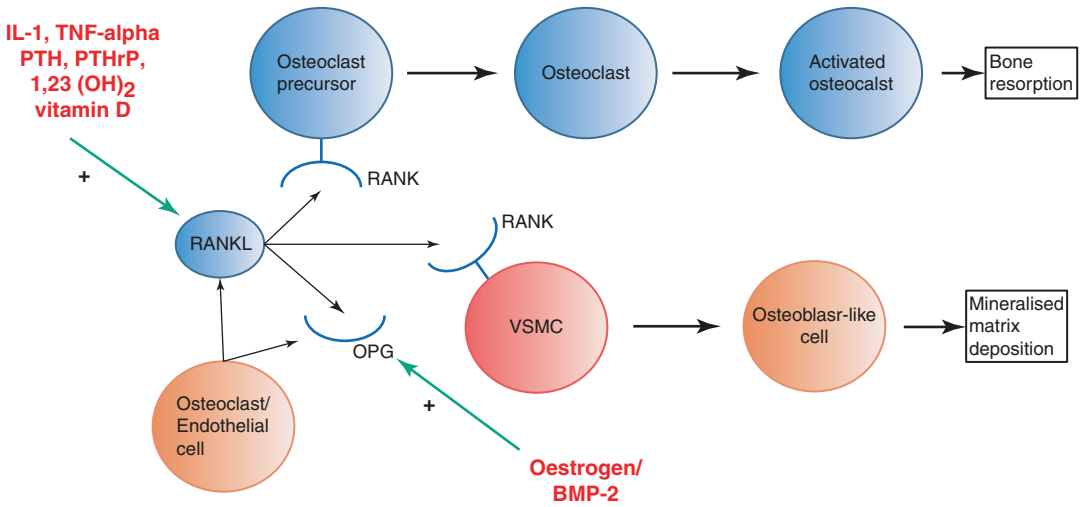


Fig. 1.13 Simplified diagram showing potential RANK/RANKL/OPG involvement in bone remodeling and in vascular calcification. Receptor activator of nuclear factor kappa-B ligand (RANKL) from osteoblasts or endothelial cells binds to the Receptor Activator of Nuclear Factor kappa-B (RANK) of osteoclast precursors, or vascular smooth muscle cells (VSMCs). This leads to differentiation into mature osteoclasts in the bone, which are involved in bone resorption, whereas in vascular calcification, VSMCs undergo a phenotypic transition into osteochondrogenic cells that can deposit mineralized matrix. Osteoprotegerin (OPG) is the decoy receptor for RANKL, and a potential inhibitor for mineralization. Factors affecting the RANK/RANKL/OPG signalling pathway. Oestrogen and Bone morphogenic Protein-2 (BMP-2) induce osteoprotegerin (OPG) expression whereas 1,25(OH)2 Vitamin D3, PTH, PTHrP, IL-1 and tumor necrosis factor a (TNFa) induce RANKL. OPG is a decoy receptor for RANKL blocking its binding to RANK. Thus, it is the RANKL: OPG ratio that determines the rate of osteoclastogenesis. (Quoted with amendment under open access scheme from Tsang [287])

Wnt Signaling

Wnt is a cytokine involved in the development and homeostasis of various organs. In 2001, low-density lipoprotein receptor-related protein 5 (LRP5) was identified as the gene responsible for osteoporosis pseudoglioma syndrome and regulation of bone mass. Since LRP5 belongs to the low-density lipoprotein receptor family, this finding garnered the attention of researchers in the bone, mineral, and Wnt research fields. In bone, Wnt signaling dominate osteoblast differentiation pathways and act via binding to a receptor complex consisting of LDL receptor-related protein 5 (LRP5) orLRP6 and one of ten Frizzled molecules (The Frizzled family is composed of seven-transmembrane-spanning receptors) [158, 159]. The so-called canonical Wnt signaling pathway is active in all cells of the osteoblastic lineage and involves the stabilization of β-catenin and regulation of multiple transcription factors [160, 161]. Wnt/β-catenin signaling is also important for mechanotransduction, fracture healing, and osteoclast maturation [162–164]. The terminology of canonical vs. noncanonical is historic (Canonical means the overarching and most significant, it refers to specific pathways" as those specific of tissues, cell lines, etc. Noncanonical pathways are those that deviate from the canonical paradigm. The noncanonical pathway refers to the β-catenin-independent pathway). In the classical example of the Wnt pathway, canonical refers to the pathway components that lead to stabilization of beta-catenin in response to certain Wnt ligands. Any other biological outcomes of Wnt signaling are termed noncanonical.

The activation of canonical Wnt-signaling promotes osteoblast differentiation from mesenchymal progenitors at the expense of adipogenesis, which leads to improved bone strength, while suppression causes bone loss [165] (Fig. 1.14). Canonical Wnt signaling in osteoblast differentiation is modulated by Runx2 and osterix [166].

Different Wnt ligands and Frizzled receptors can engage various signaling responses. Wnt5a binds to Ror2 receptors and activates noncanonical signaling pathways, thereby promoting osteoclast differentiation and bone-resorbing activity. In contrast, Wnt16 activates non-canonical Wnt signaling in osteoclast precursor cells and suppresses the Rankl-induced activation of Nf-κb and Nfatc1, thereby inhibiting osteoclast differentiation [158].

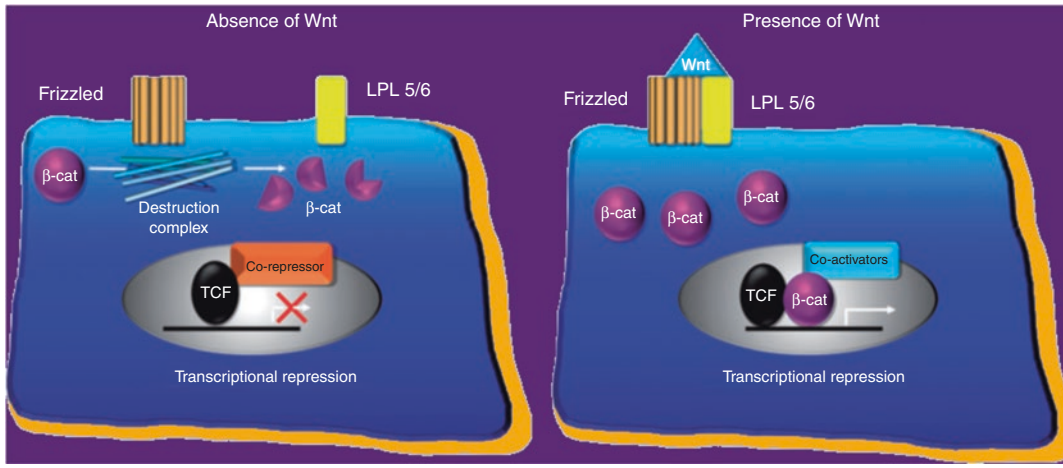


Fig. 1.14 Schematic illustration of canonical Wnt signaling. In the absence of Wnt, Frizzled and its coreceptors LPL5/6 do not interact. The destruction complex, present in the cytoplasm, degrades b-catenin and target gene expression is repressed. In the presence of Wnt, Frizzled binds to its coreceptors and blocks the action of the destruction complex. b-catenin accumulates in the cytoplasm, translocates to the nucleus displacing transcriptional corepressors and recruiting coactivators leading to an increased expression of key target genes involved in osteoblast differentiation. (Quoted with permission from Kendre and Bassett [110]

Wnt signaling is a prime target for bone active drugs and the approach include inhibition of Wnt antagonist like Dkk1, sclerostin, and Sfrp1 with neutralizing antibodies and inhibition of glycogen synthase kinase 3 β (GSK3 β), which promotes phosphorylation and degradation of β-catenin. One of the most promising approaches, which will be discussed later in this book, is the inhibition of the osteocyte protein sclerostin, which exerts tonic inhibition of osteoblast activity [167]. Sclerostin is the product of the *SOST* gene, which is mutated and downregulated in patients with sclerosteosis and van Buchem disease [168], which are diseases characterized by high bone density. Expression levels of sclerostin are repressed in response to mechanical loading and intermittent PTH treatment [169]. Preliminary studies with a humanized monoclonal antibody against sclerostin have shown bone anabolism in both animals as well as humans [117, 170].

Hormonal Impact on Bone Remodeling

Parathyroid Hormone (PTH)

PTH is a polypeptide hormone secreted by the chief cells of the parathyroid glands. It acts to raise the level of calcium in the bloodstream with direct actions on bone and the kidneys, and indirectly on the intestine via the influence on vitamin D. The hormone has a physiological, negative feedback loop that is influenced by the amount of calcium present in the blood. When there is a decreased concentration of plasma calcium, there is less binding to calcium-sensing receptors (CaSR) on the parathyroid gland. This will lead to an increased release of PTH to raise the levels of calcium. PTH has an indirect action on the osteoclasts by increasing the activity of receptor activator of nuclear factor kappa ligand (RANKL), which regulates the osteoclastic activity of bone resorption and leads to more calcium released into the plasma. In contrast, high levels of plasma calcium bind to the CaSR on the parathyroid gland and inhibit the release of PTH. Stimulating the CaSRs causes a conformational change of the receptor and stimulates the phospholipase C pathway. This ultimately leads to higher intracellular calcium, thereby inhibiting exocytosis of PTH from the chief cells of the parathyroid gland. This is only one piece to the calcium homeostasis as PTH has actions at the kidneys and intestines to regulate the levels of calcium and phosphate [171, 172].

Estrogen

A deficiency of estrogen leads to increased bone remodeling, where bone resorption outpaces bone formation and leads to a decrease in bone mass. It is believed, based on animal studies, that estrogen may influence local factors that regulate the precursors of osteoblasts and osteoclasts. Estrogen may block the production and action of interleukin-6 (IL-6), which would hinder bone resorption. Also, it is believed that the survival of osteoclasts thrives in the deficiency of estrogen, where the degree of bone turnover would be greater [173].

Calcitonin

Calcitonin, a polypeptide hormone, is released from thyroid C cells in response to elevated calcium levels. Regarding bones, calcitonin binds to calcitonin receptors on osteoclasts to inhibit bone resorption. It is believed that calcitonin does not play a prominent role in calcium homeostasis in adults, but it may be more important in skeletal development. However, calcitonin is clinically used as a treatment option to treat osteoporosis [174].

Growth Hormone

Growth hormone (GH), a peptide hormone secreted by the pituitary gland, acts through insulin-like growth factors to stimulate bone formation and resorption. Growth hormone acts directly and indirectly via insulin-like growth factor (IGF) to stimulate osteoblast proliferation

and activity, but it also stimulates the bone resorption activity of osteoclasts; however, the cumulative net effect of this dual activity favors bone formation [175].

Glucocorticoids

Glucocorticoids decrease bone formation by favoring the survival of osteoclasts and causing the cell death of osteoblasts. There is an increase in RANKL action and a decrease in osteoprotegerin (OPG). OPG is a cytokine receptor and member of the tissue necrosis factor superfamily that acts as a decoy receptor for RANKL, so it would normally hinder RANKL–RANK interaction and activity.

Thyroid Hormone

Thyroid-stimulating hormone (TSH), thyroxine (T4), and triiodothyronine (T3) cause bone elongation at the epiphyseal plate of long bones through chondrocyte proliferation and also stimulate osteoblast activity. In states of hypothyroidism or hyperthyroidism, the degree of bone turnover is low and high respectively. The rate of bone turnover is due to the effect of T3/T4 on the number and activity level of osteoblasts as well as osteoclasts. For example, the high metabolic state of thyrotoxicosis causes increased osteoblast function and increased osteoclastic number and activity and leads to a higher bone turnover [176]. Fig. 1.15 shows the major endocrine influences on bone remodeling.

Bone Modelling Vs. Remodeling

Bone Modeling

Bone modeling describes the process whereby bones are shaped or reshaped by the independent action of osteoblasts and osteoclasts. The activities of osteoblasts and osteoclasts are not necessarily coupled anatomically or temporally as is the case in bone remodeling. Bone modeling defines skeletal development and growth and is responsible for the shaping of bones and their movement through space. Even in adults, adaptation to permanently changed strain leads to modeling of bone, an example of which is tibial modeling after harvesting fibula for reconstructive surgery [177]. Abnormalities in bone modeling cause skeletal dysplasias or dysmorphias.

One important example of modeling is to preserve skeletal shape during linear growth. In the metaphysis, below the growth plate, there is osteoclastic resorption on the periosteal surface, while there is new bone formation on the inner endosteal surface thus converting the shape of the epiphysis into the diaphysis [178, 179]. When these processes are disrupted, for example, following antiresorptive (bisphosphonate) treatment of childhood osteogenesis imperfecta, a dramatic inhibition of normal metaphyseal modeling "Metaphyseal inwaisting" is seen [180]. Modeling is also responsible for radial growth of the diaphysis of long bones. Here, osteoclastic resorption occurs on the endosteal surface, while osteoblastic bone formation occurs at the periosteal surface thus increasing the overall diameter with age.

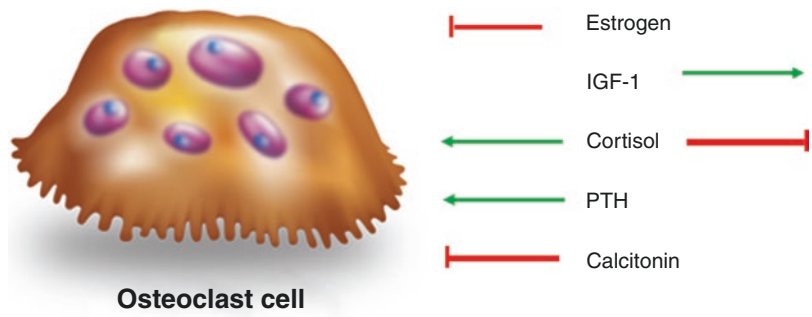


Fig. 1.15 Schema showing the major endocrine influences on bone remodeling. IGF-1, insulin-like growth factor-1; PTH, parathyroid hormone

The majority of bone modeling is completed by skeletal maturity but modeling can still occur even in adulthood such as in an adaptive response to mechanical loading and exercise and in renal bone disease [181–184]. Bone modeling has been demonstrated in aging humans. Modeling-based bone formation contributes to the periosteal expansion, just as remodeling-based resorption is responsible for the medullary expansion seen at long bones and ribs with aging [185].

How is bone modeling controlled? Physical activity can stimulate bone modeling. This is seen for example in tennis players where the arm used for tennis has a higher bone mass than the other arm [186]. Bone modeling is also controlled by other factors as modeling-based bone formation was also seen at the ribs, which are not axially loaded, in the denosumab nonhuman primate study [187]. It is therefore likely that bone modeling is controlled by genetic factors in combination with environmental factors such as physical strain and probably hormonal factors, as it has been demonstrated that the parathyroid hormone (PTH) and inhibition of sclerostin can stimulate modeling-based bone formation [188, 189].

Bone Remodeling

The purposes of remodeling are many including the replacement of old and damaged bone with new bone and calcium homeostasis (long-term homeostasis). Bone remodeling is most prominent on cancellous bone surfaces and it is estimated that 80% of bone remodeling activity takes place in cancellous bone, although cancellous bone only comprises 20% of bone. The relative importance of cortical remodeling increases with age as cancellous bone is lost and the remodeling activity in both compartments increases [190]. Disturbance of bone remodeling, such as in osteoporosis, with a net bone loss passes in three phases: (1) A reversible bone loss because of increase in the remodeling space, i.e., the amount of bone resorped but not yet reformed during the remodeling cycle. This mechanism leads to decrease in average trabecular thickness and cortical width, and to increase in cortical porosity. (2) An irreversible bone loss caused by negative bone balance, where the amount of bone formed by the osteoblasts is exceeded by the amount of bone resorbed by the osteoclasts at the same remodeling site. Consequently, progressive thinning of trabecular elements, reduced cortical width and increased cortical porosity is seen. (3) Finally, perforation of trabecular plates by deep resorption lacunae leads to complete irreversible removal of structural bone components [191]. In the cortical bone, remodeling takes place at both the periosteal and endocortical surfaces, but it also occurs inside the compact cortical bone [192, 193]. At the cortical surfaces remodeling is a surface-based process similar to the process in cancellous bone (Fig. 1.16), whereas intracortical remodeling is characterized by osteoclasts drilling through the compact bone in the cutting cone followed by osteoblasts filling the cylindrical void in the closing cone (Fig. 1.17) [194, 195]. This is called a Haversian remodeling system.

By removing old and damaged bone targeted remodeling plays a key role in maintaining the mechanical strength of bone. However, excessive remodeling and repair poses a risk to bone strength as it destabilizes bone and introduces stress concentrators [195]. Even targeted remodeling may be harmful. For example, excessive strain causes regional microdamage, which leads to targeted remodeling removing the damaged bone and a larger volume of the surrounding undamaged bone, this temporary volume deficit increases the strain in neighboring bone and the potential establishment of a vicious cycle between damage and repair [196]. Furthermore, bone is an important player in calcium homeostasis. There are several examples of bone being a dynamic part of calcium homeostasis, for example, during pregnancy and lactation or when male deer grow antlers, the latter being an extreme example in which sufficient calcium can only be attained by temporarily removing it from the skeleton [197]. The potential conflict between preserving bone strength and providing calcium to the rest of the body becomes more obvious with aging when vitamin D production and, thereby calcium absorption, decreases and sec-

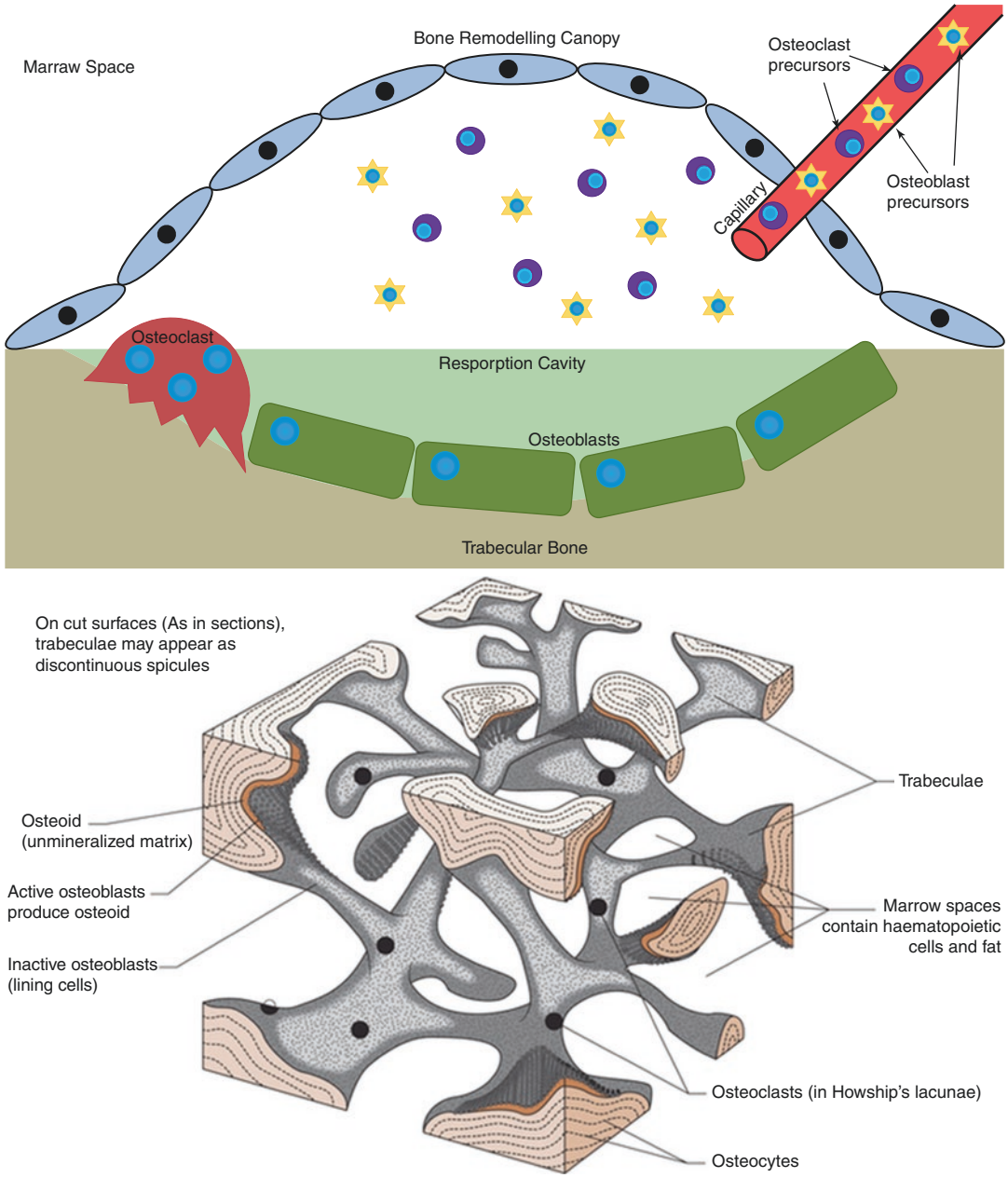


Fig. 1.16 Trabecular remodeling is a surface-based process. Osteocyte apoptosis, induced for example by the disruption of osteocyte canaliculi caused by bone matrix microdamage, leads to release of paracrine factors that increase local angiogenesis and recruitment of osteoclast and osteoblast precursors. (Quoted under open access scheme Creative Commons Attribution License (CC BY) from: Owen and Reilly [288])

ondary hyperparathyroidism develops in order to maintain adequate serum calcium levels by increasing bone resorption. Furthermore, the estrogen insufficiency in postmenopausal women also leads to increased remodeling activity. Increased resorptive activity in a young individual is accompanied by complementary increased formation and the balance at each bone resorption unit is neutral, therefore the bone loss is merely reflecting an opening of the remodeling

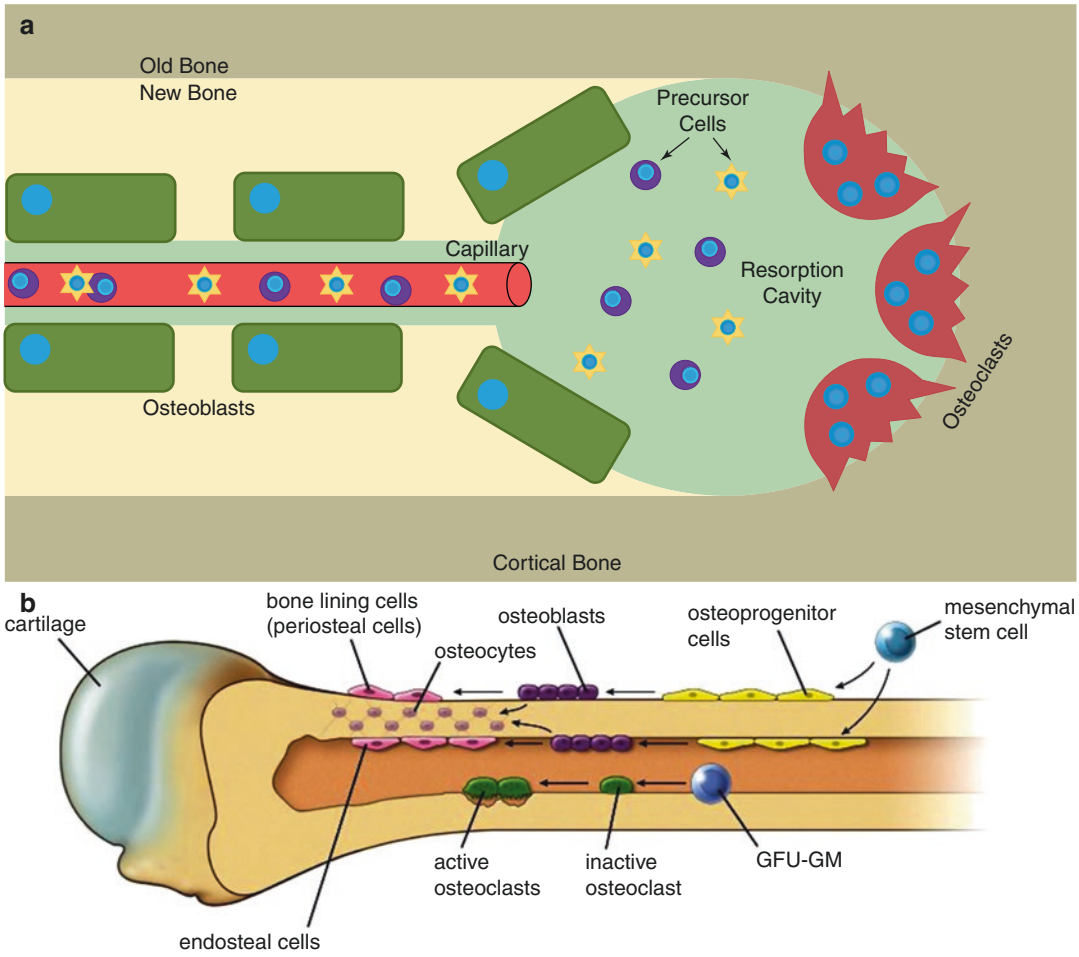


Fig. 1.17 A and B: Cortical bone remodeling: In the cortical bone, remodeling takes place at both the periosteal and endocortical surfaces, as well as inside the compact cortical bone. (Quoted under open access scheme Creative Commons Attribution License (CC BY) from: Owen and Reilly [288])

space and is therefore reversible. The situation in postmenopausal women and elderly men is very different. The balance between resorption and subsequent formation at each bone resorption unit is negative with increased resorptive activity, leading, therefore, to bone loss that is irreversible due to thinning of the trabeculae, loss of trabeculae, and thinning of the cortex (Fig. 1.18).

Bone remodeling also plays a role in the maintenance of acid/base balance, and the release of growth factors embedded in bone. Moreover, it provides a reservoir of labile mineral (short-term homeostasis) and it is the only mechanism by which old, dying, or dead osteocytes can be replaced [198].

Applied Bone Biology

Abnormalities of the Bone Remodeling Cycle

In the bones of healthy adults, the remodeling cycle displays tight coupling between bone resorption and bone formation. Accordingly, several metabolic bone diseases including osteoporosis, hyperparathyroidism, Paget's disease, and osteopetrosis are characterized by loss of such coupling.

The cellular pathophysiology of osteoporosis is heterogeneous and differs according to the underlying pathogenesis. In postmenopausal

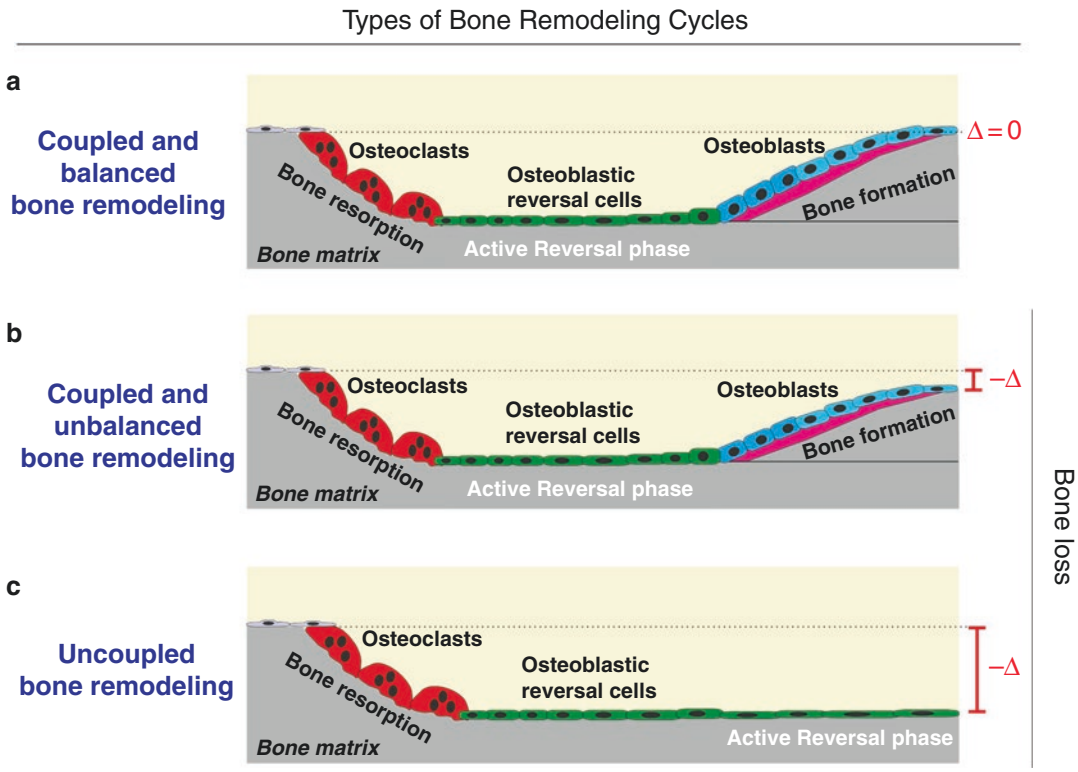


Fig. 1.18 Types of remodeling cycles: Three types of bone remodeling cycles. According to the present hypothetical model, bone loss in PMO depends on the relative abundance of three concurrent types of bone remodeling cycles. They all start with bone resorption, but differ greatly by the degree of restitution of bone matrix. A: the cavity is completely refilled. It is the prevailing type of bone remodeling cycle occurring in physiological conditions and in PHPT. B: the cavity is only partially refilled, as a result of a failure of the bone formation process. It is the type commonly considered responsible for bone loss in PMO. C: the cavity remains completely unfilled, as a result of an arrest of the reversal phase, so that bone formation is not even initiated. Its contribution to bone loss in PMO is most often overlooked but is highlighted in the present study. (Quoted with permission from Andersen et al. [289] (license number: 4879510361059))

osteoporosis, the most common abnormality is an increase in remodeling rate accompanied by reduced bone formation at the level of the individual bone remodeling unit, resulting in increased bone turnover and a negative remodeling balance. However, in some postmenopausal women with osteoporosis, bone turnover appears to be reduced, even when no secondary cause is apparent [199]. Where osteoporosis is due to underlying disease, changes in bone remodeling vary according to the underlying etiology but many forms of secondary osteoporosis are characterized by low bone turnover and negative remodeling balance, with episodes of increased bone turnover during periods of disease activity [200]. In glucocorticoid-induced osteoporosis, the most common cause of secondary osteoporosis, there is an initial transient phase of increased bone turnover superimposed on reduced bone formation at the tissue and cellular level that persists throughout the duration of glucocorticoid use [201]. The changes in bone remodeling determine the associated structural changes. In contrast to increased bone turnover with a net result of bone microarchitecture disruption; bone structure is relatively well preserved in low turnover states [202]. In addition, changes in other determinants of bone strength, such as the degree and heterogeneity of mineralization, matrix and mineral structure, and microdamage repair, are largely dependent on the underlying alterations in bone remodeling.

Bone Modeling/Remodeling as Therapeutic Targets

Antiresorptives

Reduction in bone turnover is common to all anti-resorptives regardless of the mechanisms by which they inhibit osteoclast activity. At the cellular level, the predominant effect of antiresorptive drugs is to inhibit the recruitment and activity of osteoclasts, thus decreasing the rate of remodeling and reversing the transient deficit created by resorption cavities in which formation has not yet occurred or been completed, allowing for a modest increase in BMD. The decrease in remodeling rate allows infilling of previously created resorption cavities and stabilises trabecular bone structure. Although the negative remodeling imbalance persists, its impact is limited by the decrease in number of remodeling sites on the bone surface. These drugs probably do not fully correct the negative remodeling balance, but since the number of remodeling units is greatly reduced, the effect of any negative imbalance is decreased. Reduced remodeling is associated with increased secondary mineralization of bone, which further contributes to the increase in BMD [203]. Anti-resorptive agents approved for osteoporosis include the bisphosphonates (alendronate, risedronate, ibandronate and zoledronic acid), denosumab, and raloxifene.

Essentially, antiresorptive therapy preserves existing bone mass and structure and increases the degree and homogeneity of mineralization. In cortical bone, denosumab can improve cortical bone structure at several sites, including the hip, increasing cortical thickness and decreasing porosity [204–207]. A possible explanation for this observation is that denosumab maintains physiological bone modeling [195, 208]. In addition, the accessibility of cortical bone to denosumab might be greater than the accessibility to bisphosphonates, because of differences in pharmacokinetic properties [209].

Suppression of bone remodeling allows a longer time for secondary mineralization to occur, resulting in an increase in both the degree of matrix mineralization and its homogeneity. The differences in mechanisms of action between bisphosphonates and denosumab provide explanations in clinical outcome and opportunities in sequential therapy (Fig. 1.19). Bisphosphonates attach to hydroxyapatite preferably on metabolically active bone surfaces, where they are "ingested" by osteoclasts and promote osteoclast apoptosis. Bisphosphonates can remain in bone tissue for up to 10 years. Denosumab acts by binding to and inhibiting RANKL in circulation, leading to the loss of mature osteoclast formation. Denosumab accesses every bone remodeling unit within circulation, and its distribution does not depend on the activity of bone remodeling [209]. Studies with bisphosphonates have shown that the degree of mineralization increases towards or even above normal, depending on the bisphosphonate administered [210–215]. In postmenopausal women treated for 3 years with annual infusions of zoledronic acid, posttreatment mineralization values were higher than those obtained in a historical reference population [213].

The effects of denosumab on bone matrix mineralization is likely to be similar to bisphosphonates where substantial increases also occur. Changes in other properties of bone matrix and mineral have also been reported in association with bisphosphonate therapy. In women treated with alendronate for 3 years, a higher mineral to matrix ratio in cortical bone was demonstrated compared to untreated controls. Crystallinity, carbonate/protein, and collagen maturity indices were not significantly altered compared to untreated controls [210]. However, higher collagen maturity and crystallinity in iliac crest cortical bone were reported in women who had been treated with alendronate for between 6 and 10 years [211]. In another study in which indices of bone quality were assessed in actively forming trabecular bone surfaces in postmenopausal women treated with alendronate or risedronate, mineral maturity/crystallinity and pyridinoline/divalent collagen cross-link ratio were significantly lower in risedronate-treated women than in those treated with alendronate [215].

The effects of anti-resorptive drugs on cortical bone are of particular interest, given the high

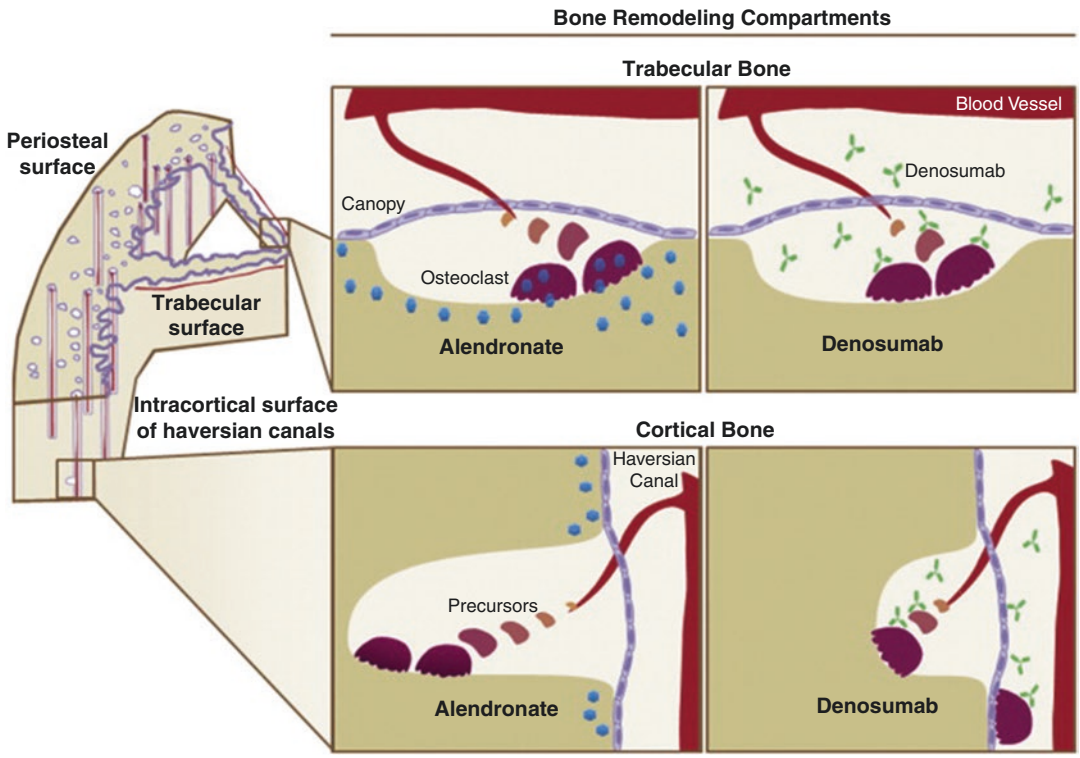


Fig. 1.19 Remodeling is initiated within bone remodeling compartments (BRCs) at points beneath the canopy of cells lining trabecular bone (upper panels) and cortical bone Haversian canals (lower panels). Osteoclast precursors differentiate into bone-resorbing osteoclasts within BRCs. In trabecular bone, alendronate and denosumab inhibit resorption similarly; osteoclasts engulf matrix containing alendronate, and denosumab accesses osteoclasts via the extracellular fluid. In cortical bone, osteoclasts encounter little peri-Haversian canal matrix containing alendronate and so resorb bone but denosumab accesses BRCs as freely as it does in trabecular bone. Available via license: CC BY-NC-ND 3.0

proportion of cortical bone at sites of nonvertebral fractures, the substantial contribution of these fractures to the overall fracture burden and the relatively low anti-fracture efficacy of interventions at these sites. Investigation of these effects is not straightforward, since changes may vary according to skeletal site. Also there have been limitations reported regarding current approaches to the in vivo assessment of cortical bone structure, particularly with respect to measurement of cortical porosity and thickness. Reduced cortical porosity in the distal radius, tibia, and iliac crest has been reported in women treated with bisphosphonates when compared to placebo-treated women [216–219], although this finding has not been universal [220]. Increased tibial cortical thickness was demonstrated after 2 years in a longitudinal study in postmenopausal women randomized to alendronate or placebo, although no significant treatment benefit was seen at the radius.

Earlier studies provided partial insights into the effects of antiresorptive drugs on cortical bone at selected sites, but the available data suggest that the predominant effect of bisphosphonates is to reduce or prevent age-related changes in cortical bone structure, with little evidence for improvement over baseline values. Conversely, there is evidence that denosumab improves cortical bone structure and strength at several sites, including the hip [221–223]. These differences are consistent with the greater increase in hip BMD with denosumab versus alendronate observed in a comparator and the continued increase in spine and hip BMD up to 8 years in denosumab-treated postmenopausal women

[224, 225]. It has been suggested that because of the low surface area/mineralized bone volume in intracortical bone there is less surface to which bisphosphonates can adsorb, whereas circulating denosumab has greater accessibility to intracortical sites [19]. In addition, it is possible that the increase in serum PTH levels that follows profound suppression of bone turnover after injection of denosumab may exert anabolic effects [226]. The recent demonstration in ovariectomized cynomolgus monkeys that modeling-based formation at endocortical and periosteal surfaces in the proximal femur and ninth rib was maintained, despite potent inhibition of remodeling activity, provides another potential mechanism for the effects of denosumab on BMD and bone strength [227]. However, the relevance of these findings to humans is currently unclear, since it is uncertain whether modeling-based bone formation occurs on endosteal surfaces in the normal adult human skeleton. Modeling-based formation was not reported in iliac crest bone from women treated with denosumab [228], although its presence at weight-bearing sites remains a possibility. Finally, whether the differences between denosumab and bisphosphonates in their effects on cortical bone translate into greater antifracture efficacy at nonvertebral sites is unknown, since no head-to-head studies with fracture as the outcome have been conducted.

Anabolic Agents

Anabolic skeletal effects can be achieved through changes in bone remodeling, bone modeling, or a combination of the two. Principally, anabolic agents have been defined by their ability to increase bone formation relative to resorption. This may occur as a result of modeling-based bone formation or when there is a positive remodeling balance due to increased formation at the level of the basic multicellular unit (BMU). In the latter situation, the increase in bone mass depends critically on the remodeling rate; if this is low, changes in remodeling balance will have little impact on bone mass, whereas substantial gains can be achieved when a high remodeling rate is associated with a positive remodeling balance. Anabolic effects on bone may also be achieved if there is uncoupling of bone resorption and formation during bone remodeling. Coupling describes the co-ordination of bone resorption and formation in time and space and refers to tissue-level remodeling (Fig. 1.20) [209].

The available osteoanabolic therapies for osteoporosis are human recombinant PTH peptide [1–34], also known as teriparatide, recombinant human parathyroid hormone (rhPTH 1–84) (which is identical to endogenous parathyroid hormone (PTH) and binds PTH-1 receptors in the bone, kidney, and has an indirect effect on cal-

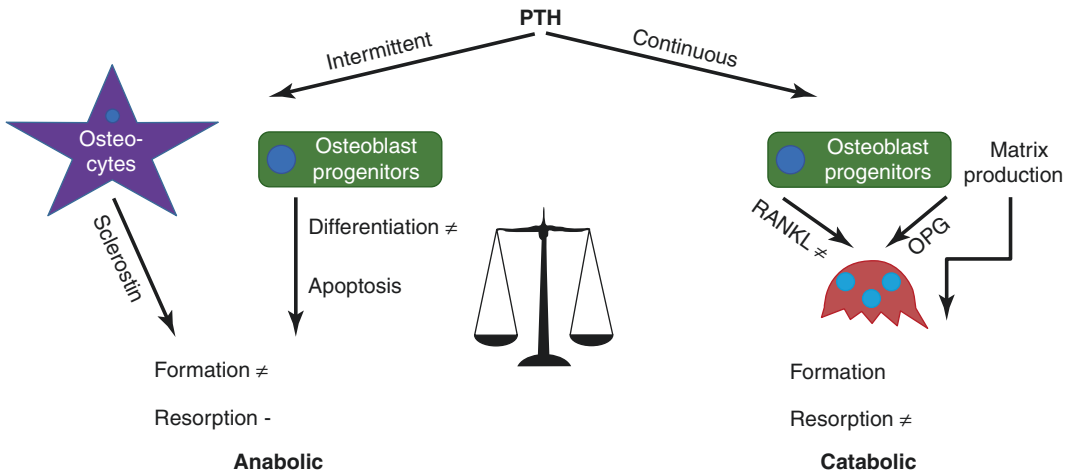


Fig. 1.20 The anabolic or catabolic effects of PTH on bone depends on application modality. (Quoted under open access scheme Creative Commons Attribution License (CC BY) from: Owen and Reilly [288])

cium reabsorption in the intestine), known as Preotact. There is also a highly selective and high affinity parathyroid hormone-related protein (PTHrP) analogue which binds to the PTH1 receptor, known as abaloparatide. Intermittent administration of these PTH peptides is associated with large increases in BMD in the spine and more variable changes in cortical bone depending on the site and the duration of therapy. Bone histomorphometric studies in postmenopausal women treated with teriparatide have demonstrated that increases in bone mass are achieved in trabecular bone by the formation of new bone on quiescent surfaces (modeling), mixed modeling/remodeling in which remodeling units are overfilled and formation extends beyond the limits of the resorption cavity, and increased remodeling rate associated with a positive remodeling balance [229–231]. These changes are associated with increased connectivity of the trabecular bone structure and improvement in the structure model index [232, 233].

Increases in trabecular thickness are small and, in most studies, have failed to achieve statistical significance, possibly as a result of the splitting of thickened trabecular by tunneling osteoclastic resorption [234]. At sites that are rich in trabecular bone, such as the spine, large increases in bone mineral density are seen and in the pivotal clinical trial in postmenopausal women with osteoporosis, a 65–69% reduction in vertebral fractures was demonstrated after a median duration of 21 months [235]. Interestingly, the skeletal response to teriparatide shows evidence of waning after 12–18 months, for reasons that are not currently understood but do not appear to be related to the formation of neutralizing antibodies [236]. Alternative explanations include downregulation of PTH receptors or depletion of bone target cells.

In cortical bone, the changes in BMD with PTH peptide therapy are less consistent and vary according to the skeletal site and the duration of therapy. In the proximal femur, areal BMD shows only small changes over the first 6–12 months of therapy and may even decrease transiently while in the distal radius, significant decreases in areal BMD have consistently been reported [235–238]. Measurement of vBMD in women treated with teriparatide for 12 months demonstrated increases in cancellous bone in the spine and hip, but decreases in cortical bone in the proximal femur, distal radius, and tibia [239]. The likely cause of these latter changes is an increase in cortical porosity and the formation of hypomineralized bone on the endosteum; increased femoral neck bone strength has been reported with longer term treatment (18–24 months) [240, 241]. Histomorphometric analysis of iliac crest bone in teriparatide-treated women indicated that increased intra-cortical porosity is partially or wholly reversed by subsequent bone formation in bone remodeling units [242]. Cortical thickness mapping on CT images of the proximal femur has shown focal increases in cortical thickness following teriparatide therapy in postmenopausal women at sites exposed to normal mechanical loading [243]. Although modeling-based periosteal bone formation in human iliac crest bone has been reported, it has not been demonstrated in cortical bone at other sites as assessed by changes in bone size [240].

Taken together, the available data indicate that intermittent administration of teriparatide stimulates modeling-based bone formation on cancellous, endosteal, and periosteal surfaces, an effect that is most evident in the early stages of treatment. However, the majority of the anabolic effect in cancellous bone is achieved through remodeling with overfilling of remodeling units. In cortical bone, the effects vary according to site, and may also be modulated by the degree of mechanical loading; increased total bone area, increased cortical porosity, and the formation of hypomineralized new bone can occur in the early stages of treatment, which results in little change, or a decrease in BMD at sites such as the hip and radius. In the Fracture Prevention Trial of teriparatide, the number of nonvertebral fractures was relatively small and although a significant reduction in all fragility nonvertebral fractures was seen, the number of hip fractures was too small (placebo group n = 4, teriparatide 20 μg/day n = 1, teriparatide 40 μg/day n = 3) to enable assessment of efficacy at this site [244, 245]. PTH (1–84) has also been shown to reduce verte-

bral fractures in postmenopausal women but reduction in nonvertebral fractures has not been demonstrated [246]. While preservation of bone strength at the radius and tibia have been reported in women treated with teriparatide, treatment with PTH (1–84) was associated with reduced bone strength at these sites in one small open label nonrandomized study [247]. Further research is required to establish whether there are true differences between these two peptides.

In concordance, in a cohort of 2463 women at high risk of postmenopausal fractures, abaloparatide resulted in an 86% reduction in vertebral and a 43% reduction in nonvertebral fracture. In comparison, daily subcutaneous PTH 1–34 (teriparatide) resulted in an 80% reduction in vertebral and a 30% reduction in nonvertebral fracture. Furthermore, after 18 months of abaloparatide treatment, total hip BMD increased by 3.4% and lumbar spine BMD by 9.2% [248]. Effects of abaloparatide on bone turn over, have not been reported; however, in postmenopausal women treated for 12–18 months with abaloparatide, bone remodeling indices in cancellous iliac crest bone were generally similar to those treated with teriparatide [249].

However, in view of the potential for adverse effects on cortical bone structure at the hip during the early stages of treatment with PTH, these drugs should be used with caution in patients at high risk of hip fracture.

Bone Formation-Sparing Antiresorptive Treatment

Resorbing osteoclasts adhere very tightly to the bone surface, seal off the resorption lacunae, and generate an acidic environment in the resorption lacunae by secreting protons. Bone mineral is dissolved by the acidic environment and the collagen and other noncollagenous proteins are degraded by proteases such as metalloproteinases and cathepsin K [250]. There are no currently available medications fulfilling this role. Odanacatib, an inhibitor of cathepsin K, was once assessed for treatment of osteoporosis and bone metastasis; however, increased stroke risk forced the manufacturing company to scrap the medication. Though there is no current medication available exerting this mechanism of action, we felt it is of value, at least from the research point of view, to share the available data on odanacatib therapy.

Treatment with odanacatib offered a different mechanism of action compared to other biologic anti-resorptive agents such as denosumab; as treatment with odanacatib leaves the osteoclasts alive and unaffected, but inhibits bone resorption by inhibiting cathepsin K activity [250].

The effects of odanacatib on bone was investigated in adult rhesus monkeys. Treatment with odanacatib resulted in increased BMD and bone strength at the lumbar spine and the hip [251, 252]. Histomorphometric analyses of vertebrae, proximal femur, and transiliac bone biopsies demonstrated that odanacatib reduced cancellous bone remodeling in the lumbar vertebrae and hip, and decreased intracortical remodeling at several femoral sites in monkeys. However, treatment with odanacatib preserved or enhanced endocortical bone formation and dose-dependently stimulated modeling-based bone formation at the periosteal surfaces [252]. The effect of odanacatib on cortical bone was also investigated at the central femur. Treatment with odanacatib-stimulated bone formation both at the periosteal surface and at the endocortex. At the endocortex, bone modeling was stimulated whereas bone remodeling was reduced. The intracortical remodeling was also reduced. These changes led to increased cortical thickness and volume [253].

Whether a similar increase of modeling-based bone formation with odanacatib occurs in humans, particularly in estrogen-deprived and older individuals in whom the viability and/or activity of lining cells could be reduced, was subjected to study. An interaction between mechanical loading and cathepsin K inhibition on bone modeling has been postulated, which if true, could explain some differences in bone-mass gain observed with odanacatib at loaded (i.e. hip) compared with less loaded (i.e. radius) sites. The mechanisms by which cathepsin K inhibition, which primarily occurs at remodeling sites, can increase bone modeling, particularly at the peri-

osteal surface, also remains to be elucidated. However, as noted earlier, the phase III trial was stopped by the manufacturing company in 2016, because of increased risk of stroke.

Combined Anabolic and Antiresorptive Treatment

Osteocytes are terminally differentiated osteoblasts which become embedded in newly formed bone matrix and produce sclerostin. As noted earlier in this chapter, sclerostin binds to lipoprotein-related peptide (LRP) 5/6 and thereby inhibits LRP5/6 from binding to the frizzled receptor and activating the Wnt pathway [254, 255]. Activation of the Wnt canonical pathway induces translocation of β-catenin to the nucleus of the osteoblasts and subsequently gene transcription that stimulates bone formation through stimulation of osteoblast differentiation, proliferation, and survival [256]. Osteocytes control bone formation by the release of sclerostin as sclerostin inhibits osteoblastic bone formation. Individuals who produce reduced amounts of sclerostin have a high bone mass and reduced fracture risk [257, 258], and therefore inhibition of sclerostin by antibodies is being investigated as a potential new anabolic treatment of osteoporosis. The anabolic effects of sclerostin inhibition are mediated through an early and transient increase in bone formation combined with a sustained decrease in bone resorption.

Inhibition of sclerostin by romosozumab, a sclerostin antibody, has been investigated in cynomolgus monkeys [259]. BMD and strength increased dose-dependently. Histomorphometric analyses of bone samples revealed increased bone formation on trabecular, periosteal, endocortical, and intracortical surfaces despite decreased resorptive activity. The study also demonstrated that inhibition of sclerostin by romosozumab predominantly stimulates modeling-based bone formation at both cancellous and endocortical surfaces [188].

In iliac crest biopsy samples obtained from postmenopausal women in the fracture study in postmenopausal women with osteoporosis (FRAME) [260], large increases in bone formation were seen in cancellous and endocortical bone after 2 months of treatment with romosozumab although the effect was no longer evident after 12 months of treatment. The eroded surface was significantly reduced at both timepoints, and trabecular bone volume, microarchitecture, and cortical thickness were significantly improved at 12 months. Data from animal studies have shown increased modeling bone formation in response to sclerostin inhibition, but the relative contributions of bone remodeling and modeling to bone formation in humans remain to be established [259].

Drugs that Act on the Bone Mineral/Matrix Composite

Strontium ranelate provides an interesting example of a drug that has little effect on bone remodeling yet increases bone strength and reduces fracture risk [261, 262].

The mechanism by which it exerts these effects has not been clearly established but is likely to be related to the incorporation of strontium into hydroxyapatite crystals in bone mineral [263, 264]. Assessment of bone turnover markers and bone histomorphometry in postmenopausal women demonstrates only a weak anti-resorptive effect and, contrary to earlier expectations based on preclinical studies, no anabolic effect [265, 266]. Although it is now not widely used, strontium ranelate illustrates the potential for targeting treatments directly at the bone mineral/matrix composite rather than at bone remodeling.

Bone Turnover and Fracture Risk

The immediate clinical consequence of osteoporosis is fracture. However, a discrepancy was noted on comparing the occurrence site of osteoporotic fractures. Earlier studies revealed that significant reduction of vertebral fractures occurs early in the course of therapy, typically within 6 months, whereas reduction of nonvertebral fractures and hip fractures specifically has not

been observed before at least 1 year of therapy [267, 268]. This could be explained by the fact that vertebral fragility is primarily determined by focal areas of erosion creating stress risers on trabeculae [269], whereas weakness in the peripheral skeleton results from trabecular and cortical bone loss, particularly cortical porosity, that becomes predominant only in older age [270]. In turn, the elimination of stress risers, which is proportional to the potency of the various antiresorptives, is sufficient to explain the early decrease of vertebral fractures; whereas long-term reversal of the negative bone mineral balance seen in the peripheral skeleton, particularly the progressive restoration of the cortical bone volume, is essential to reduce nonvertebral fractures. As a corollary, spine bone mineral density (BMD) changes have been found to explain less than 50% of vertebral fracture risk reduction [271–275], whereas more recently hip BMD gain with potent parenteral anti-resorptives such as zoledronic acid and denosumab has explained up to 60–90% of nonvertebral fracture risk reduction [276, 277]. Nevertheless, relatively large changes at the hip are needed to significantly influence fracture risk, for example, a 6% BMD gain is equivalent to 1% nonvertebral fracture risk reduction with denosumab [268].

Building Better Bones: Sequential and Combination therapy for Osteoporosis

Unlike most chronic diseases, osteoporosis treatments are generally limited to a single drug at a fixed dose and frequency. Nonetheless, a major challenge in managing patients with established osteoporosis is the increasing reluctance to treat patients with antiresorptive medications for more than 3 to 5 years. This has been attributed to the concern over uncommon but serious side effects such as atypical femur fracture and osteonecrosis of the jaw, as well as the longstanding regulatory 2-year limit on parathyroid-hormone receptor targeted anabolic therapies [278–280]. Furthermore, no approved therapy has been shown to be able to restore skeletal integrity in most osteoporotic patients and the long-term use of osteoporosis drugs is controversial. Thus, it is expected that over a lifetime, the use of more than one medication will be required for many patients with established disease. And consequently, it is imperative that we understand the selective effects of osteoporosis medications when used sequentially or in combination so that we can construct optimal treatment plans in individual patients.

In clinical trials, denosumab given after bisphosphonate continued to increase bone mineral density (BMD) and produced significantly greater gains in BMD at all measured sites when compared to all bisphosphonates. Consequently, denosumab can be given after a bisphosphonate when the treatment goal in BMD gain has not been achieved. However, bisphosphonates also should be given after denosumab discontinuation to prevent BMD loss. Both VERO and ARCH studies proved that anabolic treatment for osteoporosis is more effective than bisphosphonates at preventing vertebral fractures in a high-risk population (with previous vertebral fractures) in both treatment-naïve or bisphosphonate-treated patients [281]. Consequently, anabolic treatment should be considered either as a first-line treatment in patients with previous vertebral fractures or in case a low-traumatic fracture occurs while on bisphosphonate treatment. However, the duration of anabolic treatment is limited and requires antiresorptive medication after discontinuation. The sequential treatment approach in osteoporosis is slightly limited with the result of DATA study, which showed that switching to teriparatide after denosumab led to BMD loss and should be considered with caution. According to the DATA study, teriparatide combined with denosumab gives better BMD gain than both treatments alone [282]. This is the only currently recommended approach using combined treatment in osteoporosis which remains controversial because of the high cost and lack of evidence regarding antifracture benefit. However, in another study, the DATA-Switch study, assessing sequential therapy; results revealed that in postmenopausal osteoporotic women switching from teriparatide to denosumab, bone mineral density

continued to increase, whereas switching from denosumab to teriparatide results in progressive or transient bone loss [283]. These results should be considered when choosing the initial and subsequent management of postmenopausal osteoporotic patients.

Challenges in Developing Treatments for Osteoporosis

In clinical trials conducted in postmenopausal women with osteoporosis, reductions in fracture risk of up to 70% in the spine, 40% in the hip, and 15–20% at nonhip nonvertebral sites have been demonstrated. The limited efficacy at nonvertebral sites is a concern, given the high burden and cost of these fractures [284]. Although poor compliance with osteoporosis management and/or adherence to therapy, as well as continuing falls risk, are likely to contribute to the small effect on nonvertebral fractures provided by currently approved interventions, drug-specific factors may also operate. In particular, failure to improve cortical bone mass and structure adequately, which may be of high relevance. An important challenge, therefore, is to develop drugs that produce greater increases in cortical bone strength throughout the skeleton and provide more effective protection against nonvertebral fractures.

A second challenge is related to the diversity and severity of changes in bone remodeling, mass, microarchitecture and composition in primary and secondary osteoporosis. At present, a "one size fits all" approach is widely used, with anti-resorptive therapy providing the first-line option for the vast majority of patients regardless of the underling pathophysiology and disease severity, but this may be suboptimal in achieving maximum efficacy. As more drugs with differing mechanisms of action are developed, it may become possible to take a more personalized approach to treatment (Fig. 1.21). However, at present the required evidence base to support this approach is lacking.

Finally, increasing concerns about rare but serious skeletal side effects of treatment have emerged, particularly with anti-resorptive drugs. Although suppression of bone turnover is associated with beneficial effects on BMD and fracture risk it has also been implicated on the pathogenesis of atypical fractures and osteonecrosis of the jaw [279, 285]. While the benefit/risk balance for treatment remains positive in patients at high risk of fracture, these adverse effects have been widely publicized and have had a significant impact on prescribing habits and patient uptake. Further studies are required to minimize their occurrence through a better understanding of their pathophysiology and improved identification of risk factors for their development.

In conclusion, to preserve its essential load bearing, protective, and homeostatic functions, the skeleton must undergo continual remodeling and repair. The bone remodeling cycle ensures that old or damaged bone is replaced, and that mineral homeostasis is maintained. Bone remodeling is a highly regulated and stereotyped process characterized by osteoclastic bone resorption followed by osteoblastic bone formation. These two processes are tightly coupled to ensure that bone mass is ultimately preserved.

The osteocyte is the key orchestrator of the bone remodeling cycle. These long-lived, terminally differentiated osteoblasts are entombed within the bone matrix, connected by an extensive dendritic network and act as the skeletal mechanosensor. They respond to microdamage and changes in loading by initiating bone remodeling, and once the repair is complete, they inhibit further bone resorption and formation to maintain bone mass. Furthermore, osteocytes also secrete Fibroblast growth factor-23 (FGF23), respond to hormones such as parathyroid hormone to initiate bone resorption and thus maintain mineral homeostasis.

Recent studies of current and potential therapeutic options for osteoporosis have revealed a range of mechanisms through which bone strength may be improved. Uncoupling of bone remodeling, with suppression of bone resorption and maintenance or stimulation of bone formation provides a new approach that may be more beneficial to cortical bone in particular than currently approved interventions. Whether this translates into greater efficacy in reducing nonvertebral

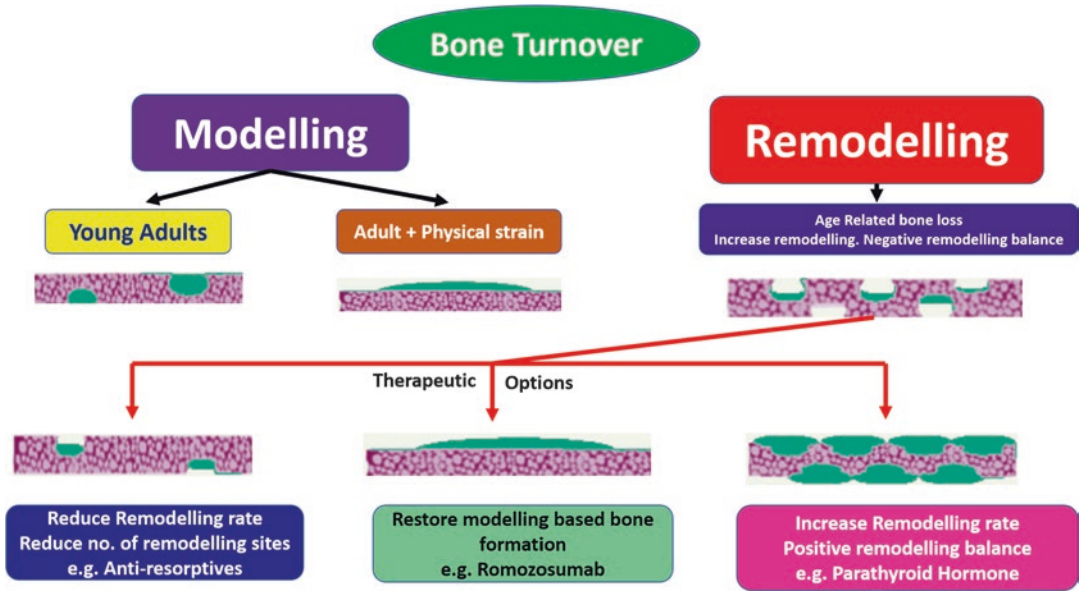


Fig. 1.21 Bone modeling/remodeling as therapeutic targets

fractures and the long-term bone safety of these approaches remains to be established. Nevertheless, the future holds promise for a broad armamentarium of options that should enable a more tailored approach to treatment of the individual patient, based on the underlying changes in bone remodeling, structure, and composition.

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Muscle Health

2

Yasser El Miedany

Introduction

Skeletal muscle is one of the most dynamic and plastic tissues of the human body. In humans, skeletal muscle comprises approximately 40% of total body weight, contains 50–75% of all body proteins, and accounts for 30–50% of whole-body protein turnover. Muscle is mainly composed of water (75%), protein (20%), and other substances including inorganic salts, minerals, fat, and carbohydrates (5%). In general, muscle mass depends on the balance between protein synthesis and degradation; both processes are sensitive to factors such as nutritional status, hormonal balance, physical activity/exercise, and injury or disease. The various protein compartments (structural, contractile, and regulatory) have received significant scientific attention because of their important contribution to mobility, exercise capacity, functioning, and health [1].

Skeletal muscles contribute significantly to multiple bodily functions. From a mechanical point of view, the main function of skeletal muscle is to convert chemical energy into mechanical energy. In turn, this will generate force and power, maintain posture, produce movement that influences activity and allows for participation in social and occupational settings, maintain or enhance health, and contribute to functional independence. From a metabolic perspective, the role of skeletal muscles include a contribution to basal energy metabolism, serving as storage for important substrates such as amino acids and carbohydrates, the production of heat for the maintenance of core temperature, and the consumption of the majority of oxygen and fuel used during physical activity and exercise. Of particular interest is the role of skeletal muscles as a reservoir of amino acids needed by other tissues such as skin, brain, and heart for the synthesis of organ-specific proteins [1, 2]. Further, amino acid release from muscles contributes to the maintenance of blood glucose levels during conditions of starvation. Of relevance to disease prevention and health maintenance, a reduced muscle mass impairs the body's ability to respond to stress and chronic illness.

This chapter discusses the evolution of muscle health as a key factor of the broad musculoskeletal health, and its important role in health and healthy aging. It combines the basic, yet up to date, information about muscle health, the muscle bone interaction, together with discussions on the muscle health in aging and disease and approaches to management of muscle loss.

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Muscles in Health

Muscles play a central role in the body metabolism. Maintenance of the protein content of certain tissues and organs, such as the skin, brain, heart, and liver, is essential for survival. These organs and essential tissues rely on a steady supply of amino acids via the blood, to serve as precursors for the synthesis of new proteins balancing the persistent rate of protein breakdown which occurs in all tissues. This role is compounded in conditions where there is deficiency or absence of nutrient intake, where muscle protein serves as the principal reservoir to replace blood amino acid taken up by other tissues [3–5]. In fact, in the fasting state, blood amino acids serve not only as precursors for the synthesis of proteins but also as precursors for hepatic gluconeogenesis [6]. Consequently, provided muscle mass is adequate to supply the required amino acids, the protein mass of essential tissues and organs, as well as the necessary plasma glucose concentration, can be maintained relatively constant despite the absence of nutritional intake.

The demands for amino acids in most organs and tissues do not vary significantly from the fed to the post-absorptive state because little surplus protein is accumulated. A post-absorptive state is a metabolic period that occurs when the stomach and intestines are empty. During a post-absorptive state, the body's energy needs are fulfilled from energy previously stored in the body. This state is typically reached four or more hours after food has been consumed, usually overnight and in the morning before breakfast (Absorptive state is the period in which the gastrointestinal tract is full and the anabolic processes exceed catabolism. The fuel used for this process is glucose). Furthermore, the hepatic uptake of gluconeogenic amino acids decreases with nutrient intake [7]. Consequently, the primary fate of ingested amino acids is incorporation into muscle protein to replete the reserves of amino acids lost in the fasting state. Under normal conditions, gains in muscle protein mass in the fed state balance the loss of muscle protein mass in the post-absorptive state.

The ability of net muscle protein breakdown to maintain plasma amino acid concentrations is remarkable, provided adequate muscle mass is available. For example, obese individuals (with increased muscle mass) were able to maintain normal concentrations of plasma amino acids after 60 days of fasting [8]. In contrast, depletion of muscle mass is incompatible with life. For example, there is a strong association between the depletion of body cell mass (presumably reflecting depletion of muscle mass) and the length of survival of seriously ill patients with AIDS [9]. This was supported by the work carried out by Keys and his colleagues [10, 11] who concluded that the depletion of muscle mass is the cause of death in human starvation.

Muscle Mass

The important functions of muscle have attracted the attention to the muscles' role in health. In standard clinical assessment of the patients, vital signs are routinely assessed and recorded. These include blood pressure, pulse, respiratory rate, height and weight as well as BMI. However, these measurements, though have long been regarded as practical and sensitive outcomes for the prediction of health risks, do not reflect a full and true picture of the individual's overall health.

At the organizational level, the body can be separated into chemical or anatomical distinct compartments. The 2-compartment model divides the body weight into fat mass and fat-free mass [12]. Skeletal *muscle mass* is the largest component of adipose tissue–free body mass in humans [13]. *Lean mass* also known as lean body mass is a fat-free and bone mineral–free component that includes muscle and other components such as skin, tendons, and connective tissues (Fig. 2.1). *Appendicular lean soft tissue* is the sum of lean soft tissue from both arms and legs [14, 15]. A large proportion of total-body skeletal muscle is found in the extremities, and a large proportion of appendicular lean soft tissue is skeletal muscle (Fig. 2.2) [14, 16].

Body composition can be variable among individuals of the same body size, confounding

the association between body weight and health. Abnormalities in body composition such as low muscle mass are powerful predictors of morbidity and mortality, particularly in clinical settings where the disease or illness itself can lead to this condition (Fig. 2.3) [17, 18]. Therefore, skeletal muscles can be considered a primary driver of the relationship between body composition and clinical outcomes, as it is involved in mobility, strength, and balance [19].

Muscle Bone Interaction

In musculoskeletal tissues, muscle and bone interact mechanically and functionally. Numerous lines of evidence suggest the remote interactions between muscle and bone as well as their local interactions. Genetic, endocrine, mechanical, and age-related factors influence both muscle and bone simultaneously (Fig. 2.4). There has been growing interest in muscle/bone relationships as well as muscle biology, in spite of the finding that some of the physiological and pathological mechanisms related to both muscle and bone still remain unclear. There are several aspects of the interactions between muscle and bone.

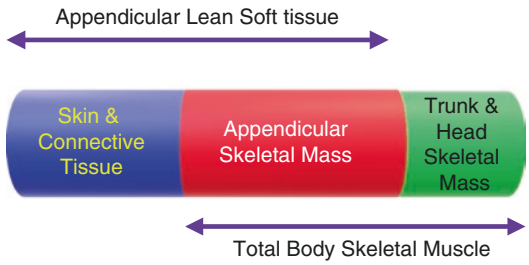

Fig. 2.1 Relations between appendicular lean soft tissue (ALST) and total-body skeletal muscle (SM) mass

Bone and Body Composition

Higher body mass index (BMI) is related to higher bone mineral density (BMD) and reduced fracture risk. The mechanism is presumably due to an increased strain on bone imposed by higher body mass, estrogen production from the greater amount of adipose tissue and the cushioning defense of the hip by gluteofemoral adipose tissue, which reduces impact forces upon falling. Furthermore, hip fracture risk was found to be increased with decreasing BMI independently of physical activity in a large prospective study on postmenopausal women [20].

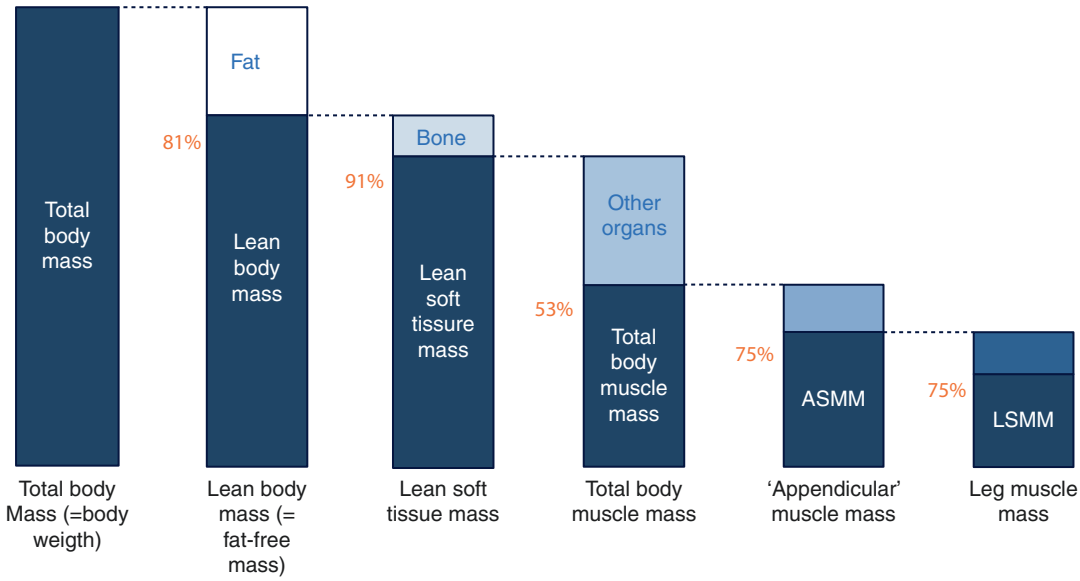

Fig. 2.2 Body compartments based on reference man

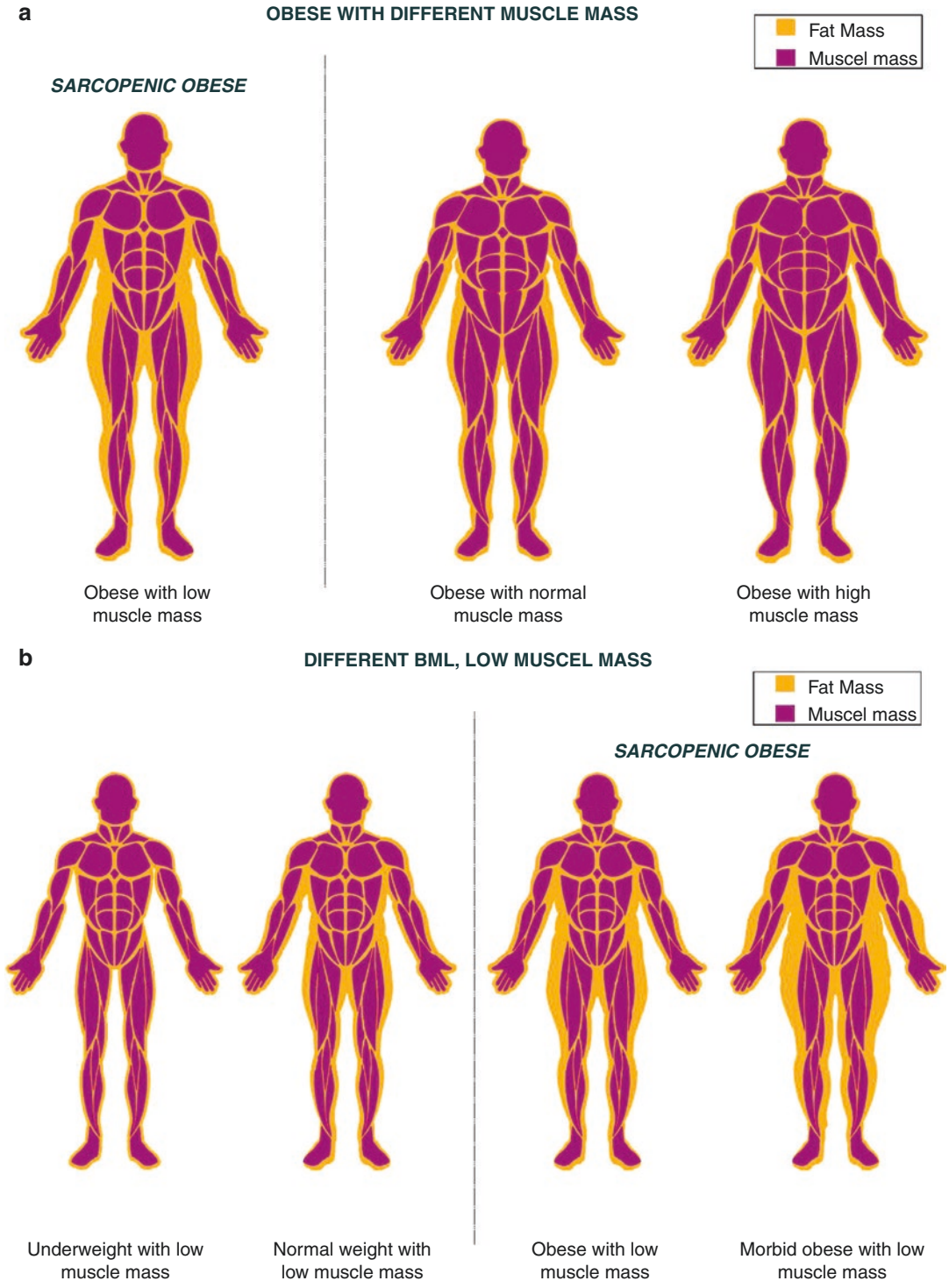

Fig. 2.3 Body composition across the body weight continuum. Low muscle mass can occur in people with obesity (**1a**) and at any body weight (**1b**) BMI: body mass index. (Quoted from Prado et al. [327] under open access scheme)

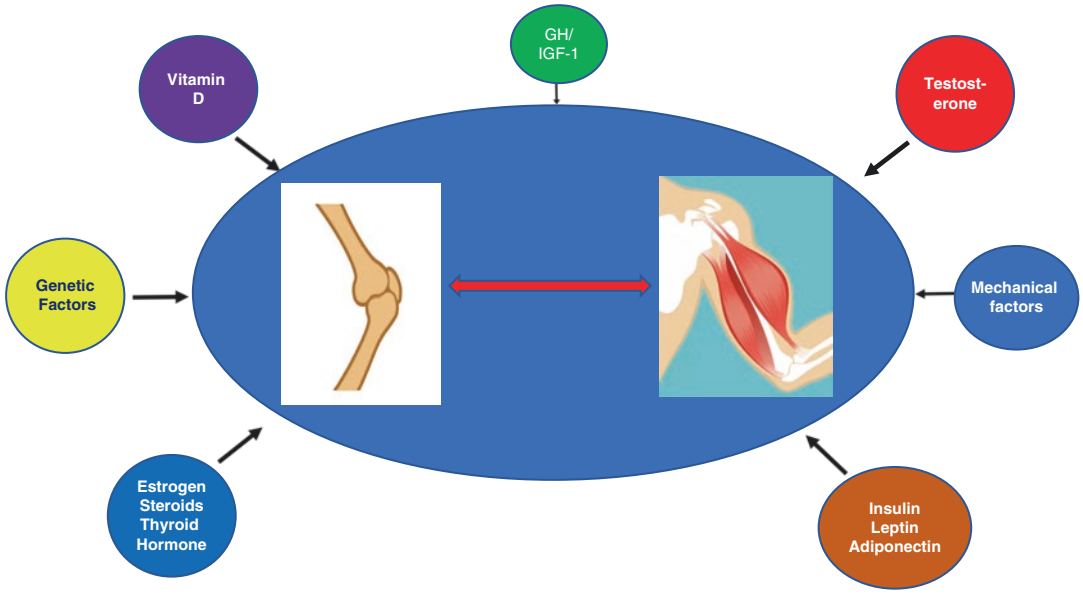

Fig. 2.4 Factors affecting the interactions between muscle and bone. GH/IGF-I growth hormone/insulin-like growth factor I

Relationships Between Muscle and Bone in Clinical Studies

Lean body mass is related to BMD in elderly men, and it explained 20% of the variability in BMD at the femoral neck [21, 22]. Repetitive loading exerted exercise-induced benefits on bone mass and muscle area in a year-long study of 10- to 17-year-old tennis players [23]. The change of muscle area explained 32% of the variability in the exercise-induced benefits in bone mass, which seemed to be higher than that in post-menarcheal girls.

Controversy exists as to whether higher fat mass positively or negatively affects fracture risk. Earlier studies suggest that higher fat mass might be related to increased fracture risk, although it positively affects BMD. Although body weight has increased dramatically in older people in Western countries and Asia, many, if not most, osteoporotic fractures occur in overweight or obese people, and obese men may be particularly susceptible [24, 25]. This may be due to lower physical activity induced by obesity, leading to disability or institutionalization. Alternatively, adipocytokines produced from adipose tissues might negatively affect bone to increase fracture risk.

Muscle parameters are related most strongly to cortical area and total shaft area, but explained <10% of variability in those bone parameters in mid-thigh computed tomography analysis. This was supported by the finding that small muscle area as well as low cortical thickness was significantly associated with fractures in both sexes [26]. This study suggested also that bone and muscle loss proceed at different rates with aging and sex-related patterns.

Numerous studies indicated that higher lean body mass is related to increased BMD and reduced fracture risk, especially in postmenopausal women [27]. Age-related sarcopenia is affected by two components for diagnosis: low muscle mass and function [28]. Decreased muscle mass does not often parallel functional disability. Muscle mass and muscle strength were also independently associated with postmenopausal osteoporosis, and they should be considered separately in clinical practice [29]. In addition, middle-aged and elderly community-

dwelling European men with reduced muscle mass had significantly lower BMD and higher prevalence of osteoporosis [22].

Weight loss therapy to improve health in obese older adults causes further bone loss. The addition of exercise training to weight loss therapy among obese older adults prevented weight loss-induced increase in bone turnover and attenuated weight loss-induced reduction in hip BMD, and the change in lean body mass was one of the independent predictors of change in hip BMD in that study [30]. The increase in sclerostin levels with weight loss was also found to be prevented by exercise in obese older adults, and an inverse relationship was found between the changes in sclerostin and lean body mass [31]. Since sclerostin suppresses the canonical Wnt-β-catenin signal, which inhibits muscle differentiation, sclerostin may be related to exercise-induced changes of muscle and bone through its production from osteocytes, which induces sensitization to the mechanical signal.

In another study, long-term body composition changes were followed for 6 years in French women [32]. Lean body mass and fat mass did not change in premenopausal and perimenopausal women. However, lean body mass and bone mass decreased, but fat mass increased in postmenopausal women. Age was the most important determinant of body composition changes, although menopausal status was a significant determinant only for the changes in bone mass. The comparisons of cross-sectional versus longitudinal associations of lean body mass and fat mass with BMD in children showed that cross-sectional associations for lean body mass and fat mass with bone may not reflect longitudinal associations.[33].

An increase in muscle mass produces stretching of collagen fibers and periosteum at the interface, resulting in the stimulation of local bone growth. Alternatively, higher blood flow to bone might lead to an increase in bone strength, since blood flows to limbs, at a level proportional to muscle mass.

As for the relationships between muscle and treatment, high-frequency, low-intensity vibrations increased bone mass and muscle strength in upper limbs in a prospective clinical trial on 65 disabled children [34]. A recent study also indicated that low appendicular muscle mass of the upper limbs and low grip strength are related to poor cortical and trabecular microarchitecture, partly independently of each other, in older men [35]. The associations were significant after adjustment for confounders including body size.

Several factors have been involved in the bone and muscle interaction. This was reviewed in an article written by Kaji [20] on the interaction between muscle and bone. In the section below, these factors will be discussed and how they influence bone as well as muscles:

Bone and Muscle Interactions During Development

A close relationship between bone and muscle is observed during development and growth. Several studies suggest that the Indian Hedgehog pathway (the Hedgehog signaling pathway is a signaling pathway that transmits information to embryonic cells required for proper cell differentiation) and fibroblast growth factor (FGF)-2 may play important roles in the interactions between muscle and bone during development [36]. The peak velocity for lean body mass precedes that of BMD, indicating that an increase in muscle mass during growth stimulates the increase in bone mass [37], Circulating insulin-like growth factor (IGF)-I promotes bone mass accrual during puberty, although muscle secretes IGF-I as one of the potential sources.[36]

Genetic Factors

Since both bone and muscle cells are derived from mesenchymal stem cells, similar genetic factors are considered to influence bone and muscle. Risk factors affecting osteoporosis sarcopenia are heritable at approximately 60–70% heritability [38]. Osteoporosis and sarcopenia may be affected by genetic polymorphisms of several genes, such as androgen receptor, estrogen receptor, catechol-O-methyltransferase, IGF-

I, vitamin D receptor, and low-density-lipoprotein receptor-related protein-5. In a young adult twin study, the relationship between lean body mass and BMD was shown to be influenced by genetic factors, compared with the relationship between fat mass and BMD [39]. Several genes, such as growth and differentiation factor-8 (GDF-8), myocyte enhancer factor-2C (MEF-2C), and proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), have also been detected in genome-wide association studies as being linked to both sarcopenia and osteoporosis [40].

Endocrine Factors

There are numerous physiological and pathological endocrine factors that influence both muscle and bone. Vitamin D, the growth hormone (GH)/IGF-I axis and testosterone are the most important hormones that affect muscle and bone simultaneously. Moreover, estrogen, glucocorticoid, thyroid hormone, insulin, leptin, and adiponectin also regulate muscle/bone relationships. Other major factors may affect both muscle and bone negatively. These include nutritional state, physical activity, atherosclerosis, hormones, and post-inflammatory cytokines [28].

Vitamin D

Vitamin D exerts various effects on bone and muscle cells. Vitamin D insufficiency is very common in elderly people. The measurement of serum 25-hydroxyvitamin D (25[OH]D) level is recommended as an initial diagnostic test in patients at risk of vitamin D deficiency [41]. Vitamin D deficiency is defined as 25(OH)D below 20 ng/mL (50 nmol/L) in the guidelines. A recent systematic review showed that the average increase in serum 25(OH)D concentration was 0.78 ng/mL (1.95 nmol/L) per microgram of vitamin D3 supplement per day in the absence of concomitant use of calcium supplements [42]. Post-hip fracture use of prescribed calcium plus vitamin D or vitamin D supplements and anti-osteoporotic drugs seemed to lead to lower mortality in both sexes, although vitamin D alone did not seem to be effective in the elderly [43, 44].

Human skeletal muscle has a receptor for 1,25(OH)D, and vitamin D receptor genotype variations affect BMD and muscle strength. The changes of muscle fibers as well as muscle differentiation-related genes, such as Myf-5, myogenin, and E2A, occur independently of calcium metabolism in vitamin D receptor-deleted mice. Severe osteopenia and sarcopenia are observed in patients with vitamin D-deficient osteomalacia. A higher prevalence of atrophy among type II fibers in osteoporotic patients with low levels of 25(OH)D has been reported. Vitamin D deficiency causes increased risk of falls through the effects of vitamin D deficiency on bone as well as through its effects on muscle, and vitamin D supplementation reduces the risk of falls in vitamin D-deficient patients. An increased risk of falls is directly linked to fractures. However, intermittent large doses of vitamin D (oral cholecalciferol at 150,000 IU every 3 months) were not effective for falls, mobility, and muscle strength in older postmenopausal women [45]. Marantes et al. [46], also reported that low 25(OH)D or high parathyroid hormone (PTH) levels did not contribute significantly to sarcopenia or muscle weakness in community adults. This study suggests the age-dependent differences between vitamin D state and sarcopenia.

The interrelationships between muscle and bone related to vitamin D action and the molecular mechanisms by which vitamin D affects both bone and muscle are unclear at present. A recent study revealed that 1,25(OH)D3 induces myogenic differentiation by inhibiting cell proliferation, decreasing IGF-I expression, promoting myogenic differentiation through increasing IGF-II and follistatin expression, and by decreasing myostatin [47].

GH/IGF- I Axis

Growth hormone (GH) as well as insulin-like growth factors (IGF-1) induces muscle hypertrophy as well as bone development and the preser-

vation of bone mass. GH deficiency causes reduction in muscle and bone mass and an increase in fat mass. Several studies indicate that serum IGF-I levels are positively related to lean body mass and a reduction of fracture risk. Thus, the GH/IGF-I axis is one of the crucial pathways for the maintenance of bone mass and strength. IGF-1 enhances the proliferation of muscle progenitor cells and their integration with existing fibers during muscle repair. The level of mechano growth factor (MGF), which is derived from the IGF-I gene by alternative splicing, declines with aging, and MGF administration activates muscle stem cells that are important for muscle repair and hypertrophy [48]. Osteoporosis was found to be associated with a preferential type II muscle fiber atrophy, which correlated with BMD and reduced the level of Akt, a component of the IGF-I/PI3kinase/Akt pathway, in a muscle biopsy study of older people, although muscle atrophy was less related to disease duration and severity in osteoarthritis [49]. The Akt Pathway, or PI3K-Akt Pathway, is a signal transduction pathway that promotes survival and growth in response to extracellular signals. Key proteins involved are PI3K (phosphatidylinositol 3-kinase) and Akt (Protein Kinase B).

In female-to-male transsexuals after long-term cross-sex hormonal therapy after ovariectomy, as well as the transsexual men on long-term testosterone therapy, higher muscle mass and greater grip strength were demonstrated as well as lower fat mass and increased trabecular BMD; although there was a larger radial cortical bone size and a lower cortical volumetric BMD at the radius and tibia in these men [50]. These data suggest that testosterone and estrogen differently affect muscle and bone, and that testosterone may mainly affect bone size, but not BMD, partly through muscle factors in cortical bone. Although raloxifene, a selective estrogen receptor modulator, is effective for the treatment of osteoporosis, GH cotreatment with 17β-estradiol increased lean body mass and BMD at the lumbar spine and femoral neck to a greater extent than raloxifene in hypopituitary women [51]. These findings suggest that raloxifene significantly attenuates the beneficial effects of GH on body composition.

IGF-binding proteins (IGFBPs) play some role in the GH-IGF-I axis, both dependently and independently of IGF-I. Appendicular skeletal muscle mass was found to be associated with cortical thickness and trabecular BMD in a cohort study [52]. In that study, serum IGFBP-2 levels were the most robust negative predictors of appendicular skeletal muscle in both sexes and might provide new insights into potential biomarkers that reflect the health of the musculoskeletal system.

Sex Hormones

Estrogen and testosterone regulate bone and muscle simultaneously. Androgens play a significant role in the development and maintenance of muscle and skeletal integrity in both men and women. Testosterone levels are correlated with BMD and muscle strength. Androgen deficiency is characterized by loss of bone and lean tissue [40]. Although skeletal muscle is one of the most powerful determinants of bone strength, sex differences in the bone–muscle relationship may be important for explanations of sex differences in bone growth, age-related bone loss, and fracture risk [53].

In young adulthood, there are apparent sex differences in the correlation of muscle area to bone area. More of the variation in bone dimensions is explained by muscle area in men. Women have higher values of bone in relation to muscle, but the lower percentage of the variation in cortical area in women is explained by muscle mass [53]. Higher endogenous free testosterone levels are associated with higher BMD, greater lean body mass and greater fat mass in women aged 65 and older [54]. These findings suggest the possibility that testosterone or selective androgen receptor modulator might be implemented as a drug for the treatment of both sarcopenia and osteoporosis in women as well as men.

Glucocorticoid Excess

Glucocorticoid is used for the treatment of patients with rheumatic, hematologic, neuro-

logic, and chronic pulmonary diseases. Simultaneous negative influences of glucocorticoid excess in Cushing's syndrome or its exogenous administration on both muscle and bone are well known. Glucocorticoid excess induces an increase in fracture risk, especially at trabecular bone and in elderly patients, through decreased bone quality as well as decreased BMD. However, how glucocorticoid excess affects the interactions between muscle and bone remains not fully known. Earlier study revealed that femoral neck BMD was negatively related to percent lean body mass in postmenopausal women with glucocorticoid treatment; although the influence of body composition on vertebral fracture risk seemed to differ depending on age [55]. Moreover, glucocorticoid use was independently related to 25(OH)D deficiency in a large sample of children and adults [56], bearing in mind that vitamin D deficiency affects both muscle and bone.

Diabetes Mellitus

Diabetes is also an important causal disease for secondary osteoporosis. Although osteopenia and severe increase in bone fragility are known in type 1 diabetes, numerous recent studies indicated that fracture risk is increased in type II diabetes too, presumably via a decrease in bone quality, sarcopenia and an increased risk of falls. Proximal dominant myopathy is observed in some diabetic patients, and a preferential and diffuse involvement in type II fibers has been described. Skeletal muscle in type 2 diabetes is characterized by insulin resistance, impaired glycogen synthesis, impairments in mitochondria and lipid accumulation. Bone quality in type 2 diabetes is decreased, potentially due to the effects of advanced glycation end-products on collagen, impaired osteoblast activity, and lipid accumulation. Muscle density was also found to be positively related to physical activity and negatively associated with markers of fat distribution and risk for type 2 diabetes, when fat and muscle indices were assessed by peripheral quantitative computed tomography at forearm and foreleg [57].

Body weight control and exercise therapy as well as drug therapy for diabetes modulate the interactions between muscle and bone. Although body weight control may reduce both muscle and bone mass in diabetic patients, 1 year of an intensive lifestyle intervention in adults with type 2 diabetes along with weight loss was related to a modest increase in hip bone loss despite improved fitness and glycemic control [58]. Several studies suggest that resistance training (strength training) may impose potent and unique benefits in type 2 diabetes by treating the dysfunction of both muscle and bone induced by diabetic metabolic abnormalities [59]. Resistance exercise involves the movement of high loads using resistance from either machines or weights for a smaller number of repetitions. Aerobic exercise is recommended as the usual exercise therapy for diabetes [20].

Mechanical Factors

Mechanical stress changes, such as immobilization and lack of gravity, greatly influence both muscle and bone. Astronauts lose both muscle and bone mass. Muscle loss is recovered about 6 months faster than bone loss in astronauts [60]. Several lines of evidence have shown that low-magnitude mechanical signals are anabolic to bone and muscle [61, 62]. Clinical studies also suggested that low-intensity vibration signals stimulate bone and muscle formation as well as increase muscle force activity. They stimulate mesenchymal stem cell proliferation and bias their differentiation toward osteoblastogenesis and away from adipogenesis [63], suggesting that fate selection in hematopoietic progenitors can be determined by mechanical signals.

Muscle and Bone Coupling

Several studies have indicated that higher muscle mass is closely related to increased BMD and reduced fracture risk in postmenopausal women. Calcium ions are also critical for muscle contraction, and hypocalcemia induces muscle tetany. In

addition, muscle and bone are simultaneously influenced by pathological states, such as glucocorticoid excess and vitamin D deficiency. These findings raise the possibility that there might be interactions between muscle and bone metabolism [27].

Fractures that are covered with relatively intact muscle were found to improve more rapidly than fractures associated with more severe damage. Muscle flaps applied to autogenous bone grafts also improved healing. Proinflammatory cytokines, in particular tumor necrosis factor (TNF)-α, at the site of fracture induced the differentiation of stromal cells present in the muscles into osteoprogenitor cells and promoted bone fracture healing [64]. Another study also demonstrated that muscle-derived stem cells take on a primary role in the reparative response in the setting of severe injury to the periosteum [44]. These findings suggest that muscle tissues play important physiological and pathological roles through certain interactions between muscle tissues and bone metabolism.

Links from Muscle to Bone

Data from Diseases and Gene Mutations

Fibrodysplasia ossificans progressiva (FOP) has provided an important clinical clue as a disease linking muscle to bone [27]. It is a rare autosomal dominant disorder with skeletal malformations and progressive extraskeletal ossification. Heterotopic ossification of the muscles, tendons, ligaments, and fascia begins in childhood and can be induced by trauma or for no clear reason, leading to extra-articular ankylosis of all major joints in the axial and appendicular skeleton, which renders movement impossible.

A heterozygous constitutively activating mutation (R206H) in bone morphogenetic protein (BMP) type I receptor, the activin receptor type I (ACVR1/activin-like kinase 2 [ALK2]), is found in patients with the classic form of FOP. Constitutive activation of the BMP signaling molecule Smad1 or Smad5 induces ectopic bone formation in FOP. These findings indicate that constitutive activation of BMP signaling by the ALK2 mutation is responsible for the molecular pathogenesis of FOP. The serum from a patient with FOP was found to include some soluble factors that might enhance osteoblast differentiation and BMP-2 expression in mouse osteoblastic cells [65]. Middle-age onset of heterotopic ossification was reported in a case of FOP with the mild alteration of ALK2 from a unique missense mutation (G325A) [66]. BMP-9 is involved in the pathophysiology of heterotopic ossification, with its activity depending on the skeletal muscle microenvironment, such as damage [67]. Overactive BMP signaling is involved in the pathogenesis of heterotopic ossification and Duchenne muscular dystrophy due to a mutation of the dystrophin protein that connects the cytoskeleton of muscle fibers to the underlying basal lamina [68]; although ALK3, a BMP receptor, is involved in the muscle regeneration process. BMP signaling in the satellite cells may exacerbate the disease in Duchenne muscular dystrophy.

Local Factors Affecting Muscle Ossification

Since ossification does not occur in muscle tissues in the physiological state, there might be some local regulators that enhance or suppress ossification specifically in muscle tissues. Several cell populations exist in muscle. In an earlier study, Wosczyna and coworkers [65] identified a tissue-resident stem/progenitor population that exhibits robust osteogenic potential and represents a major cell of origin for heterotopic ossification in the skeletal muscle interstitium. Another study revealed that several bone-related factors, such as Tmem119, osteoactivin, and Frizzled-3, were induced by ALK2 (R206H) overexpression (Fig. 2.2). Among them, Tmem119 is a PTH-responsive Smad3-related factor, interacting with Smad1/5 and Runx2 in osteoblastic differentiation [69, 70]. Tmem119 was found to promote the differentiation of myoblasts into osteoblasts, suggesting that it may play a critical role in the commitment of myoprogenitor cells to the osteoblast lineage [69].

Humoral factors linking muscle to bone

Several lines of evidence suggest certain interactions between muscle tissues and bone metabolism (Fig. 2.5). Muscle tissues produce local growth factors, which have anabolic effects in bone tissues, for example, IGF-I and IGFBP-5, which are secreted from muscle tissues. These findings raise the possibility that there might be some humoral factors that are produced in muscle tissues and affect bone in an anabolic fashion (Fig. 2.3). Among muscle-derived bone anabolic factors are Osteoglycin and family with sequence similarity 5, as well as member C (FAM5C). Osteoglycin is the seventh member of the small leucine-rich proteoglycans (PGs), which could represent be the mechanosensitive gene that mediates an anabolic response of mechanical loading [71]. FAM5C was reported be related to various cellular functions as well as pathological conditions, such as atherosclerosis and inflammation [72]. The levels of osteoglycin and FAM5C as well as the effects of the conditioned medium from osteoglycin-modulated myoblastic cells were positively correlated to osteoblast phenotype and mineralization in osteoblastic cells. Moreover, osteoglycin and FAM5C proteins were detected in human serum. These findings suggest that osteoglycin and FAM5C may be crucial humoral bone anabolic factors that are produced from muscle. However, clinical studies and in vivo studies using muscle-specific gene-deleted or transgenic mice are required.

Exercise therapy and an increase in muscle mass are considered to be very effective for an increase in BMD and a reduction in fracture risk in osteoporotic patients. However, therapy to improve these factors is clinically very difficult as the physical activity of osteoporotic patients is usually disturbed. Humoral bone anabolic factors, produced in muscle tissues, may be important as the target molecules for the treatment and prevention of osteoporosis.

There are various other factors that are produced in muscle tissues (Fig. 2.6). Many of these, such as IGF-I, interleukin (IL)-15, osteonectin, MMP-2, IL-7, and FGFs, may play some roles in bone metabolism [73]. Circulating myokine, irisin, which is induced by exercise, enhances the generation of brown-like adipocytes, and systemic administration of this protein has been shown to enhance lean body mass. Zhang et al. [74], and Boström et al. [75] reported that irisin promotes osteoblast differentiation through the

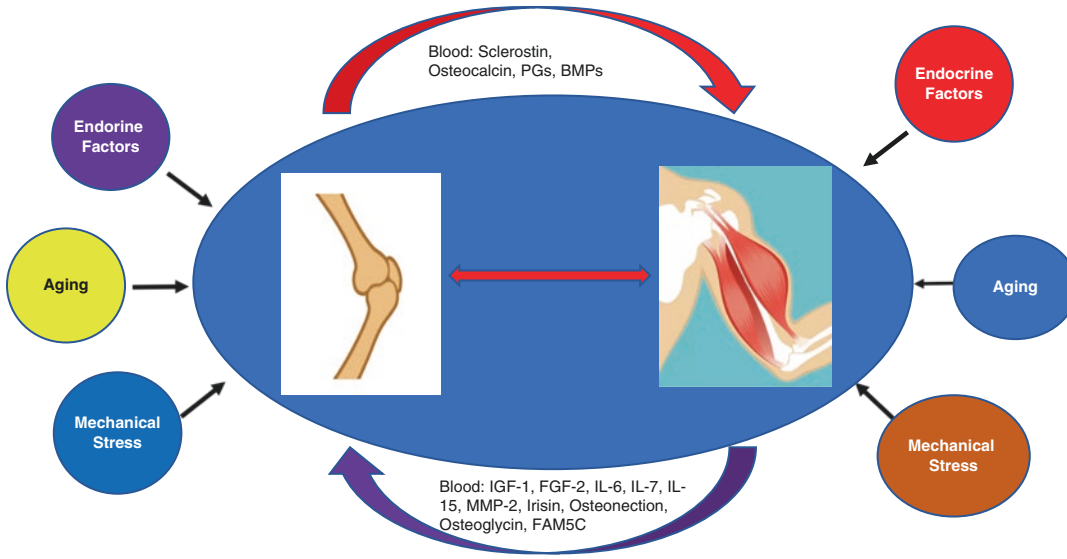

Fig. 2.5 Systemic humoral factors produced from muscle or bone tissues affect each other. MMP-2 matrix metalloproteinase-2, IGF-1 insulin-like growth factor I, FGF-2 fibroblast growth factor-2, IL interleukin, FAM5C family with sequence similarity 5, member C, PGs proteoglycans, BMPs bone morphogenetic proteins

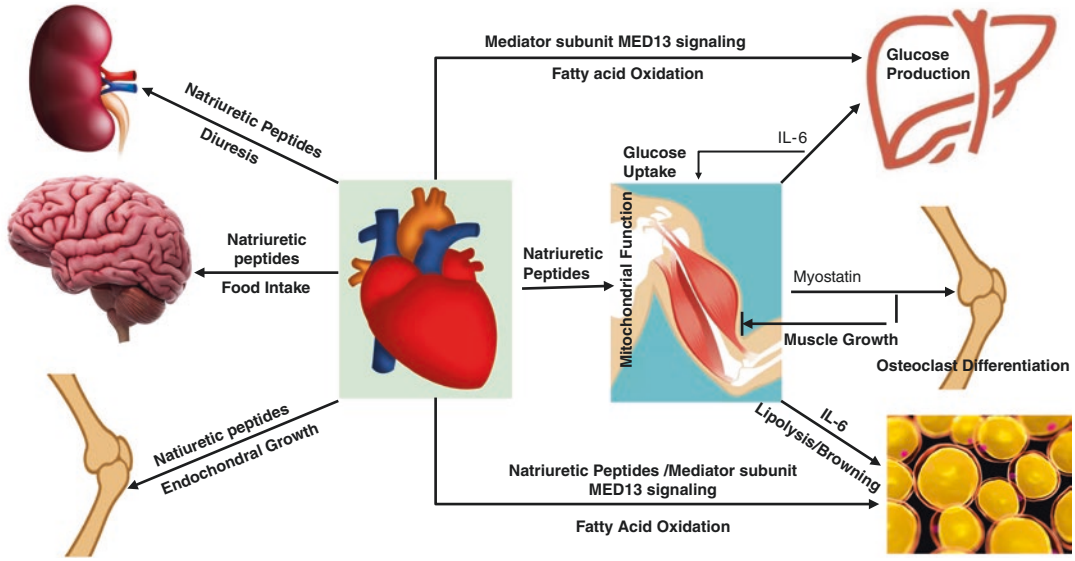

Fig. 2.6 Endocrine signaling from skeletal muscles to body organs
Myostatin and IL-6 signal from skeletal muscle to body organs, do also exert autocrine functions as they suppress muscle growth and enhance glucose uptake. Natriuretic peptides released from the heart regulate diverse processes in distal tissues. The Mediator subunit MED13 acts in the heart to enhance fatty acid oxidation in liver and white adipose tissue.

Wnt-β-catenin pathway and inhibits osteoclast differentiation by suppressing the receptor activator of nuclear factor-kappa B ligand (RANKL)/nuclear factor of activated T cells (NFAT)c1 pathway. Other studies carried out on female mice devoid of osteocalcin or osteocalcin receptor showed that they display a 10–20% decrease in muscle mass, mainly due to decreased muscle fiber diameter. Muscle fiber regeneration is compromised and the response to injury is altered in the absence of undercarboxylated osteocalcin function, suggesting that undercarboxylated osteocalcin could regulate muscle mass, function, and regeneration [76, 77].

IL-6 is secreted by muscle with exercise and affects glucose and bone metabolism. Mechanically loaded myotubes secrete soluble factors other than IL-6, which affect osteoclast formation [78]. The Wnt-β-catenin signaling pathway is an important regulator of bone mass as well as muscle growth. Osteocytes are involved in the regulation of bone mass in response to mechanical stress, presumably through the production of sclerostin [31, 36]. Muscle produces other factors that protect and preserve osteocyte viability in response to glucocorticoids which are not yet fully identified [78].

Myostatin

Myostatin is a member of the transforming growth factor (TGF)-β superfamily and a well-known inhibitor of skeletal muscle growth [79]. It has been suggested to have target effects on bone and tendon [36, 78]. The loss of myostatin produces hyperplasia and gross hypertrophy in muscle tissues, with increases in muscular function and bone mass [79, 80]. Conversely, mice overexpressing myostatin display muscle wasting and generalized atrophy with a cachectic phenotype. Anti-ACVR2B-Fc has been shown to increase lean body mass, fat metabolism and bone formation markers in postmenopausal women. However, a trial using this same agent in boys with muscular dystrophy was suspended because of the development of unexpected gum- and nosebleeds [36]. Moreover, a myostatin inhibitor (GDF-8 propeptide-Fc) did not alter BMD and bone strength in aged mice, although it increased muscle mass [76]. These findings suggest that pharmacological inhibition of myostatin

in mice has a more pronounced effect on skeletal muscle than on bone.

Links from Bone to Muscle

In contrast to the links from muscle to bone, influences from bone to muscle also exist. Bone marrow mesenchymal stromal cells support osteogenesis as well as bone resorption in bone tissues. A study revealed that bone marrow mesenchymal stromal cells stimulate myoblast proliferation through vascular endothelial growth factor (VEGF) from mesenchymal stromal cells [77], suggesting that bone mesenchymal cells influence muscle cells. IGF-I, MGF, myostatin, VEGF, and hepatocyte growth factor (HGF) may be anabolic and metabolic factors regulating muscle mass. These factors are produced in bone cells.

Osteocytes are abundant in bone tissues and noted as endocrine cells that affect different organs, such as kidneys and parathyroid glands. A study showed that mechanically loaded MLO-Y4 osteocytes produce various factors, such as IGF-I, MGF, VEGF, and HGF [81]. Moreover, osteocytes produce factors such as Wnt3a and prostaglandin E2 (PGE2) that support myogenesis and muscle function [82]. Gorski et al. [83], recently reported that osteocytes normally inhibit the growth and differentiation of skeletal muscle by secreting bone morphogenetic proteins (BMPs), which are modulated by circulating leptin. Therefore, there are several ways, through which osteocytes may affect muscle mass.

Techniques of Muscle Imaging: Measurement of Lean Body Mass and Muscle Mass

In recent years, four main techniques have been commonly used to estimate muscle mass: bioelectric impedance (BIA), dual energy X-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI). They were proposed to replace anthropometry [84–86] In addition to these, several emerging techniques for the assessment of muscle mass have been developed and are now available. Each relies on a different technological approach and assesses different aspects of muscle mass (e.g. total body muscle mass, appendicular muscle mass, or mid-thigh muscle cross-sectional area).

Dual Energy X-Ray Absorptiometry

Dual energy X-ray absorptiometry is the most widespread technique for measuring body composition [87]. Two different energy spectra are used in DXA scanning to differentiate two materials: either bone or soft tissue, which is the basis for the measurement of bone mineral density (BMD) and content or lean soft tissue mass and fat mass in locations where bone is absent. Taken together, DXA provides an estimate of three body compartments, that is, lean, bone, and fat. At bone locations, lean and soft tissue are interpolated from the surroundings. These measurements can be performed for the whole body and for several regions (e.g. trunk, arms, and legs) [88, 89]. The principle of using DXA for measurement of body composition is based on the notion that when a beam of X-rays is passed through a complex material, the beam is attenuated in proportion to the composition and thickness of the material. The use of two different energy spectra is the basis to separately quantify the amount of bone mineral and soft tissue or of fat and lean mass. Lean soft tissue and adipose tissue are mostly comprised by water and organic compounds, which restrict the flux of X-rays less than bone [84, 90]. DXA is able to assess total body lean soft tissue mass (which includes skeletal muscle mass as well as the mass of all other organs) and appendicular lean soft tissue mass (i.e. an estimate of the muscle mass contained in the limbs, which represents about 75% total body skeletal muscle mass) [87].

Appendicular lean soft tissue mass measured by DXA is highly correlated with both MRI ($r = 0.88$; $P < 0.001$) and CT ($r = 0.77–0.95$, $P < 0.0001$) measures of skeletal muscle volume [91–99] In vivo precision errors depend on DXA equipment, population, local versus whole body

Table 2.1 Strengths and weaknesses of measuring muscle mass by dual energy X-ray absorptiometry

Strengths	Weaknesses
Non-invasive with small down of radiaton (<1 μSv for whole-body scans) [41]	Projectional technique, individual muscles cannot be assessed separately.
Relatively cheap, compared with CT scan or MRI.	Not portable, which may preclude its use in large-scale epidemiological studies and studies in the home setting.
Rapid	Availability is limited in some care settings.
Allows measurement of three body compartments.	Body thickness and abnormalities in hydration status (e.g. water retention, heart, kidney, or liver failure) can affect muscle mass measure [42].
Low precision errors	Very tall and very obese people cannot be measured.
	Cannot quantify fatty infiltration of muscle. It is a bias as the diagnosis of sarcopenia obesity.
	Does not measure skeletal muscle mass in non-limb regions of the body (e.g. trunk).
	Several devices and several software packages and software versions resulting in different results.

Quoted from Buckinx et al. [16] under open access scheme
CT computed tomography, *MRI* magnetic resonance imaging

measurements, age, and degree of obesity. Recently published values for appendicular lean soft tissue mass range from below 1–3.0%. Higher errors of 4% were reported for bilateral muscle mass of the arms. Precision of DXA is high. According to Hangartner, the precision error, expressed in %CV, for lean body mass was 1.2% [100]. Strengths and weakness of the DXA technique are summarized in Table 2.1.

Note that DXA half-body analysis in obese subjects appears to be closely comparable to whole-body analysis for fat mass, non-bone lean mass, and percent fat, though there are no data on the comparability at appendicular sites.43 Dual energy X-ray absorptiometry is a candidate for providing a reference technology for assessing lean mass (as a proxy of muscle mass) and body composition in research and clinical practice. There is however a need for standardization. Standardization can be approached using phantoms or humans. Existing body composition phantoms are not anthropometric and cannot be used as absolute reference standards for soft-tissue composition. Therefore, a recent International Society for Clinical Densitometry report concluded that "No phantom has been identified to remove systematic difference in body composition when comparing in vivo results across manufacturers." As a consequence, "an in vivo crosscalibration study is necessary when comparing in vivo results across manufacturers" [101].

Still for a unique standardization, the use of phantoms would be preferable because an in vivo cross calibration is influenced by age, gender, ethnicity, as well as healthy versus diseased subjects [102–104]. Ideally, the calibration materials and equations used to derive lean mass should be standardized across manufacturers or cross-manufacturer algorithms should be developed by industry to standardize the output. It is also important to standardize the local regions of interest, such as trunk, arms, and legs, which are significantly different across manufacturers [105, 106].

Computed Tomography

Computed tomography (CT) was the first method introduced that could quantify regional skeletal muscle mass with high accuracy [107]. CT determines the cross-sectional distribution of the X-ray absorption coefficient, which after normalization to the absorption of air and water is called CT value and measured in Hounsfield units (HU). CT slices of predefined width can be analyzed for different tissues, using manual segmentation or automated software. For example, muscle area,

or in case of the analysis of a stack of images, volume of individual muscles, or a group of muscles can be determined. By definition, the HU value of air is −1000 and of water 0. Bone, skeletal muscle, adipose tissue, and visceral organs have specific Hounsfield unit ranges, allowing for their identification in the cross-sectional images. The tissue area/volume (cm^2/cm^3) of the cross-sectional/stack of images is subsequently calculated by multiplying the number of pixels/voxels for a given tissue by the pixel area/voxel size. Muscle mass can be derived by multiplying muscle volume by 1.04 that is the assumed constant density (kg/cm^3) of adipose tissue-free skeletal muscle [16, 107].

Compared with DXA, CT is a 3D imaging technique that allows for quantitative assessment of individual muscles. Moreover, the muscle tissue composition can be quantified, either by separate segmentation of muscle and adipose tissue or by analyzing muscle density, that is, the HU distribution within the segmented muscle [108].

In vivo precision errors for muscle volume or mass measurements have rarely been reported. In concordance, re-analysis precision errors are low due to its high resolution (typically 50 microns or less) [109]. This is important because with advanced 3D imaging, precision of muscle area and mass depend more on image segmentation than on repositioning. For re-analysis, intraclass correlation coefficients (ICC) between 0.98 and 1.00 ($P < 0.001$) [110] in quantifying both adipose tissue and muscle mass [111] were reported.

Major disadvantages of CT are limited access to the radiological departments that operate it and considerably higher cost and radiation exposure than for DXA. Despite calibration of HU to water, calibration of CT across models and scanner manufacturers is still required when comparing scans from different devices. In addition, very obese patients may not fit into the scanner and image quality will be poor. Also, the operation of a CT scanner requires highly qualified personnel. The widespread implementation of CT imaging in the field of sarcopenia has been hampered by the previously mentioned.

Magnetic Resonance Imaging

The introduction of MRI in the 1980s expanded the initial use of CT as a mean of developing three-dimensional images of skeletal muscle, adipose tissue, and other organs. This development is usually referred to as structural or anatomic imaging [86]. The resolution is very high, and MRI is safe without any radiation exposure. With the advancement of the MRI technique, the time for reliable image acquisition has decreased significantly. In addition, most modern MRI scanners can accommodate obese subjects. Limitations in the use of MRI in clinical and research settings are largely related to the high cost, the technical expertise required for analysis, and the effect of respiratory motion on image quality for whole-body assessments. Multiple slices are required to assess the composition of the total body, including total body skeletal muscle mass [112]. Finally, the existence of multiple protocols for data acquisition impacts the standardization of this technique for the study of muscle mass [102]. Bearing all these considerations in mind, MRI is presently better suited for small-scale research studies in which accurate measurements of muscle quantity and quality are needed.

Bioimpedance Analysis

Bioimpedance analysis (BIA) was pioneered in the 1950s and 1960s by Hoffer, Nyboer, and Thomasset [113–115]. Since then, BIA has become a broadly applied approach used in body composition measurements and healthcare assessment systems [116].

BIA is based on the notion that tissues rich in water and electrolytes (i.e. skeletal muscle) are less resistant to the passage of an electrical current than lipid-rich adipose tissue (i.e. bone) [117]. All BIA systems exploit these tissue-specific conductivity differences to quantify body-compartments. In bioimpedance measurements, the human body is divided into five inhomogeneous segments, two for the upper limbs,

two for the lower limbs, and one for the trunk [116]. Many available BIA system designs range from single to multiple frequency, employ contact or gel electrodes, and measure whole-body electrical or segmental pathways [86]. All BIA systems measure impedance and/or its two components, resistance (caused by the total water across the body) and reactance (due to capacitance of cell membrane). These electrical measurements in turn can be incorporated into body composition prediction equations that are population specific [86]. Advantages and disadvantages of BIA are listed in Table 2.2.

Due to the large number of factors conditioning BIA reliability: instrument related factors (i.e. intra-instrumental and inter-instrumental variability, electrode quality, and electrode positioning), technician-related factors (i.e. intra-operator and inter-operator variability), subject-related factors (i.e. subject preparation such as position, overnight fast or empty bladder, body temperature, skin conductibility, age, and ethnicity), and environment-related factors (i.e. temperature), BIA does not seem to be ideal for measuring lean body mass, mainly due to the problem of the individual prediction error. One study showed that the reliability of BIA to assess appendicular lean mass was high, with an ICC of 0.89 (95%CI: 0.86–0.92) when performed by the same operator, and an ICC of 0.77 (95%CI: 0.72–0.82) when performed by two different operators. Nevertheless, in this study, agreement between appendicular lean mass assessed by DXA and predicted by BIA was low [ICC = 0.37 (95%CI: 0.25–0.48)] [117–119]. There is a potential large prediction error on the individual level with BIA. Indeed, there is a systematic positive bias with an overall underestimation of lean body mass measurements by BIA 60. It is, however, one of the few alternatives when other more precise techniques are not feasible.

Table 2.2 Strengths and weaknesses of estimating muscle mass by bioelectrical impedance analysis (BIA)

Strengths	Weaknesses
Inexpensive and easy to use [4]	Measurements are sensitive to subjects' conditions such as hydration, recent activity, and time being horizontal [58, 59]
Precise measurement of body resistance and reactance	Large individual prediction error for estimated muscle mass
Safe and non-invasive method [17]	Need of age, gender, and ethnic-specific prediction equation to estimate muscle mass
Portable tool and can be used in most environments [57]	No BIA-specific equations validated in patients with extreme BMI
Does not require highly trained personnel	Multiple devices with different body composition outputs

Quoted from Buckinx et al. [16] under open access scheme

BIA bioelectrical impedance analysis, *BMI* body mass index

Emerging Techniques for the Assessment of Muscle Mass

Because of the limitations of the current techniques to assess lean mass (cost, accuracy, feasibility), new techniques have appeared. Among these techniques, creatine (methyl-d3) dilution (D3-creatine) is of some interest [120, 121].

Creatine is present predominantly (~95%) in skeletal muscle. Roughly 2% of creatine is converted to creatinine per day, via an irreversible, non-enzymatic mechanism, so that ~2 g per day of creatine is replaced in the whole body. Based on the assumption that conversion of creatine to creatinine is constant among and within subjects, the daily excretion rate of creatinine has been used as a metric of whole body creatine pool size [122]. Reviews of this method show that a relatively broad range of muscle mass per gram of urinary creatinine (17–22 kg) has been used to estimate muscle mass, leading to large variability in muscle mass estimates between studies, and further suggest limitations to this method in certain patient groups, such as those affected by renal failure [123].

Furthermore, there are inherent limitations to this method (in addition to the problem of inaccurate 24-h urine collections): pH and temperature affect the non-enzymatic conversion rate of creatine to creatinine, and there is degradation and metabolic removal of creatinine in the body,

so all creatinine produced is not excreted in the urine [124]. The results are also dependent on the intake of meat that increases the excretion of creatinine. Thus, accurate assessment requires a meat-free diet for about 1–2 weeks.

Electrical impedance myography is a noninvasive, painless approach to muscle assessment based on the application and measurement of high-frequency, low-intensity electrical current. Measurements are made over a small area of interest, with energy being applied to the body and the resultant surface patterns analysed. Several parameters are obtained, including the tissue's reactance, resistance, and phase angle that can provide a quantitative measure of muscle condition [125]. The central concept of electrical impedance myography is that skeletal muscle can be modeled as a network of resistors and capacitors. The intracellular and extracellular matrices of muscle tissue act as resistors, and any atrophy that reduces the cross-sectional area of muscle tissue would be expected to increase the resistance. The lipid bilayers that constitute muscle membranes act as capacitors, and as muscle atrophies, the cumulative capacitance of the muscle membranes increases [126]. Electrical current is used, and the output is a set of quantitative parameters describing muscle state, with presently little emphasis on imaging (though this remains possible) [127].

Ultrasound is an imaging technique that can determine thickness and cross-sectional areas of superficial muscles. In particular, with ultrasound analysis, it is possible to measure key parameters of muscle architecture, such as muscle volume, fascicle length, and pennation angle. Fascicle length, which is an estimate of muscle fiber length, is defined as the length of a line coincident with the fascicle between the deep and superficial aponeuroses. Fascicle length indicates the range of lengths over which the muscle is capable of actively producing force, known as the excursion potential. Pennation angle represents the angle of the muscle fibers that constitute a muscle fascicle relative to the force-generating axis, and directly affects both the force production and the excursion, larger angles of pennation limiting the excursion potential [128].

Ultrasound has the advantage of being portable and involves no ionizing radiation. A number of studies have confirmed the reliability of this technique for measuring the size of the quadriceps muscle in health. For example, an ICC of 0.97 (95%CI: 0.92–0.99) was found for the test–retest reliability of ultrasound at the rectus femoris [129]. However, a major problem is the impact of the applied pressure on the probe on the measurement result. Even though, this method of body composition analysis is not widely used for sarcopenia screening and staging [130, 131], in the near future, it may become a valid method to assess muscle in different settings [132].

Biomarkers are another way to assess muscle mass. Previous studies have shown that the serum levels of the collagen type III propeptide correlate well with whole body lean mass [133], as do the circulating levels of collagen type VI peptides containing the IC6 epitope [134]. Nedergaard et al. have shown that the anabolic response to reloading following immobilization was inversely related to the levels of the matrix-metalloproteinase-generated collagen type VI fragment C6M.74 Both collagen types III and VI are known to be important constituents of the extracellular matrix of skeletal muscle [135, 136]. Therefore, fragments produced during muscle tissue turnover may be correlated with lean body mass [133]. Dysregulation of microRNAs may also contribute to reduced muscle plasticity with aging [137].

Towards a Reference Standard

The considerations above indicate that no currently available technique serves all the requirements for the measurement of muscle mass. Each has limitations and in particular, there is a dearth of information on accuracy. Moreover, none are fully standardized. Thus, there is at present no gold standard. Notwithstanding, there is need to develop a reference standard against which alternative techniques can be evaluated. Major disadvantages of CT are limited access to the radiological departments that operate it, considerably higher cost and radiation exposure

than for DXA. Limitations in the use of MRI in clinical and research settings are largely related to the high cost and the technical expertise required for analysis and limited access. The main challenge for BIA is the availability of population-specific equations to predict lean mass (or other body composition parameters) according to the reference standard used to validate the BIA equation. In fact, several good equations are available; but many clinicians rely on the outputs generated by the device itself (which is using an built-in equation, most often kept "hidden" by the manufacturer).

These considerations suggest that, despite many limitations [138], DXA may be considered the current reference technique for assessing muscle mass and body composition in research and clinical practice. An important reason for preferring DXA above BIA is that DXA measures body composition on an individual level, while BIA uses a prediction equation (so it estimates muscle instead of measuring it), and is hampered by large prediction error on the individual level. Also, BIA standardization will be more complicated than DXA standardization due to the multitude of available BIA devices. In addition, DXA has been used successfully to estimate skeletal muscle mass as part of RCT's [139–141]. Currently, it is the preferred and effective measurement technique in this context.

To ensure the accuracy of DXA measurement, standardization is needed. Calibration materials and equations used to derive lean mass should be standardized across manufacturers. An important item on the research agenda is to standardize the local regions of Interest, such as trunk, arms, legs, that are significantly different across manufacturers. Finally, consensus is required in adopting a reference population in much the same way as has been achieved for the use of DXA in osteoporosis [142].

It is important to note that the adoption of a reference standard does not proscribe the use of any of the techniques in clinical research or clinical practice. Indeed, this is to be encouraged. There is a useful analogy with the use of BMD in the assessment of osteoporosis. The reference standard is BMD at the femoral neck [16, 143], but in clinical research and clinical practice many assessment tools are widely used (e.g. BMD at other skeletal sites, CT, quantitative ultrasound, and trabecular bone score). The caveat is that where the opportunity arises BMD should also be reported using the reference technology applied to a reference population and is now a requirement in many of the bone journals.

The adoption of DXA as a reference standard with a defined normal range provides a platform on which the performance characteristics of less well-established and new methodologies can be compared. It also permits comparisons between studies and between countries.

Different Indices to Express Lean Body Mass

Skeletal muscle index (SMI) is a measure to express lean mass in relation to height or weight. Unfortunately, the common use and terminology of SMI is inconsistent [144]. It is either defined as appendicular skeletal muscle mass divided by height^2 and measured in kg/m^2 or as skeletal muscle mass divided by body mass × 100, which is a unitless index, although some authors distinguish them as appendicular lean mass/ht^2 and SMI [145]. SMI can be derived from BIA or from DXA measurements. Both SMI definitions have previously been shown to predict disability and functional limitations in large, epidemiologic studies of older adults [146, 147]. However, the classification of community dwelling older adults as sarcopenic or non-sarcopenic differed markedly for the two definitions. The weight-based SMI classified significantly more community-dwelling older adults as sarcopenic than the height-based index, a trend more deep-seated in men than women. More recently even a third definition, the application lifecycle management/BMI index was proposed [145]. Due to the discrepancies observed, a clearer terminology should be developed, and it seems necessary to use that index that can best describe the associa-

tions between muscle mass and important clinical outcomes in epidemiological studies.

Nutrition and Muscle Health

How to eat for healthy muscles is important, not only to promote healthy muscles state but also to facilitate its repair after a vigorous workout and help minimize muscle wasting. Furthermore, the quality of the food eaten may vary subject to the individual physical activity status; for example, while exercise is a critical component of maintaining and building muscle, sedentary individuals have dietary requirements essential for muscle repair. Eating the right foods helps the person not only maintain a healthy muscles mass but also help maintain ongoing optimal bone health, muscle function, and strength. Different types of food contribute to muscle health in various ways, these include:

Proteins

While all elements of dietary intake are critical for the maintenance of muscle mass, it is the regular adequate consumption of protein, that is essential to stimulate protein synthesis [148–150]. An inadequate protein intake appears to influence muscle tissue mainly by reducing the synthesis rather than increasing the degradation of muscle protein [151]. Dietary protein supplies the materials required to replenish and remodel muscle cells between physical activity sessions. For optimal muscle health, the protein-rich foods must contain essential amino acids, the protein building blocks which human body cannot synthesize. These amino acids are abundant in animal protein sources, such as milk products, meat, poultry, eggs, and seafood. Milk protein is particularly good for healthy muscles because of its branched-chain amino acid content that assists muscle repair. Plant-based foods often lack one or more essential amino acids, but by eating a variety of items that have some amino acids, for example, legumes with whole grains, the person may get all the essential amino acids needed by his/her body.

Dietary Protein Requirements for Optimal Muscle Mass and Strength

The current recommended dietary allowance of protein for adults aged 19 years and older is 0.8 g/kg body weight per day. This level was determined from short-term, i.e., 10–14 days, nitrogen balance studies [152]. It is an estimation of the minimal protein intake needed to maintain nitrogen balance in healthy young adults [153], based on the concept of preventing deficiency as opposed to promoting optimal health [154]. However, nitrogen balance is not directly related to functional outcomes including maintenance of skeletal muscle and bone health [153, 154]. There is a consensus that optimal daily intake is higher than 0.8 g/kg [153]. However, there is some concern that consuming dietary protein in excess of the RDA may promote renal damage [155]. Protein restriction may be appropriate for existing chronic kidney disease (CKD), although severe restriction can lead to protein–energy wasting in non-dialysis-dependent CKD [156].

However, there is no evidence for a detrimental effect of high protein intakes much above the recommended dietary allowance in healthy persons with normal renal function [153, 155]. In older adults, taking into account the attenuated anabolic response to dietary proteins, a moderate increase from 0.8 to 1.0–1.2 g/kg per day [157] may be optimal for skeletal muscle health without affecting renal function.

Vitamin D

Vitamin D can exert its effects by genomic and nongenomic pathways. Both can be involved in muscle function. Besides the muscle cell (type II fibers), vitamin D could also influence neuromuscular action. Evidence for the vitamin D receptor (VDR) in muscle cells and cell lines has been

found by several investigators with different methods such as mRNA, calcium-binding protein, and VDR antibodies [158–160]. The active vitamin D metabolite 1,25(OH)^{2}D stimulates differentiation of myoblasts [161]. Furthermore, it stimulates calcium influx, phosphate transport, and muscle fiber differentiation. 1,25(OH)^{2}D may also bind to a membrane receptor, activating cyclic AMP or arachidonic acid. Subsequently, calcium is actively transported into the sarcoplasmic reticulum, increasing intracellular calcium, necessary for cross-bridge formation, and hence muscle contraction [162].

Earlier studies showed significant relationship between vitamin D status and physical performance [163–165]. Lower serum 25(OH)D levels were associated with a lower performance on the timed get-up-and-go test and timed chair stand test. The Osteoporosis Prospective Risk Assessment (OPRA) Study in Malmö in 986 women aged 25 years or older showed positive correlations between serum 25(OH)D levels and gait speed, the Romberg balance test, and thigh muscle strength [166]. Adolescent girls between 12 and 14 years old were also studied in Manchester, UK. A positive relationship between serum 25(OH)D levels and jumping velocity, jumping height, power, fitness index, and force was observed [167, 168]. In contrast, a German study did not find a significant association between muscle strength and serum 25(OH)D in postmenopausal women with osteoporosis [169]. In general, the associations between serum 25(OH)D and muscle strength or performance are significant in the lower range of serum 25(OH)D and may not apply in the "normal" or higher range. In the LASA Study, a threshold for this association was observed for serum 25(OH)D between 50 and 60 nmol/l [170].

Nutrition intervention studies also indicated a positive role for vitamin D in the development and preservation of muscle mass and function. In a randomized controlled trial in elderly institutionalized women with documented vitamin D insufficiency (documented as vitamin D levels of less than 50 nmol/L), the effects of different doses of vitamin D were tested on muscle strength, muscle mass, and bone density [171]. Vitamin D supplementation at the conventional dose of 800 IU daily resulted in a level of circulating vitamin D greater than 50 nmol/L in all women at 6 months. During supplementation, muscle mass (assessed in the upper leg by CT scanning) did not change. However, supplements of vitamin D were associated with an improvement in dynamic muscle strength and hip bone density, supporting the well-established need for vitamin D supplementation in elderly institutionalized populations. The increases in muscle strength and function have been ascribed to binding of active vitamin D to specific vitamin D receptors found in human skeletal muscle that promote protein synthesis and cellular growth [172, 173]. Vitamin D supplementation for 3 months in a small, uncontrolled study resulted in significant increases in the relative number and size of type II muscle fibers in elderly women [174], and 1000 IU of vitamin D a day in elderly stroke survivors increased type II muscle fiber mean diameter by 2.5-fold over a 2-year period [175].

Homocysteine Levels, Vitamin B12, and Folic Acid

Studies [176, 177] revealed the intakes of vitamin B12 and folic acid were able to rectify high levels of homocysteine. A high serum level of homocysteine (hyperhomocysteinemia) has been reported a risk factor for cardiovascular disease. Hyperhomocysteinemia was also reported to be associated with fractures in three large prospective cohort studies, the Rotterdam Study, LASA, and the Framingham Study [177]. This association with fractures was independent of bone mineral density in the LASA and Rotterdam studies. The occurrence of fractures was attributed to a change in bone quality (change in collagen cross-links) or a higher fall incidence. On another front, higher homocysteine levels were associated with greater decline in physical function [178]. In the NHANES, elevated homocysteine levels were associated with lower quadriceps strength and gait speed and more disability in older persons [179]. Furthermore, in patients with peripheral

arterial disease, elevated homocysteine levels were associated with lower calf muscle density [180]. Similarly, the OPRA Study of 996 women of 75 years old showed a relationship between high homocysteine levels and poor physical performance [180].

Nutritional interventional studies suggested that Vitamin B12 and/or folic acid might improve postural stability and/or muscle function and strength. A prospective intervention study in Japan in patients who sustained a stroke showed that vitamin B12 and folic acid decreased fracture incidence compared with placebo [181]. However, further randomized clinical trials are still required to assess this relation.

Acid-Producing Diets

Although a dietary acid load does not change the intracellular pH of the muscle cells, it has been suggested that chronic intake of excess acid-producing nutrients such as meat and cereal grains in combination with a low intake of the alkalizing fruits and vegetables [182] may lead to a chronic acid challenge and to negative effects on bone [183] and muscle.

Earlier studies revealed that an acidic environment is an established stimulus for muscle catabolism. The efflux of amino acids from muscle was found to increase with early starvation [3]; trauma, sepsis, and burns [184–187]; chronic renal failure [188]; and in obese subjects who were acidotic while on weight loss diets [189]. Furthermore, correction of acidosis has been shown to reverse nitrogen excretion (muscle wasting) in chronic renal failure patients [190] and in obese subjects on ketogenic diets [191].

Muscle wasting appears to be an adaptive response to acidosis [192, 193]. The released amino acids are converted to glutamine in the liver, and glutamine is used by the kidney to increase synthesis of ammonia [194]. Ammonia accepts protons and is excreted as ammonium ions, thereby mitigating the acidosis. The underlying mechanisms by which alkali supplementation benefits muscle mass and performance remains not fully clear. In experimentally induced acute metabolic acidosis in humans, there is upregulation of muscle proteolytic pathways (i.e., ubiquitin–proteosome pathway) and downregulation of muscle protein synthetic pathways (i.e., IRS-1/PI3K/Akt signalling pathway) [195]. The effect of acidosis on muscle may also be mediated through the suppression of IGF-I [196].

Recently, diets high in alkali-producing fruits and vegetables (and low in net acid-producing compounds) have been associated with the preservation of lean tissue mass in older adults [197]. In addition, three prospective studies have demonstrated that intake of excess alkali in the form of potassium or sodium bicarbonate reduces urinary nitrogen excretion and thus potentially spares body protein stores in healthy older adults [198–200]. One of these studies demonstrated that longer term administration of bicarbonate (daily for 3 months) also had favourable effects on lower extremity muscle strength and power in healthy older postmenopausal women, suggesting that bicarbonate has a sustained effect on skeletal muscle performance [199].

There is some evidence that acid–base balance and vitamin D may be interdependent in their effects on muscle. For instance, acidosis may influence the action of vitamin D on muscle indirectly. The hydroxylation of vitamin D into active and inactive metabolites is pH dependent. The enzymes involved require an optimal pH of around 7.4. A higher or lower pH tends to result in a lower activity of the enzymes regulating 25-hydroxyvitamin D metabolism [201]. But the variation of medium pH from 7.2 to 7.4 did not increase 1,25-dihydroxyvitamin D3 production [202]. On the other hand, chronic metabolic acidosis increased serum concentration of 1,25-dihydroxyvitamin D in humans [203]. There is probably a difference between the effects of acute versus chronic pH changes. The crystallization of the vitamin D receptors requires an optimal pH of 6.0, at least in vitro [204]. In addition, pH variations could modify vitamin D binding proteins as well as vitamin D receptor interactions within target tissues. Alternatively, acidosis may be one mechanism by which vitamin D insufficiency adversely affects muscle. Animal studies suggest that vitamin D deficiency results

in a metabolic acidosis whereas repletion with vitamin D results in a metabolic alkalosis [205, 206]. Clinical evidence for interaction of acid–base with vitamin D in their effects on muscle requires further investigations.

Nutrition interventional studies revealed that alkali-producing diets favoured lean tissue mass in older adults [197]. In another study, administration of bicarbonate improved lower extremity peak muscle power and endurance over a 3-month period in non-exercising healthy older women [207]. This went along with a lowering of nitrogen excretion, confirming a previous observation in postmenopausal women that ingestion of a neutralizing dose of potassium bicarbonate, reduced nitrogen excretion [200].

Exercise is the only nonpharmacologic intervention with anabolic effects on muscle. There is some rationale to expect that alkali may enhance the effect of exercise on muscle. During exercise, lactic acid efflux across the muscle membrane accompanied with a decrease in intracellular pH [208]. Intracellular acidosis may act directly on the myofibrils and accounts for some of the suppression of muscle contractile force and fatigue during high-intensity exercise of very short duration (1–7 min) [209]. An increase in extracellular bicarbonate buffering capacity by ingestion of $NaHCO_3$ facilitates the efflux of lactate and H+ from muscle cells, thereby delaying the critical decrease in intracellular pH, which negatively affects muscle glycolysis and contributes to fatigue and delayed exercise recovery [210].

Clinical evidence for an interaction of alkali supplementation and exercise is limited. The impact of acute HCO_3 administration on physical performance has been studied in healthy young subjects. Price et al. [211] noted improved exercise tolerance during cycling in subjects consuming 0.3 g/kg of $NaHCO_3$ compared with controls (those consuming 0.04 g/kg of NaCl). $NaHCO_3$, 0.4 g/kg, has also increased quadriceps torques compared with control [110]. This suggests that HCO_3 improves nonoxidative glycolysis in isometric contraction, resulting in reduced fatigue and enhanced recovery. However, other acute intervention studies have found no impact of HCO_3 on sprint performance [212], power output and fatigue [213], or resistance exercise performance [214]. Thus, evidence for a synergistic effect of alkali administration and exercise on muscle performance remains inconclusive.

In conclusion, chronic ingestion of a dietary acid load appears to contribute to age-related declines in muscle function, and also possibly in muscle mass in older adults. Diet modification to reduce the acid load is likely to benefit muscle as well as bone.

Muscle in Aging Adults and in Disease

Muscle Health in Aging

Commencing from the mid-twenties muscle mass and muscle strength decline through middle-age, particularly in habitually sedentary individuals [13, 215, 216]. This is initially a slow process, with a strength loss of approximately 10% per decade. Strength loss further accelerates after the age of 60–70 years. Thus, the older adults are expected to have only 30–40% of their peak adult strength. Putative cellular mechanisms of aging include oxidative stress, chronic low-grade inflammation/impaired immune function, increased macromolecular damage and genomic instability, cellular senescence, and reduced stress resistance [217–220]. However, malnutrition, which is very common in the older adults, with a consequent significant risk of micronutrient deficiencies, is very likely to exert an impact on muscle loss [217–219, 221]. Therefore, it can be said that the aging process is characterized by a decline in muscle mass and strength; when this process outreaches pathological levels it is defined as sarcopenia. Subsequently, such musculoskeletal impairment causes an important burden of disability and disease in older patients; a better understanding of pathogenesis and muscle–bone crosstalk could lead to improvement prevention strategies and therapeutic options.

Measurement of Muscle Health in Aging

Originally, the decline in muscular strength was thought to be caused by a loss of muscle mass [222]. In an approach similar to the measurement of bone health, researchers focused on developing diagnostic criteria for muscle health based on classifying individuals as having high or low indices of muscle mass relative to a healthy young adult norm [223–225]. There is now a growing body of evidence spanning over three decades [226, 227], that suggests muscle mass and strength are not as closely linked as previously assumed [228, 229]. Prior to a change in absolute mass or cross-sectional area (CSA), muscle undergoes a series of physiological changes with aging that are implicit in a decrease in strength. There is a reduction in the number of motor units and a resultant increase in the size of motor units because of the compensatory collateral sprouting by surviving neurons [230–232]. Furthermore, maximal motor unit firing rates are reported to be 35–40% lower than young adults [233] and exhibit greater variability in motor unit discharge [234]. Subsequently, at the tissue level the excitation–contraction coupling processes are thought to be impaired due to impairments in calcium release from the sarcoplasmic reticulum. These changes are compounded by an increase in inter and intramuscular adipocyte content [235] that is thought to directly impair cross-bridge kinetics [236]. As a result of the increase in fat infiltration and connective tissue, the net contractile mass is less. In fact, noncontractile mass can account for 15% of total muscle CSA, an estimate that is 2.5-fold greater than in young controls [237].

Consequently, there is a growing interest in the measurement of age-related change in muscle performance rather than size alone. As a result, the consensus in Europe [238] and America [239] among expert working groups is that muscle health should be assessed in terms of muscle mass, muscle strength, and functional capability. Low relative skeletal muscle (SM) mass has been shown to be associated with functional impairment [147] measured by the short physical performance battery (SPPB) [240]. Increasing knee extensor torque has been associated with improved walking speed and the ability to rise from a chair [241, 242]. Knee extensor speed of contraction has been found to be predictive of gait speed in mobility limited older adults [243]. Despite established relationships between muscle mass, strength and functional capability in mobility limited older adults, comparatively little is known about the time course and transition to functional impairment in healthy older (>50 year) adults [244].

Furthermore, there has been considerable variability in the components of muscle mass, strength and functional capability which have been investigated in addition to variability in the tools of assessment and protocol for measurement. This is in stark contrast to the validated measurement of bone health across the adult life span [245, 246]. The following section will discuss the identification of muscle mass indices, strength and functional capability as well as their change with aging, and where possible to provide an estimate of the rate of change.

Age-Related Change in Muscle or Lean Tissue Mass

Currently, imaging methods including magnetic resonance imaging (MRI) and computed tomography (CT) represent the accepted criterion method for quantifying whole body and regional skeletal muscle (SM). This is due to their ability to distinguish between fat, skeletal muscle, and other nonmuscle fat-free components such as connective tissue [247–249]. Dual energy x-ray absorptiometry (DXA), more commonly used in the assessment of bone health, has been found to be a reliable cost-effective method for quantifying whole body and regional non-osseous lean tissue mass (LTM) with a low radiation dose [247, 249]. Despite a strong correlation between CT and DXA in the estimation of SM ($r = 0.88$, P\0.001), reporting the age-related decline in SM

using DXA requires caution as it has been shown to overestimate whole body and regional SM. This methodological issue may mask age or therapeutic related changes in SM [91, 235, 250].

Numerous studies have attempted to quantify the rate of decline in SM as though it is a uniform process which begins at the completion of growth [251]. The suggestion that lean tissue mass (LTM) begins to decline in the third decade stems from studies evaluating the decline in skeletal mass relative to body mass which produces an inflated decline due to an increase in fat mass [147]. Janssen et al. [225] suggest age is not associated with appendicular SM, as measured by MRI, until after 45 years. Furthermore, changes in whole body LTM as measured by DXA or hydro-densitometry, albeit less-sensitive measures of SM, are subtle enough not to be detected until after 60 years in either cross-sectional [252] or longitudinal [253] analysis. Estimating the age-related decline in SM across the adult lifespan is difficult due to incomplete data sets across age ranges which have led to researchers using equations to predict declines [223, 224]. This has been compounded by existing literature containing multiple ethnic groups. There is considerable variability in the age-related decline in SM among Hispanics, African-American, Caucasian, and Asians. The rate of change in SM in these ethnic groups differs between men and women [147, 224, 251]. Therefore, it is recommended age-related change in SM is reported according to gender and ethnicity.

Age-Related Change in Muscle Quality

Declines in grip and knee extensor strength have been shown to occur independent of changes in limb circumference, anthropometrically determined lean body mass and thigh CSA, determined by CT [246]. Recent evidence, noted above, has had the benefit of modern imaging techniques and commercially available dynamometers to accurately quantify muscle mass and strength. This has served mainly to reaffirm the earlier findings of Larsson et al. [226] and others reported above. Many of these studies indicate that the loss of strength is somewhat greater than loss of muscle mass with aging [235, 253, 254] implying that muscle quality may be reduced. The quality of functional SM or lean tissue mass (LTM) can be expressed as strength per unit of tissue. Valid and reliable measurements of segmental SM or lean tissue mass (LTM) combined with measures of muscle function, e.g. maximal voluntary strength, allow for the development of an appropriate index of muscle quality. It is suggested that muscle quality may be able to better distinguish between those with high and low functional capability [238, 242].

Since 1992, the BLSA has measured peak torque (0–308/s) of the arms and legs and non-osseous lean tissue mass (LTM) (DXA) [255, 256]. Muscle strength was reported to have a greater rate of decline than lean tissue mass (LTM), this difference began in people aged ~50 years and increased with age. There was an age-associated linear decline when muscle quality was expressed as knee extensor torque per CSA or Lean tissue mass (LTM) [257]. However, the definition of muscle quality is strength per unit lean tissue mass (LTM) and therefore, in theory, it would seem more appropriate to express muscle quality as upper leg (combined knee extensor and flexor) strength per unit upper leg lean tissue mass (LTM). To this aim, Lynch et al. [256] and Francis et al. [258] have expressed the combined upper leg torque per kg of total and upper leg lean tissue mass (LTM) respectively. Using this index the decline in men was 5.1% [256] and 8–10% per decade in women [258]. Despite the definition of muscle quality many authors have chosen to represent muscle quality using only knee extensor torque per total upper leg SM or lean tissue mass (LTM). We have previously reported that the index of muscle quality becomes more variable when the knee flexors are included and that knee extensor torque explained a greater proportion of the variance in the combined measure. These explanations may explain the bias in the literature toward using knee extensor strength only when generating indices of upper leg muscle quality. In light of these measurement considerations, the preferential decline

in knee extensor SM and strength relative to the knee flexors, and the fact that the knee extensors are used in power activities that are usually sustained across the lifespan such as climbing stairs, we suggest that the most appropriate index of muscle quality is knee extensor torque per unit SM or lean tissue mass (LTM).

Functional Capability

Aging is associated with changes in body composition (increase in body fat and decreases in muscle and bone mass) which together with a decline in cognitive, visual, and hearing function, sleeping disorders, depression, and increased fatigue lead to a decline in physical function and significantly increases the risk for disability and loss of independence [259]. Muscle strength is a strong predictor of severe mobility limitation, slow gait speed, increased fall risk, risk of hospitalization, and high mortality rate. For example, older adults with low muscle strength have a 2.6-fold greater risk of severe mobility limitation, 4.3-fold greater risk for slow gait speed, and 2.1-fold greater risk of mortality compared to older adults with high muscle strength [260]. The loss of muscle strength in elderly cannot be explained only by the characteristic presence of skeletal muscle atrophy. Several research studies showed that other factors such as changes in central nervous system drive, peripheral nerve dysfunction, alterations in the neuromuscular junction structure and function, fat infiltration, and a number of complex cellular and molecular changes at the level of single muscle fibers impair muscle force generation and power production [261].

The relative effort required to perform functional tasks increases with advancing age [262]. Research designed to report the age-related decline in functional capability, require measures which can distinguish meaningful gradations of capacity and change over a wide range of abilities. Cohorts >50 years provide a challenge in the heterogeneity of their functional capabilities. Test batteries need to be able to reflect activities of daily living (ADL) and yet capture meaningful performance data relevant to the individual. As such there is a paucity of literature to report an estimate of the age-related decline in functional capability as we have done in the previous sections above.

The SPPB [240] is the most commonly employed method of assessing the ability to perform ADL in mobility limited older adults. The battery uses a test of gait speed (6 m), lower extremity function (time taken to rise from a chair 5 times) and balance (semitandem and tandem stands) to make up a 12-point scoring system. The SPPB was validated in 5000 older adults (71 years) and was found to predict nursing home admission. Since then many studies have used the SPPB to report older adult (65 years) physical capability [263–265]. Furthermore, performance in this test battery or components of it have been associated with components of SM and muscle function discussed above.

Although 6–10 m gait speed tests may be considered highly representative of ADL they may suffer from either a floor or ceiling effect. In the case of the floor effect, a frail older adult may not be able to complete five chair rises and therefore cannot attain the minimum test score. Alternatively, in the case of the ceiling effect, the majority of physically active older adults may achieve the maximum test score, meaning the test cannot detect meaningful gradations of capacity and change over a wide range of abilities. For example, recent evidence from Francis et al. group [266] and Glenn et al. study [267] suggest that short (≤10 m) gait speed tests cannot detect change where expected in healthy older (50–70 years) and middle aged (55–64 years) adults respectively. This is largely due to the relative health of both cohorts indicated by a habitual gait speed (1.4 m/s) far in excess of the gait speed suggested to be indicative of disability (<0.8 m/s). Furthermore, the link between muscle mass, strength, and functional capability using these tests may not be as strong in middle-aged or healthy older adults compared to frail or mobility-limited older adults. Buchner et al. [268] reported that the relationship between leg strength and gait speed (15.2 m) was nonlinear. For stronger participants, there was no relationship between strength and gait speed but in weaker individuals

there was. Therefore, small changes in physiological capacity of frail older adults may lead to large changes in functional capability whereas small changes in physiological capacity of strong adults may lead to no change in functional capability assessed in this way.

Tests which can allow participants perform to a greater maximum may be more appropriate to track age-related change in functional capacity prior to disablement. The 6 min walk test (Rikli and Jones [269]) and 30 s chair rise test (Jones et al. [270]) were originally designed to combat the floor effect for i.e. for participants who could not complete a full test e.g. five chair rises. However, the authors report the tests as being capable of detecting difference in functional capability between the seventh, eighth, and ninth decade of life as well as performance differences between those with high and low self-reported physical activity. The construct validity of these tests is underlined by the fact that these data arise from normative data collected on 7183 community dwelling older (60–94 years) adults.

Most recently, we reported the 30 s chair rise test, and a 900 m extended gait speed test as capable of detecting change in functional capability between the sixth and seventh decade in healthy older adults [271]. Furthermore, knee extensor strength corrected for body mass and to a lesser extent muscle quality were associated with functional capability in healthy older women. However, when both tests were used to assess the efficacy of a 12-week progressive resistance training intervention, only the 900 meter gait speed test was responsive to the intervention [272]. The fact that these data and others [242, 246] have identified muscle strength (grip and quadriceps strength) as having stronger associations with functional capability than muscle quality may begin to question the functional significance of muscle quality as a measure in this context. This is a potentially important finding, if confirmed, given the considerable increase in time and expense to measure muscle quality relative to normalising strength to body mass. This does not discount muscle quality as an index as it may be important to understanding physiological changes at the tissue level.

Other test batteries often retain the core physical competencies assessed in the SPPB, while adding modifications in order to try and accommodate a broader range of abilities. The American Alliance for Health, Physical Education, Recreation & Dance (AAHPERD) Functional Fitness (Yaguchi and Furutani [273]) included an extended gait speed test (880 yard walk). Outside of test batteries, the extended gait speed test (Simonsick et al. [274]) and the ten step stair climb power test (Bean et al. [275]) have also been deployed to measure functional capability. None of these tests however, have the normative data of those developed by Rikli and Jones [269]. In order to report functional capability in healthy adults, specifically lower extremity functional capability across the lifespan, researchers may select tests which allow participants to perform to a greater maximum. This would facilitate collection of meaningful performance data in conjunction with laboratory measures of SM and strength. This recommendation is based on studies which intend to measure healthy well-functioning adults that would not have trouble at least in walking for 6 min or 900 m and/or completing chair rises repeatedly for 30 s. In this population, extended tests may provide meaningful information on the relative effort required to go for a walk or spend a day in a town or city. These are activities which may be impaired prior to a reduction in the ability to complete basic tasks such as rising from a chair or walking 10 m and therefore may provide a more sensitive estimate of functional decline in healthy aging.

Muscle and Inactivity/Bed Rest

Whether the age-related alterations are directly due to the aging process or mainly to disuse, is an issue the requires further studies. Indeed, with advanced age, the level of physical activity decreases and may be responsible, at least partially, for the alteration of muscle fiber quality and for muscle wasting/weakness in general. Studies have shown that the incidence of sarcopenia in both older men and women is lower in those that have a higher level of physical activity

[276]. The current experimental human model of physical inactivity is strict bed rest, 24 h a day, in a head-down(−6) position [277]. Studies aiming at simulating micro-gravity/space flight have used this model extensively. Short studies of 2, 8, and 12 days of bed rest have not reported significant effects on muscle mass or strength [278]. On the other hand, longer periods of rest (35 or 90 days) were found to induce a large decrease in force and power generating capacity of muscles of the lower limbs [279, 280]. A major contributor to such impairments is muscle atrophy affecting both type I and II fibers [281] (Muscle fiber types can be broken down into two main types: slow twitch (Type I) muscle fibers and fast twitch (Type II) muscle fibers. These fast twitch fibers can be further categorized into Type IIa and Type IIb fibers, which are also known as "fast twitch oxidative" and "fast twitch glycolytic," respectively). Atrophy is defined as a decrease in size due to a loss of organelles, cytoplasm, and/or protein. Muscle size is determined by the delicate balance between protein synthesis and degradation. Bed rest studies tend to demonstrate that proteolysis pathways are upregulated as attested by the increased activation of the ubiquitin–proteasome pathway and autophagy after 35 days of rest. Similar to the situation in sarcopenia, long periods of bed rest lead to a loss of strength exceeding the loss of mass. This suggests that a change in muscle quality occurs. The reduction in quality cannot be explained on the basis of fat or connective tissue infiltration [282] and is probably due to an alteration of the quality of the contractile elements at the single fiber level. Indeed, force, velocity, and power are all severely affected in both type I and II fiber cells [281] with bed rest. The molecular mechanisms underlying these changes is likely to include the disruption of actin–myosin cross-bridges caused by unusual posttranslational modifications of myosin such as increased phosphorylation and O-N-acetyl glucose aminylation [279]. It is important to point out that, despite these similarities, there are differences between sarcopenia and bed rest. For instance, a shift toward a faster muscle fiber type composition (increased type II to type I fiber ratio) is commonly reported after long periods of bed rest [281] whereas the opposite tends to happen during the aging process. It appears that physical inactivity results in complex changes that may be influenced by environmental conditions.

Muscle Health in Disease

Muscle plays a central role in whole-body protein metabolism by serving as the principal reservoir for amino acids to maintain protein synthesis in vital tissues and organs in the absence of amino acid absorption from the gut, and by providing hepatic gluconeogenic precursors. Furthermore, altered muscle metabolism plays a key role in the genesis, and therefore the prevention, of many common pathologic conditions and chronic diseases. The work done by Keys et al. [9] concluded that in human starvation, the depletion of muscle mass is the main cause of death. The response of muscles to diseases was reviewed earlier in an article published by Wolfe on the underappreciated role of muscle in health and disease [2]. The response of muscles to illness can be stratified into whether it was acute or chronic illness:

Muscles and the Acute Response to Critical Illness

The stressed state, such as that associated with sepsis, traumatic injury, or, advanced cancer imposes increased requirement for amino acids than does fasting [283]. This extra demand of amino acids can be provided from muscle protein breakdown. Physiologic responses necessary for recovery may include the accelerated synthesis of acute phase proteins in the liver, synthesis of proteins involved in immune function, and synthesis of proteins involved in wound healing. The demands for precursor amino acids for the synthesis of these proteins are significant. For instance, quantitative studies of wound healing suggest that a protein intake of >3 g protein/kg/day is required to provide the necessary precursors for the synthesis of proteins required for

normal healing of a burn injury to 50% of the body [284]. Coupled with the continued amino acid requirement of most tissues and accelerated requirements for liver and immune cells, actual utilization of protein in severely burned individuals may exceed 4 g protein/kg/day. This represents four times or more the normal daily intake of protein. In concordance, stimulation of hepatic gluconeogenesis in stressed states is another state where there is increased demand for amino acids [285]. To meet these increased demands, net breakdown of muscle protein is stimulated to provide abundant amino acids. This response is not readily reversed, even by aggressive nutritional support. Not surprisingly, individuals with limited reserves of muscle mass respond poorly to stress. For example, survival from severe burn injury is lowest in individuals with reduced lean body mass [286]. Loss of muscle mass is also known to be detrimental to survival from cancer. For example, in patients with lung cancer receiving radiation therapy, the amount of body protein (measured by in vivo neutron-activation analysis) predicted recurrence. In those in whom body protein decreased, recurrence and, ultimately, survival was worse than in patients who were able to maintain or increase muscle mass [287]. Although it is possible that muscle loss occurs because of impaired appetite and, consequently, reduced protein intake make those patients more susceptible to recurrence; the relation between muscle mass and recurrence is nonetheless striking.

While muscle mass plays a key role in recovery from critical illness or severe trauma, muscle strength and function are central to the recovery process. The extent and duration of the debilitation resulting from critical illness is dramatic; <50% of individuals employed before entering an intensive care unit return to work in the first year after discharge [288]. Extensive losses of muscle mass, strength, and function during acute hospitalization causing sustained physical impairment were likely contributors to the prolonged recovery. If there is a preexisting deficiency of muscle mass before trauma, the acute loss of muscle mass and function may push an individual over a threshold that makes recovery of normal function unlikely to ever occur. For this reason, >50% of women older than 65 years who break a hip in a fall never walk again [289].

Muscles Role in Chronic Diseases

Earlier studies revealed that chronic diseases related to poor lifestyle behaviours account for more than two-thirds of deaths [290]. Population-based studies assess diet, vital parameters as well as measure indices such as body mass index, blood lipids, and bone biomarkers to predict risk of disease. On the other hand, muscle mass, physical or metabolic function, are rarely evaluated to identify the role of muscles in these conditions. In contrast, alterations in muscle play an important role in the most common diseases and conditions. Outcomes of population-based studies revealed that heart disease and cancer are considered among the most prevalent chronic diseases reported [290]. Both cardiac failure and cancer are often associated with rapid and extensive loss of muscle mass, strength, and metabolic function (cachexia). With cardiac and cancer cachexia, the loss of muscle mass is an important determinant of survival [287, 291]. Sarcopenia, the progressive loss of muscle mass and function that occurs with aging, is a widespread syndrome that has a devastating effect on quality of life and ultimately survival [292]. Progressive sarcopenia is ultimately central to the development of frailty, an increased likelihood of falls, and impairment of the ability to perform activities of daily living. The major endpoint of severe sarcopenia is loss of quality of life.

Obesity and Muscle

While the central role of muscle in syndromes such as sarcopenia and cachexia, which are defined – at least in part – by loss of muscle mass and strength, has been thoroughly assessed, the potential role of muscle in the prevention of obesity is less well appreciated. The development of obesity results from an energy imbalance over a prolonged time, which means that energy intake

exceeds energy expenditure. An impact on energy balance can therefore be achieved by altering either energy intake or energy expenditure. Total energy expenditure is the sum of resting energy expenditure, the thermic effect of food, and the energy expenditure related to activity. Under most circumstances, resting energy expenditure is the largest component of total energy expenditure [293]. The energy expenditure related to muscle metabolism is the only component of resting energy expenditure that might vary considerably. The resting metabolic requirements of splanchnic tissues, brain, and skin vary slightly under normal conditions because of relatively constant tissue mass and protein turnover rates [294]. In contrast, large variations in muscle mass are possible, and the rate of muscle protein turnover (i.e., muscle protein synthesis and breakdown) may vary as well. The synthesis and breakdown of muscle protein are principally responsible for the energy expenditure of resting muscle. In considering the magnitude of energy imbalances leading to obesity, it is reasonable to view the situation over long periods of time, because obesity often develops over months and even years. A difference in energy expenditure of 100 kcal/day translates to about 4.7 kg fat mass/year. Consequently, the maintenance of a large muscle mass and consequent muscle protein turnover can contribute to the prevention of obesity [295–297].

Regardless of the energetics of muscle protein turnover, obesity can develop if energy intake is great enough. Obesity is clinically characterized by a disproportionate increase in fat mass. Less appreciated is the fact that muscle mass in obesity is also increased [298] (Fig. 2.1). Although the energy expenditure associated with larger muscle mass in obesity is insufficient to offset the excessive energy intake, the expanded muscle mass can be capitalized on to facilitate weight loss. Stimulation of muscle protein turnover in the setting of increased muscle mass could have a significant effect on resting energy expenditure and, thus, energy balance. This can potentially be accomplished through nutrition, because increasing amino acid availability, increases muscle protein turnover [299]. Furthermore, the energy to provide the ATP required for muscle protein turnover is largely derived from the oxidation of fat, because this is the preferred energy substrate of resting muscle [300]. Thus, when muscle protein synthesis was increased by testosterone injection in hypogonadal elderly men, the increase in lean body mass over time was accompanied by a decrease in fat mass [301]. Extending this notion to the situation of a hypocaloric diet for weight loss, a high percentage of protein in the diet would therefore be expected to effectively repartition nutrient deposition from fat to muscle. Recent reports of improved body composition during weight loss with high-protein, hypocaloric diets support the notion of repartitioning of nutrient intake when protein turnover is stimulated [302]. It has yet to be determined whether the same repartitioning occurs when the proportion of protein intake is increased in the circumstance of energy balance (i.e., caloric intake = caloric expenditure), but the same rationale should apply [2].

Muscle in Insulin Resistance and Diabetes

Type II diabetes develops in stages. The onset of the process involves a decreased ability of insulin to stimulate muscle to clear glucose from the blood. The so-called insulin resistance of muscle is a hallmark of the metabolic syndrome, which is considered to be a precursor of frank diabetes [303]. Insulin secretion is amplified in the initial phase of insulin resistance to enable muscle to clear glucose from plasma adequately to maintain normal glucose concentrations. As the metabolic syndrome progresses to diabetes, increased insulin secretion is unable to effectively counterbalance the ineffectiveness of insulin to stimulate muscle glucose uptake, and glucose intolerance ensues. Only in the later stage of diabetes does the pancreas lose the ability to secrete extra insulin in response to hyperglycemia. Disruption of the normal rate of muscle glucose uptake by muscle is thus central to the onset and progression of diabetes [304].

A relative increase in body fat is an appealing explanation for the decline in insulin sensitivity in both obese and elderly individuals. A higher percentage of body fat generally translates to a higher rate of appearance of free fatty acids in plasma [305], and a relation between an elevated availability of free fatty acids and insulin resistance has been recognized since the "glucose–fatty acid cycle" was proposed by Randle et al. [306] in 1963. However, over the past few years it has become evident that changes in the metabolic function of muscle itself plays a more direct role in the genesis of insulin resistance than previously appreciated. The central thesis of the glucose–fatty acid cycle is that elevated plasma free fatty acids concentrations limit glucose uptake in muscle by inhibiting the oxidation of glucose. Thus, according to this theory, the genesis of insulin resistance lay entirely with the increased availability of free fatty acids, and the muscle responded normally to that signal to limit glucose uptake and oxidation. However, other studies [307, 308] have shown that the glucose–fatty acid cycle was inadequate to explain regulation of muscle glucose uptake in a physiologic setting. Rather, alterations in metabolic function within the muscle are more likely at the heart of the genesis of insulin resistance.

Studies carried out using newer applications of magnetic resonance spectroscopy to quantify triacylglycerol deposition in muscle have revised thinking about possible mechanisms by which alterations in lipid metabolism may affect insulin sensitivity in muscle. Triacylglycerol deposition in muscle was reported to be associated with insulin resistance in a variety of circumstances [309–312], whereas obesity without insulin resistance is not associated with increased triacylglycerol deposition in muscle. Increased triacylglycerol deposition in muscle has been interpreted to be an indicator of dysfunctional muscle lipid metabolism that is likely related to insulin resistance by mechanisms independent of total body fat mass [313]. An accumulation of intracellular triacylglycerol results from an imbalance between tissue fatty acid uptake and fatty acid disposal. Fatty acid uptake by muscle is directly proportional to delivery in a wide variety of circumstances [300]. Although fatty acid delivery to muscle is generally elevated in obesity (because of a large fat mass), triacylglycerol deposition in muscle is not elevated in obese subjects who are not insulin resistant [308]. It is becoming clear that, rather than an increased delivery of free fatty acids to muscle, it is more likely that impaired disposal via oxidation is the principal basis for accumulation of triacylglycerol deposition in muscle and other potentially active products of fatty acids. In vivo capacity to oxidize fatty acids is reduced in insulin-resistant individuals. This deficiency may be more evident during exercise [314]. It is likely that this deficiency in fatty acid oxidation is due to a decline in mitochondrial oxidative function [315]. There are many potential causes of decreased mitochondrial oxidative capacity, including genetics; a lack of physical activity is most likely a major factor in patients with type 2 diabetes. Mitochondrial oxidative capacity is decreased by inactivity [316], and as little as a single bout of exercise [thereby stimulating intramuscular triacylglycerol oxidation] can transiently reverse insulin resistance [317].

Regardless of the specific intracellular mechanisms at the molecular level, it is clear that insulin resistance is not simply the result of increased fat mass and release of free fatty acids into plasma at an accelerated rate, with the muscle responding to elevated plasma free fatty acids concentrations. Rather, alterations in the metabolic function of muscle are central to the development of insulin resistance and ultimately diabetes [318, 319].

Muscle and Osteoporosis

Mechanical force on bone is essential for modeling and remodeling, processes that increase bone strength and mass [320]. Whereas body weight and weight-bearing exercises provide a direct mechanical force on bones, the largest voluntary loads on bone are proposed to come from muscle contractions. Correlations between grip strength and bone area, bone mineral content, and bone mineral density in both healthy athletes [321] and stroke patients [322] support the notion that mus-

cle contractions play a significant role in bone strength and mass. Even the correlation between body weight and bone mass [320] can be explained on the basis of the force exerted on bone by muscle contractions, in that it takes more force per unit area to move heavier bodies. Furthermore, changes in bone mass and muscle strength track together over the life span. Although it is debatable whether it is muscle strength or simply muscle mass that is important in determining bone strength and mass, it is significant that skeletal muscle mass was reported to correlate positively with bone mineral content and bone mineral density in the Mediterranean Intensive Oxidant Study (a prospective study of osteoporosis and its determinants in men) [323]. Men with the least skeletal muscle mass also had increased risks of falls due to impaired static and dynamic balance, presumably at least in part because of a decrease in muscle strength. Thus, maintenance of adequate bone strength and density with aging is highly dependent on the maintenance of adequate muscle mass and function. The relative importance of muscle compared with normal hormonal and nutritional effects on bone may be argued. Because some of the factors, such as dietary protein, insulin growth factor, and testosterone [324], that are proposed to affect bone directly also affect muscle, it is difficult to distinguish in vivo whether these factors directly affect bone if their effects on bone are the consequence of increased muscle strength, which puts greater mechanical force on bone. Regardless, the importance of muscle in prevention of osteoporosis is clear.

Muscle and Kidney Diseases

In individuals with chronic kidney disease (CKD), systemic inflammation, transient catabolic comorbidities, nutrient losses during dialysis, endocrine abnormalities (such as resistance to insulin, growth hormone, and insulin-like growth factor), hyperglycemia, hyperparathyroidism, and loss of blood during hemodialysis are prevalent. Additionally, reduced protein diets of 0.6–0.8 g/kg/day may be recommended to patients, who are not on dialysis. These factors contribute to muscle wasting, which is usually reported under the auspices of protein-energy wasting [325].

In individuals undergoing dialysis, old age, comorbidities, inactivity, low albumin and inflammation (C-reactive protein) were reported to be associated with low handgrip strength but not with low muscle mass measured by DXA scanning [326]. In the same study, body composition alone was not associated with poorer survival; however, low strength alone (hazard ratio [HR] 1.98, 95% confidence interval [CI]: 1.01–3.87, $p = 0.04$) or in combination with low muscle mass (HR: 1.93, 95% CI: 1.01–3.71, $p = 0.04$) was more strongly associated with higher mortality. These findings suggest that strength and muscle mass – while highly related – are two entities differently affecting outcomes in patients with renal impairment [327].

Approaches to Management of Muscle Loss?

There are three potential approaches to maintaining or increasing muscle mass and function: hormonal therapy, exercise, and nutrition.

Hormonal Therapy

There are three general approaches to hormone therapy: (1) Hormones can be given to replace a deficiency, (2) hormones can be given to raise the concentration above the normal value, and (3) agents can be given to block hormone action by either reducing the rate of secretion or blocking their action. All approaches may have a role in maintaining or increasing muscle mass. Replacement of testosterone in hypogonadal elderly men has successfully increased both muscle mass and strength [301]. Administration of insulin at rates sufficient to raise plasma concentrations above the naturally occurring value has been shown to have an anabolic effect on muscle in severely burned patients [328]. In the stressed state, the catabolic hormones cortisol and epi-

nephrine are counterregulatory hormones, the effects of which can be minimized by either blocking receptors, in the case of epinephrine (53), or blocking secretion, in the case of cortisol [329]. Thus, there is clearly a role for hormone therapy in maintaining and increasing muscle mass and function. New advances in synthetic hormones provide promise for expanded applications in the future. For example, the synthetic steroid oxandralone stimulates muscle growth, possibly without the same magnitude of androgenizing effects of testosterone [330]. At the same time, there are limiting factors and dangers of hormonal therapy caused by unexpected, unwanted, and often unrecognized complications. For example, it is well known that large doses of testosterone increase muscle mass and function, particularly when given in conjunction with exercise training. However, many undesirable side effects may accompany the use of testosterone or any of its many synthetic analogues, thereby limiting its clinical use on a widespread or unsupervised basis [2].

Exercise

Exercise improves muscle function and, in some circumstances, increases muscle mass as well. Improved function may not be limited to the contractile properties of muscle but also muscle metabolism. For example, exercise training improves insulin sensitivity [331]. It appears that exercise is more effective at preventing loss of muscle than of restoring lost muscle mass. Whereas exercise interventions in individuals with sarcopenia can successfully improve functionality [332], the reversal of the loss of muscle mass with aging has been more problematic. Further gains in physical strength and function resulting from exercise programs are often less effective in the elderly than would be expected in younger subjects undergoing the same training protocol [333]. The diminished responsiveness of frail elderly to the beneficial effects of exercise probably stems from the restrictions imposed by the initial sarcopenia or lack of muscle mass and strength. Elderly individuals, particularly women, are often too weak to perform the intensity of exercise necessary to induce the same magnitude of physiologic adaptations that occur in younger subjects. Rather than initiate practices to reverse sarcopenia, it would be more effective to prevent its development. Progressive loss of muscle mass [334] and strength [335] occurs throughout adult life, and in middle age the rate of loss is accelerated and maintained until old age [336, 337]. Intervention in middle age or younger ages is therefore necessary to offset the deleterious effects of sarcopenia in old age.

In his article [2] on the underappreciated role of muscle in health and disease, Wolfe reported that there is little debate regarding the beneficial effects of exercise on muscle, whether it to maintain or attempt to restore muscle mass and function. However, the most practical issue from a public health standpoint is motivation. In that light, it is important to identify the minimal exercise regimen to achieve desired results, including maximizing the interactive effects between nutritional intake and exercise on muscle protein synthesis. Furthermore, the desired result should be identified in terms of outcomes on muscle mass, strength, and metabolic function, as opposed to traditional measures of exercise training, such as the maximal oxygen consumption, which have little direct relation to health outcomes.

Nutrition

There has been a great debate on what are the end points to be targeted and relied on when the recommendations for adult protein intake are considered. It sounds logic that maintenance of muscle mass and, in particular, optimization of the physical and metabolic functions of muscle are to be considered in formulating dietary guidelines. However, available evidence to directly support this notion is limited because of the lack of studies specifically addressing this postulation. Nevertheless, there are ample relevant studies of the metabolism of muscle protein which support the concept that increasing protein intakes above current guidelines would benefit muscle. Muscle protein is directly affected by

protein intake in the diet. High dietary protein intakes increase protein synthesis by increasing systemic amino acid availability [338]. The amino acids absorbed as a result of the digestion of protein stimulate the synthesis of muscle protein and promote muscle protein synthesis in a dose-dependent way [339–341]. This metabolic response is reflected physiologically. For example, children given high protein intakes grow faster [342] and have greater muscle mass [343]. The anabolic effect of exercise is amplified by amino acids or protein [344, 345]. Protein intake above the currently recommended estimated average requirement of 0.66–0.8 mg/kg/day stimulates the fractional synthetic rate (A fractional synthetic rate (FSR) is the rate at which a precursor compound is incorporated into a product per unit of product mass [346]. The metric has been used to estimate the rate at which proteins are synthesized in the human body). The fractional synthetic rate (FSR) of muscle protein is about 0.075%/h; and muscle fractional synthetic rate has been shown to be positively correlated with strength [295]. Although the basis for the relation between fractional synthetic rate and strength is not certain, it is likely that a higher muscle protein turnover rate replaces older myofibrillar proteins with newer and better functioning proteins. Both muscle mass and strength are improved by increased availability of amino acids, even in the complete absence of activity in healthy young subjects confined to bed rest [246].

Another approach to determine the recommended protein intake for adults, has been adopted in the Dietary Reference Intakes, which relied entirely on a meta-analysis of nitrogen balance measures [337]. Nitrogen is a fundamental component of amino acids, which are the molecular building blocks of protein. Therefore, measuring nitrogen inputs and losses can be used to study protein metabolism [347]. Positive nitrogen balance is associated with periods of growth, hypothyroidism, tissue repair, and pregnancy. This means that the intake of nitrogen into the body is greater than the loss of nitrogen from the body, so there is an increase in the total body pool of protein. Negative nitrogen balance is associated with burns, serious tissue injuries, fevers, hyperthyroidism, wasting diseases, and during periods of fasting. This means that the amount of nitrogen excreted from the body is greater than the amount of nitrogen ingested. A negative nitrogen balance can be used as part of a clinical evaluation of malnutrition [348]. Nitrogen balance is the traditional method of determining dietary protein requirements [349] Determining dietary protein requirements using nitrogen balance requires that all nitrogen inputs and losses are carefully collected, to ensure that all nitrogen exchange is accounted for [350].

However, although the use of nitrogen balance may well be appropriate for establishing the nitrogen or amino acid requirements necessary to prevent deficiency, yet, it is likely inadequate to establish intakes that are optimal for maximizing muscle mass, strength, and metabolic function. This is because individuals can adapt to suboptimal protein intakes by reducing nitrogen excretion, for example, in extreme starvation individuals can maintain nitrogen balance until shortly before death by greatly reducing their nitrogen excretion [351, 352]. Thus, there is no necessary relation between nitrogen balance and any variable of muscle mass or function.

The purported limited effectiveness of nutrition could be due to the great heterogeneity in the type and duration of dietary supplement protocols. The most recently published Dietary guidelines for Americans; the recommendation for the meats, poultry, and eggs subgroup in the Healthy U.S.-Style Eating Pattern at the 2000-calorie level is 26 ounce-equivalents per week. This is the same as the amount that was in the primary USDA Food Patterns of the 2010 Dietary Guidelines. For those who eat animal products, the recommendation for the protein foods subgroup of meats, poultry, and eggs can be met by consuming a variety of lean meats, lean poultry, and eggs. Choices within these eating patterns may include processed meats and processed poultry as long as the resulting eating pattern is within limits for sodium, calories from saturated fats and added sugars, and total calories.

In conclusion, the topics of muscle and bone health as well as bone–muscle interactions has become of interest for basic, clinical, and transla-

tional scientists because of the realization of the implications of this emerging field of research. The concept that bone and muscle cells communicate both at the biochemical and molecular levels, as well as through direct mechanical interactions, are leading to new insight into how bone and muscles work together in health and disease. With life expectancy projected to surpass the centenary mark, and the realization that aging impacts on both bone and muscles, the twin bone–muscle diseases such as osteoporosis-sarcopenia are expected to exert additional, not yet fully understood, consequences on public health and the economy. Approaches to manage loss of the muscle mass are of vital importance to optimize outcomes of management. There is a considerable need to counteract the loss of muscle mass, strength, and physical function. Possible dietary interventions might include protein/amino acid formulas, creatine, and micronutrients. Exercise typically consists of strength or aerobic activity in a supervised or home-based intervention.

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Osteosarcopenia

3

Yasser El Miedany

Introduction

Osteosarcopenia is a newly described syndrome that describes the coexistence of osteoporosis and sarcopenia, two chronic musculoskeletal conditions associated with aging. Osteoporosis/osteopenia, is as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture. Sarcopenia is defined as a syndrome characterized by progressive and generalized loss of skeletal muscle mass, strength and function, with a risk of adverse outcomes such as physical disability, poor quality of life and high mortality. Both conditions often coexist in a frail subset of the elderly population, leading to significantly worsened outcomes than seen in either condition alone [1, 2].

The etymology of the term sarcopenia comes from the Greek words sarx, meaning muscle, and penia, meaning loss and refers to the aged-related progressive and generalized loss of skeletal muscle mass along with impaired muscle function (strength or physical performance) that characterizes this condition, which is also associated with negative impact on activities of daily living, frailty, and increased risk of falls [2]. Osteopenia/osteoporosis is a systemic bone disease in which the bone microarchitecture deteriorates and the bone mineral density (BMD) reduces, increasing the bone fragility and the risk of fractures—even after minor falls. The differentiation between osteopenia and osteoporosis is mostly based on the results of the BMD in which subjects are considered osteopenic when BMD is between −1 and−2.5 SD whereas BMD below −2.5 SD is considered as osteoporosis [3].

Bone and muscle are interconnected not only because of their direct contact but also chemically and metabolically. In addition, specific pathophysiological findings, such as fat infiltration and alterations in stem cell differentiation, are common to both diseases thus suggesting that sarcopenia and osteoporosis are closely linked. As osteoporosis represent wasting of the bones, while sarcopenia represent wasting of the muscles, therefore, the term osteosarcopenia has been proposed to describe individuals suffering from both diseases, which contributes to a higher risk of falls, fractures, and poorer quality of life [4, 5]. Therefore, fracture prevention approaches should include not only bone mineral density evaluation but also assessment of muscle mass and function to evaluate whether sarcopenia is also present. Consequently, in the presence of osteosarcopenia, planned interventions should therefore address the strength of not only the bone but also the muscle.

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This chapter starts by discussing osteosarcopenia and the impact of aging on the human body and the potential mechanisms of age-related sarcopenia. It will then highlight the biochemical communication between muscle and bone and how muscle and bone act as an endocrine organ. The chapter then discusses osteosarcopenia is standard practice, presenting a case finding practical algorithm as well as categories of sarcopenia and sarcopenia-like conditions. This is followed by tools of diagnosis and treatment protocols of osteosarcopenia. The chapter concludes by presenting patient-centered care approach for osteosarcopenia patients.

Aging Human Body

Aging affects almost all physiological processes, but changes in body composition and body phenotype are most observable (Fig. 3.1). There is a 5–25% decrease in basal (resting) metabolic rate, leading, most notably, to gain in body weight and body fat, even with the unchanged dietary (energy) intake and exercise habits [6]. For example, for most individuals, body fat starts gradually increasing between 20–25 years of age, until about 65 years [7]. Even more important is the redistribution of fat to the abdominal area and visceral organs, as well as its infiltration into muscle and bone.

The infiltration of fat into bone marrow is not necessarily related only to aging, but occurs early in life, as well as in anorexia and during starvation [8, 9]. On the contrary, both muscle and bone tissues decrease with age (Fig. 3.2). Muscle mass peaks at the age of approximately 30 years and then gradually declines. There is about 20–40% decrease in muscle mass by the age of 70 years, leading to sarcopenia [10]. However, it is important to distinguish between *sarcopenia* and *dynapenia*, the latter being the loss of muscle strength and not necessarily always proportionally accompanied by muscle mass loss [2, 11].

These declines are more pronounced in women than in men [12]. Aging heavily affects bone, inducing changes in bone structure – progressive decrease in trabecular thickness and increase in cortical porosity, loss of bone mass, and increase in bone turnover. Consequently, bone mineral density (BMD), which is used as a proxy for the assessment of fracture risk, declines with age starting at about 50 years of age [13]. Women may lose up to 20% of bone mass during the 5–7 years following menopause. Afterward, the loss continues at the rate of 0.5–1% per year (unless there is some adverse underlying condition or immobilization; when the rate is higher) (National Osteoporosis Foundation, available at: https://www.nof.org/prevention/general-facts/what-womenneed-to-know/). Men lose bone mass with

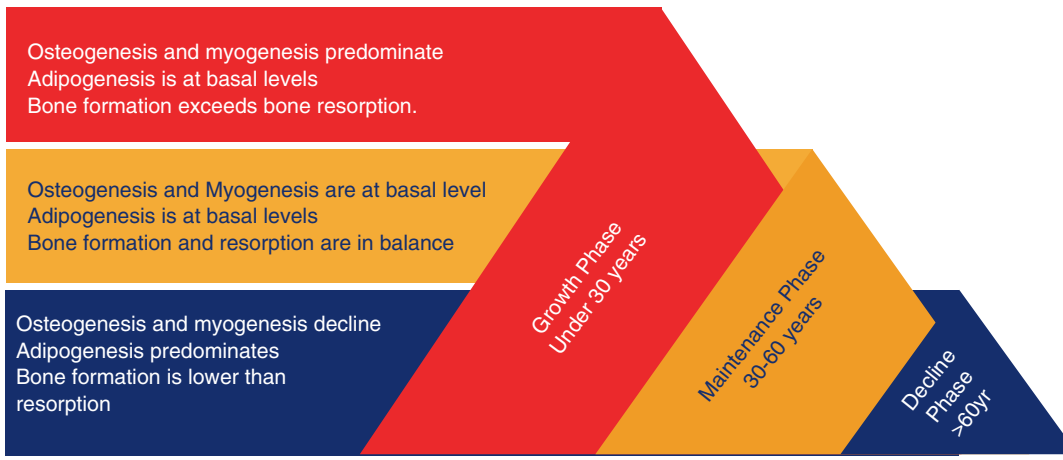

Fig. 3.1 Impact of aging on body composition. Comparison of the changes in bone mass, muscle mass, and fat mass at different age groups (<30-years old, 30–60 years old, > 60-years old)

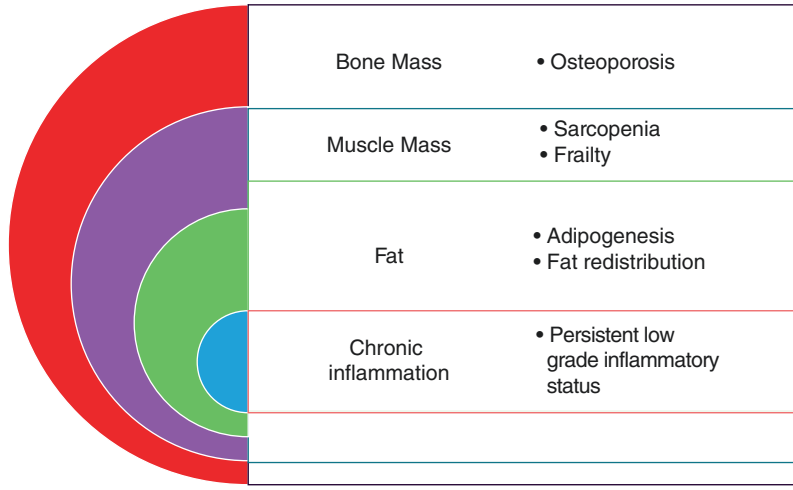

Fig. 3.2 Changes in bone, muscle, and fat tissues with increasing age, and accompanying increase in low-grade chronic inflammation. Bone mass: osteoporosis; muscle mass: sarcopenia; muscle strength and functionality: frailty; fat mass: adipogenesis (fat redistribution), low-grade chronic inflammation: persistent low-grade inflammatory status even when other illnesses are not present

age too, but the loss starts later in life and persists at about 0.5–1%/year (National Osteoporosis Foundation, available at: https://www.nof.org/prevention/general-facts/just-formen/).

Similar to bones, peak skeletal muscle mass is achieved in young adulthood. After 45 years of age, skeletal muscle mass progressively declines both in men as well as women, particularly in the lower body [14]. Epidemiological studies revealed that the prevalence of sarcopenia was up to 1–29% (up to 30% in women for older adults living in the community, 14–33% (up to 68% in men) for those living in long-term care institutions and 10% for those in acute hospital care. In general, the prevalence of sarcopenia increased with age [15]. In the European Male Ageing Study, which examined a population of 518 men aged 40–79 years with a mean follow-up of 4.3 years, appendicular lean mass started to decrease from 50 years of age, but mean annual loss was significantly greater in subjects older than 60 years. Men significantly lost gait speed and grip strength after 70 years [16].

Aging is associated with an increase in fat mass (Fig. 3.3): many tissues, including bone marrow and muscle, are gradually replaced by fat; this process takes place in men mainly after the age of 70, while in women it starts earlier with menopause and loss of estrogen. With age, muscle worsens its contractile performances due to the reduction of neuronal signaling and cell recruitment, and slower fiber regeneration [17].

Potential Mechanisms of Age-Related Sarcopenia

A variety of factors and pathways are involved in the pathogenesis of sarcopenia, such as, environmental causes, endocrine problems, motor neuron loss, activation of inflammatory pathways, and reductions in satellite cell counts [15]. Moreover, recent research suggests mitochondrial dysfunction and the activation of apoptotic signaling are critical aspects of the pathogenesis of age-related sarcopenia. Potential mechanisms of age-related sarcopenia were reviewed in a recent article published by Yoo et al. [18]. This section will focus on potential causes of age-related sarcopenia based on the information reported in that article.

Mitochondrial Reactive Oxygen Species and Mitochondrial Dysfunction

Mitochondrial reactive oxygen species (mtROS) is closely related to oxidative stress in aging skeletal muscle and is a major cause of age-induced sarcopenia. The accumulation of mitochondrial ROS in aging skeletal muscle leads to tissue degradation, skeletal muscle atrophy, muscle dysfunction, and increases in fibrous tissue [19]. MtROS production is associated with mitochondrial DNA (mtDNA) mutations induced by oxi-

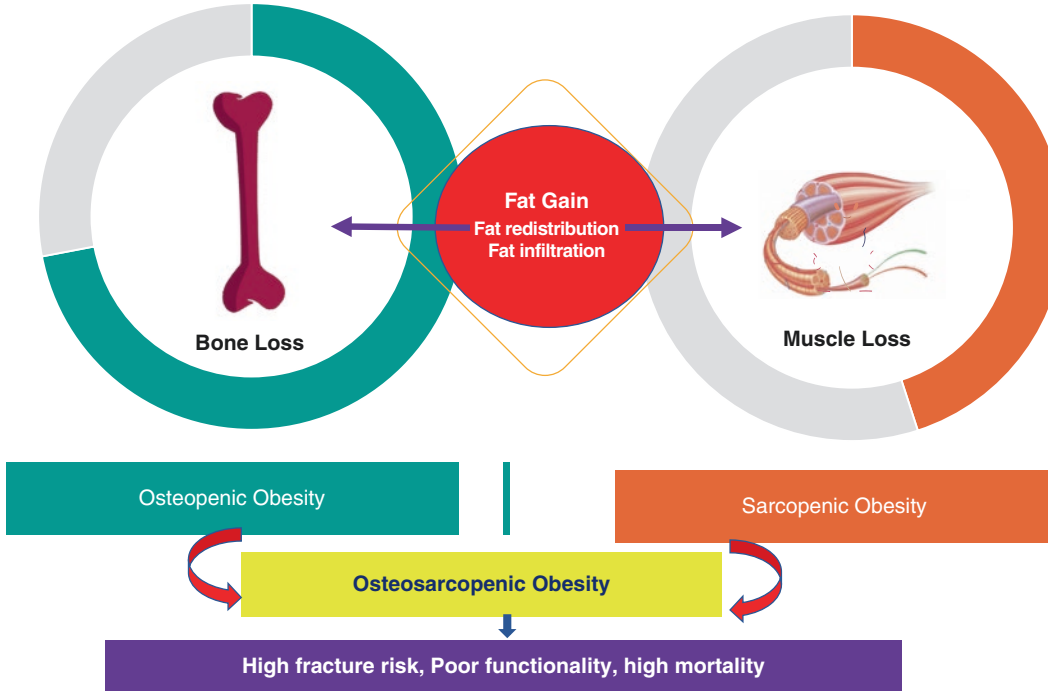

Fig. 3.3 Aging, bone, muscle, and fat. The path of bone, muscle, and fat tissues changes with aging leading to osteosarcopenic obesity and its consequences

dative stress and these mutations result in defective electron transport chain (ETC) components. The incorporations of defective subunits into the ETC disrupts oxidative phosphorylation, reduces ATP synthesis, and further increases ROS production [20]. Wanagat et al. [21] reported muscle fibers with mtDNA deletions displayed electron transport system abnormalities and fiber atrophy. On another front, Hiona et al. [22], showed rates of mitochondrial respiration and ATP production were dramatically lower in the skeletal muscles of mtDNA mutant mice. Consequently, age-induced mtROS, mtDNA mutation, and mitochondrial dysfunction are considered potential causes of sarcopenia [20].

Mitochondrial Apoptosis

Apoptosis is a highly programmed form of cell death that can be characterized by cell fragmentation, loss of muscle fibers, and muscle atrophy in skeletal muscle. Mitochondria play a major role during apoptosis, and mitochondrial dysfunctions and mtROS trigger the initial events of mitochondria-mediated apoptosis by causing the release of proapoptotic proteins into cytosol [23]. Imbalance between pro-apoptotic protein (Bax) and anti-apoptotic protein (Bcl-2) in mitochondria induces mitochondrial permeability transition pore (mPTP) opening and the release of cytochrome c from mitochondria to cytosol, which then binds to apoptotic protease-activating factor-1 (Apaf-1) and pro-caspase 9, activates caspase-3, and eventually causes DNA fragmentation [19, 23]. In addition, apoptosis is also triggered by a caspase-independent pathway whereby endonuclease G and apoptosis-inducing factor (AIF) directly trigger DNA fragmentation in mitochondria [24]. Previous studies have presented evidence that mitochondrial apoptosis is induced in senescent skeletal muscle. Song et al. [25] reported the expression of Bax protein is elevated and the expression of Bcl-2 is diminished in senescent skeletal muscle, and similarly Gouspillou et al. [26] found mPTP was more sensitive in vastus

lateralis muscles of older men. Moreover, Siu et al. [27] showed dramatic increases in AIF contents and apoptotic DNA fragmentation in gastrocnemius muscles of aged rodents. Thus, mitochondria-mediated apoptosis appears to be a major cause of age-induced sarcopenia.

Mitochondrial Dynamics

Function and structure of skeletal muscle fibers are mainly affected by mitochondrial dynamics and morphology (shape and size), which are both induced by intracellular and extracellular signals [28]. These changes in the mitochondrial dynamics and morphologies are controlled by continuous fusion and fission. Mitochondrial fusion can compensate for mitochondrial impairment, whereas mitochondrial fission can preserve function by separating dysfunctional mitochondria from healthy mitochondria. Furthermore, impaired mitochondria may fail their fusion process by inactivating fusion or activating fission machineries and thus prevent damaged mitochondria from being reincorporated into the healthy mitochondrial network [29]. Thus, mitochondrial dynamics not only determines the shapes of intracellular organelles but also has substantial effects on mtDNA regulation and mitochondrial function. Dynamin-related guanosine triphosphatases, optic atrophy 1 (OPA 1), and mitofusin 1 (Mfn 1) and its paralog mitofusin 2 (Mfn 2) [28] have been shown to be involved in mitochondrial fusion. Mfn 1 and Mfn 2 in the outer mitochondrial membrane tether adjacent mitochondria, whereas OPA 1 in the inner mitochondrial membrane mediates inner mitochondrial membrane fusion [30]. Westermann identified the proteins involved in mitochondrial fission as dynamin-related protein 1 (Drp 1) and fission protein (Fis 1) [31]. Imbalances of mitochondrial dynamics negatively affect mitochondrial homeostasis and function, and it has been recently reported that in skeletal muscle these imbalances induce senescence and muscle atrophy. For example, Chen et al. [32] reported that deletion of Mfn 1 and Mfn 2 led to mtDNA mutation, and that accumulations of mtDNA mutations resulted in mitochondrial dysfunction and muscle atrophy. In addition, Romanello et al. [33] observed overexpression of Drp 1 and Fis 1 triggered mitochondrial fragmentation and dysfunction, activated mitochondrial autophagy (mitophagy), and caused muscle fiber atrophy.

Mitochondrial Autophagy

Mitophagy is type of autophagy that results in the removal of unnecessary or impaired mitochondria. Mitophagy usually begins when membrane potential in skeletal muscle is lost because of aging and is preceded by mitochondrial fission. Recently, mitophagy in skeletal muscle has received greater research attention, especially in the context of muscle atrophy [34]. Several authors have suggested that mitophagy dysfunction may not be properly utilized due to aging, considering observations of reduced mitochondrial biogenesis and continuous accumulations of damaged organelles. For example, it has been reported the expressions of autophagy related genes, such as, LC3, Atg7, p62, Beclin 1, Bnip 3, Parkin are reduced by aging [19]. In addition, Romanello et al. [33] reported BNIP3 overexpression induced mitochondrial fragmentation, higher levels of autophagy, and muscle atrophy [33, 35], and Pagano et al. [36] reported higher expressions of Beclin 1 and LC3 II in skeletal muscles of sarcopenic 15- to 22-year-old dogs than 2- to 5-year-old dogs. Collectively, it would appear mitophagy is critical for the maintenance of mitochondrial function and muscle mass.

Myostatin

Myostatin is an extracellular cytokine and a member of the transforming growth factor β superfamily, playing a negative role in regulating skeletal muscle mass and growth [37]. During embryogenesis, myostatin is exclusively expressed in skeletal muscle and controls the differentiation and proliferation of myoblasts by inhibiting the expression of insulin-like growth factor (IGF-1) or of follistatin, which is known to be positively related

with muscle hypertrophy [37]. Furthermore, it has been reported myostatin is associated with aging. Indeed, Yarasheski et al. [38] reported that increases in serum myostatin levels were highest in physically frail older women and that they were inversely associated with skeletal muscle mass [39]. Siriett et al. [40] showed that myoD and Pax7 (potent markers of myogenesis) protein levels were significantly elevated in gastrocnemius muscles from aged mice treated with a myostatin antagonist. However, several authors have failed to demonstrate age-related changes in myostatin mRNA levels in skeletal muscle or in circulating myostatin-immunoreactive protein levels [39]. Thus, it seems further studies are needed to resolve conflicting results regarding the relation between myostatin and aging.

Inflammatory Cytokines

It has been demonstrated inflammatory markers contribute to age-related muscle wasting. For example, elevated levels of tumor necrosis factor alpha (TNF-α) were found to increase muscle catabolism by suppressing the Akt/mammalian target of rapamycin (mTOR) pathway. It also seems inflammatory cytokines may antagonize the anabolic effect of IGF-1 by inducing the development of growth hormone resistance, which decreases both circulating and muscle IGF-1 levels [41]. However, the effects of these cytokines may be more complex because interleukin 6 (IL-6) may play a role, and it can act as pro- or anti-inflammatory cytokine. Recent experimental studies have suggested that IL-6 in blood can be differentiated from muscle-derived IL-6, which can inhibit TNF-α. The involvements of cytokines in sarcopenia remain to be clarified, but nonetheless, sarcopenia appears to be a cytokine-associated aging phenomenon [42].

Bone–Muscle Crosstalks

There is an intensive and complex interaction, both mechanically (mechanostat hypothesis) [4] and biochemically (Fig. 3.4). As a "functional

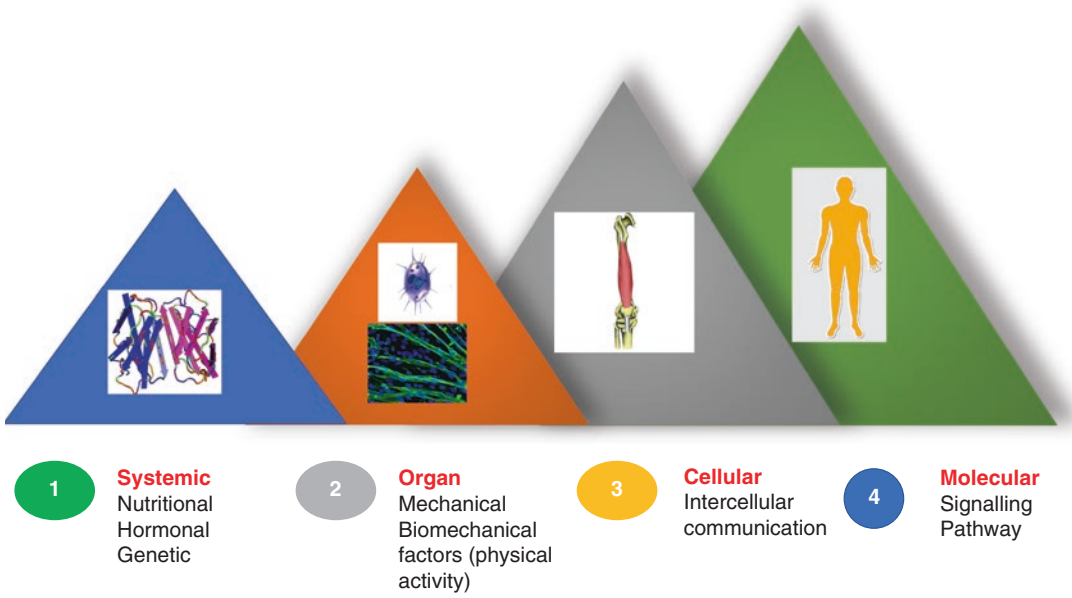

Fig. 3.4 Crosstalks between bones and muscles is a complex interplay of mechanical endocrine and paracrine signals. These include: 1. Systemic: nutritional, hormonal, genetic, nervous; 2. Organ: mechanical and biomechanical factors from physical activity; 3. Cellular: intercellular communication; 4. Molecular (signaling pathways): myokines, osteokines, cytokines, and growth factors

unit," it is thought that skeletal muscle and the long bones grow together early in life and are maintained and adapted to fit the metabolic and mechanical needs in healthy adults. In concordance, both tissues are also found to deteriorate together with disuse, disease or even with the process of aging. A review on the muscle–bone crosstalk, emerging opportunities for novel therapeutic approaches to treat musculoskeletal pathologies was published recently by Maurel and colleagues [43].

Biomechanical: The Mechanostat Theory and Biomechanical Coupling in the Musculoskeletal Unit

Biomechanical regulation of muscle and bone has been well described historically. During the growth period, muscle and bone grow in proportion to one another. This phenomenon has been the base of the biomechanical interaction theory, where bone adapts to muscle forces during development [44]. In addition, the effects of physical activity, disuse and the aging-related diseases of osteoporosis and sarcopenia demonstrate the simultaneous dependency of muscle and bone tissue quantity [45–47]. Therefore, it has long been postulated that the regulation of bone mass was solely due to mechanical adaptations to the neighboring muscle volume and its activity level.

Muscles expose bone to different kinds of mechanical stimuli depending on the muscular activity (isometric, static, plyometric, concentric, eccentric, low/high frequency, etc.). The attachment site of muscle is in local proximity to the axes of motion, which results in small lever arms. As a result, large forces have to be generated by muscle and are transmitted to the skeleton to produce the motion-required torque at the end of the lever arm (bone) [48]. It has then been proposed that such muscle-derived forces are the primary source of mechanical loading that generate the strain in bone [49].

Studies on the embryonal development of the muscular–skeletal unit provided one piece of evidence that muscle-generated forces are affecting bone directly. During this period, muscles exert forces on bone facilitating the formation of a mechanically optimal bone shape, able to resist deformation later in life. This was supported by studies carried out on paralyzed mice, where it was noted that in cases of in utero muscular dysgenesis, the long bone diaphysis acquired a round shape that is less likely to resist mechanical loading [50]. Further support for the notion that muscle forces influence bone directly is seen during the acquisition of peak bone mass with prepubertal growth. Here, exercise was shown to have significant effects on bone mass. The beneficial effects of physical activity are also seen later in life, even if to a lesser extent [51, 52].

The biomechanical coupling in the musculoskeletal unit is explained by the mechanostat theory, which states that bone adjusts its mass and architecture to experience strains within a physiological window [53]. Strains greater than this window will induce bone formation, while lower strains will lead to bone resorption. In addition to load transmission between muscle and bone, the two tissues show co-dependent hypertrophic or hypotrophic adaptations. Physical activity increases both muscle and bone mass [46], while aging or disuse leads to loss of mass in both organs [47]. However, from a disease point of view, sarcopenia does not fully account for the osteoporotic phenotype and osteoporosis does not fully account for sarcopenia, at least based on mass measures alone. This may be because bone quality and muscle function are better measures to reflect the basis of these diseases [54], or that, in addition to the biomechanical coupling of both tissues, a biochemical musculoskeletal interaction is taking place.

Biochemical Communication between Muscle and Bone: Muscle and Bone as Endocrine Organs

In the past years increasing amounts of data have been accumulating making a strong case for the endocrine relationship between muscle and bone. The endocrine nature of interaction between both tissues has been supported by the finding that fol-

Table 3.1 Myokines and the so far known effect on the bones

Myokine	Molecule	Effect on bone
Irisin	Membrane protein (Fndc5)	Promotes osteoblast differentiation
Myostatin	Growth differentiation factor-8 (GDF-8)	Osteoclastogenesis
Growth Factors	Insulin-like growth factor (IGF-1)	Increases ability of osteoblast to deposit bone
	Basic Fibroblast Growth Factor-2 (FGF-2)	Promotes osteoblastogenesis
Cytokines	Interleukin-6 (IL-6)	Increases osteoclastogenesis by promoting Receptor Activator of Nuclear factor Kappa-B Ligand (RANKL) secretion by osteoblasts
	Interleukin-15 (IL-15)	Promotes osteoblast capacity to deposit mineral matrix
	Interleukin-7 (IL-7)	Inhibitor of osteoclastogenesis in bone marrow cultures
	Interleukin-5 (IL-5)	Stimulates angiogenesis. Not yet fully identified
	Interleukin-8 (IL-8)	Not yet fully identified
Neurotrophic Factor	Brain-Derived Neurotrophic Factor (BDNF)	Regulates expression and secretion of Vascular Endothelial Growth Factor (VEGF) from osteoblasts
	Ciliary Neurotrophic Factor (CNTF)	Suppresses osteoblast differentiation in vitro
Decorin		Promotes bone matrix formation and calcium deposition
Osteoglycin (OGN)		Increases alkaline phosphatase, type I collagen and osteocalcin
Follistatin-like protein 1		Not yet fully identified

lowing exercise, muscles secrete factors into the circulation that have effects on other tissues. These factors are known as "myokines" (Table 3.1). Similarly, bone can act as an endocrine organ through the secretion of bone-specific hormones or "osteokines" (Table 3.2). Recent research studies have paid attention to the bone–muscle biochemical crosstalks, that is, the actions of muscle-derived factors on bone and bone derived-factors on muscle. This type of communication appears to act in addition to the biomechanical interaction described above. The endocrine crosstalk and in particular the crosstalk via myokines and osteokines hold the potential for improving the mechanistic understanding of tissue functions within thve musculoskeletal unit. The biochemical communication includes the following:

Myokines Interleukin 6 (IL-6) is of myokines, which was found to be produced in large amounts during exercise [55] by cells in type II muscle fibers [56]. Muscle-secreted IL-6 regulates satel-

Table 3.2 Osteokines and the so far known effects on the muscles

Osteokine	Effect on muscles
Fibroblast Growth Factor 23	regulate phosphate metabolism
Osteocalcin	Increases insulin sensitivity, promotes protein synthesis in myotubes
Sclerostin	Wnt/ß-catenin pathway
Dentin Matrix Protein-1 (DMP-1)	Not yet fully identified
Matrix Extracellular Phosphoglycoprotein (MEPE)	Not yet fully identified
Phosphate-regulating gene with Homologies to Endopeptidases on the X chromosome (PHEX)	Not yet fully identified
Receptor Activator of Nuclear Factor-kappa B Ligand (RANKL)	Not yet fully identified
Prostaglandin E2 (PEG2)	Promotes proliferation of myoblasts
WNT-3a	Enhances muscle ability to contract

lite cell (muscle stem cells) differentiation to mediate skeletal hypertrophy [57]. Furthermore, IL-6 from muscle exerts not only paracrine effects but also endocrine effects acting on distant organs, such as the liver and the adipose tissue. IL-6 null mice develop early mature-onset obesity [58]. Other interleukins have been documented since, such as IL-5, IL-7, and IL-8, which stimulates angiogenesis [59]. Muscle-derived IL-15 works to reduce adiposity and mice expressing high levels of IL-15 show increased bone mineral content [47].

Neurotrophic factors are a family of biomolecules that support the growth, survival, and differentiation of both developing and mature neurons. Most neurotrophic factors belong to one of three families: (1) neurotrophins, (2) glial cell-line derived neurotrophic factor family ligands, and (3) neuropoietic cytokines. Each family has its own distinct cell signaling mechanisms, although the cellular responses elicited often do overlap [60]. Brain-Derived Neutrophic Factor (BDNF) is highly expressed in the brain, serum, and skeletal muscle after exercise [61–63]. BDNF is involved in exercise-induced skeletal muscle regeneration [62] and fat oxidation [63]. Ciliary Neurotrophic Factor (CNTF) is a myokine inducing the suppression of bone formation at the periosteum.

Muscles secrete myostatin (growth differentiation factor-8, GDF-8), a member of the tumor growth factor family. Myostatin is a potent inhibitor of skeletal muscle cell proliferation and growth [64]. Disruption of the myostatin gene in mice induces a dramatic increase in muscle mass, caused by a combination of hypertrophy and hyperplasia. Natural mutations occurring in cattle were also associated with a significant increase in muscle mass and, recently, an inactivating myostatin mutation associated with the same phenotype was identified in humans. Studies into the molecular basis of this antimyogenic influence led to the conclusion that myostatin inhibits myoblast proliferation and differentiation through a classical tumor growth factor-beta pathway. Myostatin binds to the activin receptor type II (ActR2B) on muscle cells resulting in the intracellular phosphorylation of Smads 2 and 3, the aggregation with Smad 4 and the nuclear translocation to activate target genes [65]. Approaches that induce myostatin depletion or inactivation have led to a significant improvement in muscle regeneration processes, especially in degenerative diseases, through stimulation of satellite cell proliferation and differentiation. These promising data open the way to new therapeutic approaches in muscle diseases through targeting of the myostatin pathway [66].

Irisin is a hormone-like molecule produced by muscle post exercise. Irisin is produced by the cleavage of the membrane protein Fndc5 (a membrane protein that is cleaved and secreted as a new hormone, irisin); under the regulation of PGC1α (PPARγ coactivator-1 α). PGC1α is a transcriptional coactivator that mediates many biological programs related to energy metabolism. PGC1α is induced in muscle by exercise and stimulates many of the best known beneficial effects of exercise in muscle: mitochondrial biogenesis, angiogenesis, and fiber-type switching [67]. It also provides resistance to muscular dystrophy and denervation-linked muscular atrophy [68]. It is also capable of "browning" certain white adipose tissues in vitro and in vivo, increases energy expenditure and improves glucose tolerance of high fat fed mice [69]. Irisin is induced with exercise in mice and humans, and mildly increased irisin levels in blood cause an increase in energy expenditure in mice with no changes in movement or food intake. This results in improvements in obesity and glucose homeostasis. Irisin could be a protein therapeutic for human metabolic disease and other disorders that are improved with exercise.

Osteokines Until recent years, bone was not considered an endocrine organ, but rather as an endocrine-targeted tissue that responds to hormones like parathyroid hormone (PTH) and sex steroids. However, increasing data demonstrates that bone produces factors now referred as "osteokines" that have effects on other tissues such as muscle, liver, kidneys, and pancreas (Table 3.2).

Probably the first discovered hormone-like "osteokine" secreted by bone cells (osteocytes) was Fibroblast Growth Factor 23 (FGF23) [70]. Mutation in FGF23 is the cause of Autosomal Dominant Hypophosphatemic Rickets (ADHR). FGF23 and parathyroid hormone might work together to regulate phosphate metabolism. FGF23 is known to act on the intestine and the kidney by downregulating the expression of sodium/phosphate co-transporters responsible for absorbing and reabsorbing phosphate [71–73]. Elevated levels of FGF-23 could play a role in cardiac hypertrophy, which suggests more widespread actions of this molecule [74].

Osteocalcin, or Bone Gamma-Carboxyglutamate Protein (BGLAP), is a secreted protein produced mainly by osteoblasts. It is bound to the bone extracellular matrix but has been found in the plasma with higher levels of expression at the fetal stage (in fetal calves) as compared to adulthood (in adult cows) [75]. Osteocalcin$^{-/-}$ mice show decreased ß-cell proliferation, insulin secretion, and sensitivity [76], suggesting a regulatory role in glucose metabolism. Recently, osteocalcin was found to affect muscle tissue [77]. This has been observed by G Karsenty's group [53] who showed that delivery of osteocalcin prior to exercise increases the exercise-capacity OF young mice and restores aerobic endurance in old mice [77, 78]. Osteocalcin even increased muscle mass in old mice [75].

Sclerostin is a protein mainly secreted by osteocytes. In bone, sclerostin binds to the second or third ß-propeller of the Wnt/LRP/Frizzle tri-molecular complex inhibiting the activation of the Wnt/ß-catenin pathway [79], an important regulator of bone and muscle mass during development, growth and adaptation. The Wnt/ß--catenin pathway may play a huge role in the endocrine crosstalk between bone (osteocyte) and distant organs, as sclerostin is a secreted protein which has been detected in plasma. However, it remains controversial as to whether high levels of sclerostin in the plasma can be correlated with increased facture risk [80, 81].

Bone is also known to secrete factors like Dentin Matrix Protein 1 (DMP1) [82], matrix extracellular phosphoglycoprotein (MEPE), and phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX), all of which are involved in phosphate metabolism. Dmp1 knockout mice present with increased levels of FGF23 [83].

In addition, bone is a source for growth factors like insulin-like growth factors (IGFs), transforming growth factor-beta (TGF-beta), and bone morphogenetic proteins (BMPs) [84]. IGFs, TGF beta, and BMPs are produced by osteoblasts and other bone cells and affect osteoblast proliferation and differentiation. Growth factors are incorporated in the mineralized bone matrix and retain their activity when extracted from bone during osteoclast-dependent bone resorption. These factors can be found in the circulation, reaching the blood system via the connection of the osteocyte lacuno-canalicular system with vessels in bones.

Indirect Links

Muscle and bone are physically connected through tendons, ligaments, cartilage, and other connective tissues. All of these could also affect the muscle–bone crosstalk. It has been shown that the periosteum, which is the fibrous membrane that physically separates bone and muscle tissues, is both a functional target for muscle and bone derived factors and a gatekeeper for fluid and solute exchange between bone and muscle [85, 86]. Ex vivo experiments with fluorescent tracers of different molecular weight revealed that the periosteum is semi-permeable and possesses a cut-off size of approximately 40 kDa [87]. Myokines such as PGE2, IGF-1, IL-15, and FGF-2 satisfy this molecular weight cut-off, while other candidates of the bone–muscle crosstalk such as IL-6 and TGF-ß are less likely to meet this criterion. Their penetration time across the periosteum is higher than their bioactive lifetime [86, 87]. However, myokines secreted by muscle tissue may reach bone through the vasculature. The amount of the secretome and the factor polarity might affect the tissue-to-tissue transport. In addition, the muscular activity state seems to determine the amount of myokines released, as does age and disease state. In vivo

experiments are needed i.e., utilizing fluorescently labeled myokines to confirm the transport to bone tissue and their inter-tissue activity.

Nervous System

Muscle contraction is primarily governed by the central and somatic systems, where an action potential from the CNS stimulates motor neurons which activate muscle fibers. Neuronal inputs are fundamental for muscle physiology and muscle contraction and are an important mechanism for the muscle–bone interaction. Bone tissue relies upon neuronal actions in the muscle for its growth and development [88]. The sympathetic nervous system is also playing a role in skeletal muscle. Synthetic ß-adrenergic receptors agonists induce muscle hypertrophy and reduce skeletal muscle wasting and atrophy [89, 90]. ß2-adrenergic receptors signaling is important in skeletal muscle growth, development, and regeneration in healthy populations [91–94].

In concordance, the sympathetic nervous system has been shown to regulate bone mass. In particular, leptin signaling in the brain is responsible for skeletal changes without the need of a humoral signal. Osteoblasts and osteoclasts express functional ß2-adrenergic receptors, which if blocked lead to increased cancellous bone mass [95]. Similarly, neuropeptide Y receptors (Y1 and Y2) are related to bone homeostasis. Their deletion in transgenic mice has an anabolic effect on bone [96–98]. Other central pathways have been shown to regulate bone, such as the cannabinoid system, melanocortins, and neuromedin U [98]. As leptin regulates cancellous bone formation via ß2-adrenergic receptors signaling in osteoblasts and osteoclasts, and ß2-adrenergic receptors signaling stimulates skeletal muscle growth in disease and in healthy populations; ß2-adrenergic receptors may provide a possible link for the production and regulation of both muscle and bone tissues [64]. Research has focused on genetic, paracrine and metabolic interactions but the neuronal signaling may be a mechanism by which muscle and bone are also co-regulated.

In aging, a relationship between obesity and metabolic syndrome has been observed. Energy restriction and exercising induces changes in muscle and bone [99]. Exercise and fat loss favorably affect bone and muscle mass in overweight people [100, 101]. Fat interacts with muscle and bone [102]. Brown fat is more desirable than white fat and fat mass can be modified e.g., by exercise. The sympathetic nervous system plays a role in the regulation of fat type, but negatively affects skeletal remodeling. Myokines such as irisin, and also "osteokines" such as sclerostin, can increase the formation of beige fat, and therefore exert further effects on muscle and bone tissues as described above.

Macrophages

Another possible way to modify the muscle–bone crosstalk are macrophages. Muscles secrete factors that affect bone, while macrophages affect muscle. Macrophages belong to the same cell lineage as osteoclasts. They are derived from hematopoietic precursor cells that have the capacity to differentiate to macrophages or osteoclasts, even macrophages can differentiate into osteoclasts within a suitable microenvironment [103]. A specific type of macrophages in bone is called "osteomacs," which reside among lining cells in both the endosteum and the periosteum, and regulate osteoblast function [104]. Macrophages present as two subtypes: M1 and M2. M1 macrophages release proinflammatory cytokines while M2 macrophages promote growth and regeneration of muscle [105].

A switch can occur between M1 and M2 macrophages during regeneration [106]. M2 macrophages are highly present in injured muscle and promote regeneration and aid satellite function. These cells are part of the muscle regeneration response to unloading [107].

The Molecular Clock

Physiology and behaviour are temporally coordinated into rhythms coinciding with the 24-hour solar cycle. These circadian rhythms are under-

lined by a mechanism called the molecular clock. It comprises of a series of interconnected transcriptional–translational feedback loops [108]. This system functions to optimize the timing of cellular events in anticipating environmental changes, e.g., daylight and food availability. The mechanisms by which clocks in one tissue influence the physiology of another tissue has not been well studied. To date, only one study reports that skeletal muscle rhythms are important for the maintenance of bone health [109]. Another analysis utilizing microarray data has identified several myokines that significantly change expression following the skeletal muscle-specific knock-out of brain muscle arnt-like 1 (encoding the protein Aryl hydrocarbon receptor nuclear translocator-like protein 1), a nonredundant gene within the core feedback loop [110]. The mRNA expression of several myokines with a known effect on bone is altered in these mice [115]. Among the differentially expressed genes, muscle–bone crosstalk mediators, e.g., Fndc5/Irisin, Vascular endothelial growth factor A, Transforming growth factor beta-1, insulin like growth factor binding protein-4, Interleukin-15, myostatin, and Insulin-like growth factor binding protein-5, were reported.

Few papers have investigated the role of the molecular clock in bone tissue function, making the mechanistic understanding of a crosstalk on this level from bone to muscle difficult at this time. We can note that the deletion of proprotein convertase Mbtps1 gene (membrane bound transcription factor peptidase, site 1) in osteocytes stimulates soleus muscle regeneration, size and contractile force [111]. Many of the myogenic genes altered in this larger and functionally improved muscle were regulated by the circadian core transcriptional repressors DEC1 (Deleted In Esophageal Cancer 1) and DEC2 (Deleted in esophageal cancer 1 is a protein that in humans is encoded by the DEC1 gene) [112].

Exosomes and their microRNA cargos are other factors that could affect the muscle–bone crosstalk. Cardozo and Graham [113] published a review on the role of movement and mechanical loading of bone by skeletal muscle in the field of mechano-humoral coupling of muscle and bone.

Sarcopenia Operational Definition

Sarcopenia is a progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability and mortality. The original operational definition of sarcopenia by the European Working Group on Sarcopenia in Older People (EWGSOP) in 2010 [114], was a major change at that time, as it added muscle function to former definitions based only on detection of low muscle mass. In their revised guidelines [2], EWGSOP, muscle strength has come to the forefront, as it is recognized that strength is better than mass in predicting adverse outcomes (Table 3.3) [115–118]. Muscle quality is also impaired in sarcopenia; this term has been used to describe micro- and macroscopic aspects of muscle architecture and composition. Because of technological limits, muscle quantity and muscle quality remain problematic as primary parameters to define sarcopenia [119–121]. Detection of low physical performance predicts adverse outcomes, so such measures are thus used to identify the severity of sarcopenia.

In its 2018 definition [2], EWGSOP2 uses low muscle strength as the primary parameter of sarcopenia; muscle strength is presently the most reliable measure of muscle function (Table 3.4). Specifically, sarcopenia is probable when low muscle strength is detected. A sarcopenia diagnosis is confirmed by the presence of low muscle quantity or quality. When low muscle strength, low muscle quantity/quality and low physical performance are all detected, sarcopenia is considered severe.

Table 3.3 2018 operational definition of sarcopenia (quoted from [2])

Criteria
1. Low muscle strength 2. Low muscle quantity or quality 3. Low physical performance
Diagnosis: Probable sarcopenia is identified by Criterion 1. Diagnosis is confirmed by additional documentation of Criterion 2. If Criteria 1, 2, and 3 are all met, sarcopenia is considered severe.

Table 3.4 2018 operational definition of sarcopenia (Quoted from Cruz-Jentoft et al. [2] under open access scheme)

(1) Low muscle strength (2) Low muscle quantity or quality (3) Low physical performance
Probable sarcopenia is identified by Criterion 1. Diagnosis is confirmed by additional documentation of Criterion 2. If Criteria 1, 2, and 3 are all met, sarcopenia is considered severe.

Osteosarcopenia Clinic: Case Finding Practical Algorithm

Bearing in mind the aetiology of osteosarcopenia being multifactorial, with mechanical, biochemical, genetic and lifestyle factors all contributing to involution of the "bone–muscle unit," setting up such clinic has to consider these facts in the screening, assessment and management of the patients (Table 3.5). The European Working Group on Sarcopenia in Older People (EWGSOP) [2] has suggested an algorithm as a base for osteosarcopnia healthcare management, this is "F-A-C-S": Find, Assess, Confirm, Severity (Fig. 3.5).

In clinical practice, EWGSOP2 advised the use of the SARC-F questionnaire (Table 3.6) to find individuals with probable sarcopenia. The use of grip strength and chair stand measures was recommended to identify low muscle strength. To generate evidence that confirms muscle of low quantity or quality, EWGSOP2 recommended evaluation of muscle by DXA and BIA methods in standard clinical care, and by DXA, MRI or CT in research and in specialty care for individuals at high risk of adverse outcomes. Measures of physical performance (SPPB, TUG and 400-m walk tests) were suggested to assess severity of sarcopenia (Table 3.6).

Validated Tests and tools for Current Use

A wide variety of tests and tools are available for characterization of sarcopenia in practice and in research (Table 3.4) [122, 123]. Tool selection may depend upon the patient (disability, mobility), access to technical resources in the healthcare test setting (community, clinic, hospital or research centre), or the purpose of testing (progression monitoring, or monitoring rehabilitation and recovery).

Table 3.5 Algorithm for screening and diagnosis of sarcopenia: Find cases-Assess-Confirm-Severity (F-A-C-S)

Parameter	Approach
Find-cases	To identify individuals at risk for sarcopenia, the SARC-F questionnaire or clinical suspicion to find sarcopenia-associated symptoms have been advised for case finding approach.
Assess	To assess for evidence of sarcopenia, can be carried out by using the grip strength or a chair stand measure with specific cut-off-points for each test. For special cases and for research studies, other methods for measurement of strength (knee flexion/extension) can be used.
Confirm	To confirm sarcopenia by detection of low muscle quantity and quality, DXA is advised in clinical practice, and DXA, BIA, CT, or MRI in research studies.
Determine Severity	Severity can be evaluated by performance measures; gait speed, SPPB, TUG, and 400-m walk tests can be used.

Finding Sarcopenia Cases

In clinical practice, case-finding may start when a patient reports symptoms or signs of sarcopenia (i.e. falling, feeling weak, slow walking speed, difficulty rising from a chair or weight loss/muscle wasting). In such cases, further testing for sarcopenia is recommended [2].

EWGSOP2 recommended the use of the SARC-F questionnaire (Table 3.7) as a way to elicit self-reports from patients on signs that are characteristic of sarcopenia. SARC-F can be readily used in community healthcare and other clinical settings. The SARC-F is a 5-item questionnaire that is self-reported by patients as a screen for sarcopenia risk [12]. Responses are based on the patient's perception of his or her limitations in strength, walking ability, rising from a chair, stair climbing and experiences with falls. This screening tool was evaluated in three

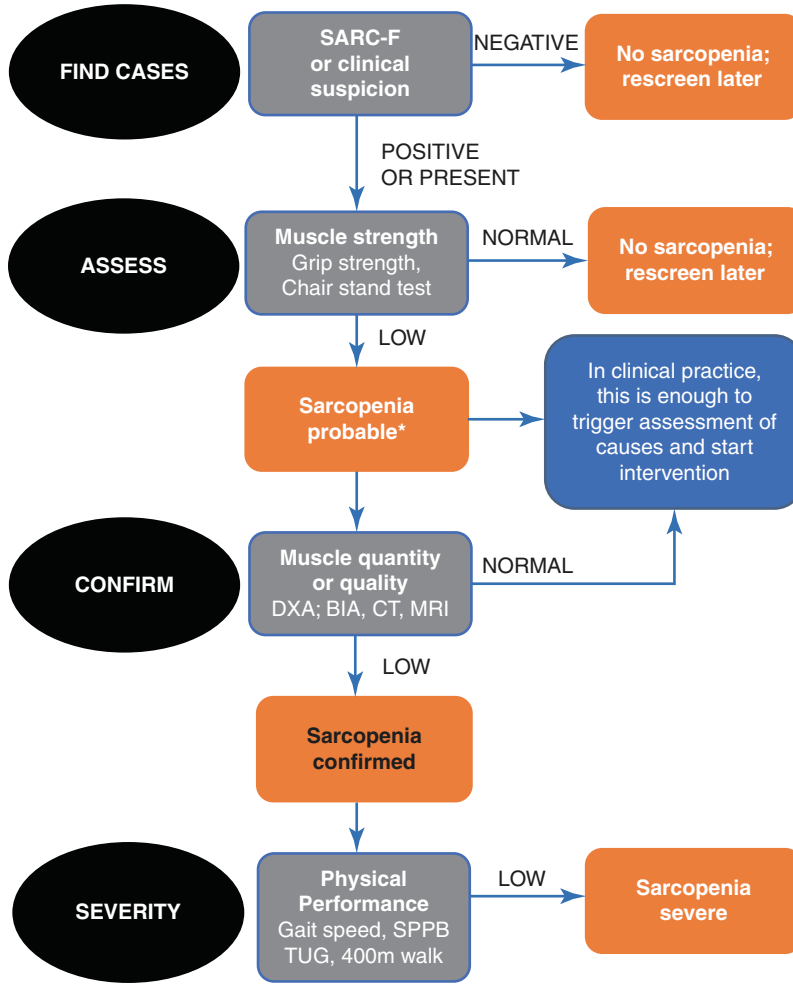

Fig. 3.5 Sarcopenia: EWGSOP2 algorithm for case-finding, making a diagnosis and quantifying severity in practice. The steps of the pathway are represented as Find-Assess-Confirm-Severity or F-A-C-S. *Consider other reasons for low muscle strength (e.g. depression, stroke, balance disorders, peripheral vascular disorders). (Quoted under open access scheme from [2])

Table 3.6 EWGSOP2 sarcopenia cut-off points (quoted from cruz-Jentoft et al. [2])

Test	Cut-off points for men	Cut-off points for women	References
EWGSOP2 sarcopenia cut-off points for low strength by chair stand and grip strength			
Grip strength	<27 kg	<16 kg	Dodds [132]
Chair test	>15 s for five rises		Cesari [136]
EWGSOP2 sarcopenia cut-off points for low muscle quantity			
Appendicular Skeletal Muscle Mass (ASM)	<20 kg	<15 kg	Studenski [154]
ASM/height^2	<7.0 kg/m^2	<5.5 kg/m^2	Kim [142]
EWGSOP2 sarcopenia cut-off points for low performance			
Gait speed	≤0.8 m/s		Cruz-Jentoft [2, 114] Studenski [154]
Short Physical Performance Battery (SPPB)	≤8 point score		Pavasini [160] Guralnik [155]
Timed-Up and Go test (TUG)	≥20 s		Podsiadlo [159]
400 m walk test	Noncompletion or ≥ 6 min for completion		Newman [143]

Table 3.7 SARC-F score. SARC-F ≥ 4 indicates risk of osteosarcopenia. (quoted from Tanaka et al., (Journal of Cachexia, Sarcopenia, and Muscle - Clinical Reports 2018; 3(1))

Component		
Strength	How much difficulty do you have in lifting and carrying 10 lb.?	None = 0 Some = 1 A lot or unable = 2
Assistance in Walking	How much difficulty do you have walking across a room?	None = 0 Some = 1 A lot, use aids, or unable = 2
Rise from a chair	How much difficulty do you have transferring from a chair or bed?	None = 0 Some = 1 A lot or unable without help = 2
Climb stairs	How much difficulty do you have climbing a flight of 10 stairs?	None = 0 Some = 1 A lot or unable = 2
Falls	How many times have you fallen in the past year?	None = 0 1–3 falls = 1 ≥ 4 falls = 2

Table 3.8 Assessment of muscles in sarcopenia patients in clinical practice as well as research

Variable	Clinical Practice	Research
Muscle Mass	Dual energy X-ray absorptiometry (DXA) Bioimpedance analysis (BIA) Anthropometry	Computed tomography (CT) Magnetic resonance imaging (MRI) Mid-thigh muscle measurement Creatine dilution test Ultrasound
Muscle strength	Handgrip strength	Knee flexion/ extension Peak expiratory flow
Physical performance (muscle function)	Usual gait speed Get-up-and-go test Timed get-up-and-go test Stair climb power test	Short physical performance Battery (SPPB) 400-m walk test

large populations—the African American Health Study, Baltimore Longitudinal Study of Aging and the National Health and Nutrition Examination study [124], and was likewise used in a study of Chinese men and women [125]. In these populations, the SARC-F was valid and consistent for identifying people at risk of sarcopenia-associated adverse outcomes.

SARC-F has a low-to-moderate sensitivity and a very high specificity to predict low muscle strength [126]. As such, SARC-F will mostly detect severe cases. EWGSOP2 recommended SARC-F as a way to introduce assessment and treatment of sarcopenia into clinical practice. SARC-F is an inexpensive and convenient method for sarcopenia risk screening. A project is underway to translate and validate SARC-F in multiple different world languages [127]. Since SARC-F is self-reported by the patient, results reflect perceptions of adverse outcomes that matter to the patient.

Alternatively, clinicians may prefer a more formal case-finding instrument for use in clinical populations where sarcopenia is likely [128]. For example, the Ishii screening test is a method that estimates the probability of sarcopenia using an equation-derived score based on three variables—age, grip strength and calf circumference [129].

Measuring Sarcopenia Parameters

The challenge in clinical practice is the assessment of sarcopenia to identify those who might benefit most from the appropriate therapeutic interventions. Among the current definitions of sarcopenia, there is a general agreement on the need for muscle mass measurement with varying recommendations on the roles of muscle strength assessment and/or physical performance. Currently, several well validated tools exist to measure these parameters (Table 3.8). The next part of the chapter discusses different approaches in the assessment of muscles in sarcopenia patients.

Muscle Strength

Measuring grip strength is simple and inexpensive. Low grip strength is a powerful predictor of poor patient outcomes such as longer hospital

stays, increased functional limitations, poor health-related quality of life and death [116, 117]. Accurate measurement of grip strength requires use of a calibrated handheld dynamometer under well-defined test conditions with interpretive data from appropriate reference populations [130]. Grip strength correlates moderately with strength in other body compartments, so it serves as a reliable surrogate for more complicated measures of arm and leg strength. Because of its ease of use, grip strength is advised for routine use in hospital practice, in specialty clinical settings, and in community healthcare [116, 117, 131–133]. The Jamar dynamometer is validated and widely used for measuring grip strength, although use of other brands is being explored [134]. When measurement of grip is not possible due to hand disability (e.g. with advanced arthritis or stroke), isometric torque methods can be used to measure lower limb strength [135].

The chair stand test (also called chair rise test) (Table 3.9) can be used as a proxy for strength of leg muscles (quadriceps muscle group). The chair stand test measures the amount of time needed for a patient to rise five times from a seated position without using his or her arms; the timed chair stand test is a variation that counts how many times a patient can rise and sit in the chair over a 30-second interval [133, 136, 137]. Since the chair stand test requires both strength and endurance, this test is a qualified convenient measure of strength.

Calculation of post-test probability (PoTP) allows a clinician to determine how much risk has shifted from a pre-test probability of approximately 30% (the prevalence of fall among community-dwelling older adults). A recent systematic review meta-analysis [138] revealed that:

- For those requiring 12 seconds or more to complete the five times sit-to-stand test (positive test), the posttest probability (PoTP) = 41%.
- For those able to complete this task in less than 12 seconds (negative test), the PoTP = 20%."

Table 3.9 Chair stand test five times

Purpose: Assesses functional lower extremity strength, transitional movements, balance, and fall risk.	
Equipment: A chair with a straight back, without arm rests, with a solid seat that is 16 inch high placed against a wall to prevent it moving A stopwatch/timer	
Instructions to the patient: 1. Sit in the middle of the chair. 2. Place each hand on the opposite shoulder crossed at the wrists. 3. Place your feet flat on the floor. 4. Keep your back straight and keep your arms against your chest. 5. On "Go," Please stand up straight as quickly as you can 5 times, without stopping in between. Keep your arms folded across your chest. I'll be timing you with a stopwatch. Ready, begin."	
Therapist instructions: Have the patient sit with their back against the back of the chair. Count each stand aloud so that the patient remains oriented. Stop the test when the patient achieves the standing position on the fifth repetition.	
Do not continue: If you feel the patient may fall during the test. If the patient must use his or her arms to stand	
Interpretation: Lower times = better scores. Age matched norms: [a]60–69 years: 11.4 seconds; 70–79 years: 12.6 seconds; 80–89 years: 14.8 seconds[a]	

[a]Bohannon [340]

Muscle Quantity

Muscle quantity or mass can be estimated by a variety of techniques, and there are multiple methods of adjusting the result for height or for BMI [139, 140]. Muscle quantity can be reported as total body Skeletal Muscle Mass (SMM), as Appendicular Skeletal Muscle Mass (ASM), or as muscle cross-sectional area of specific muscle groups or body locations.

Magnetic resonance imaging (MRI) and computed tomography (CT) are considered to be gold standards for noninvasive assessment of muscle quantity/mass. However, these tools are not commonly used in primary care because of high equipment costs, lack of portability, and the requirement for highly trained personnel to use the equipment [133]. Moreover, cut-off points for low muscle mass are not yet well defined for these measurements.

Dual-energy X-ray absorptiometry (DXA) is a more widely available instrument to determine muscle quantity (total body lean tissue mass or appendicular skeletal muscle mass) noninvasively, however, different DXA instrument brands do not give consistent results [119, 120, 141]. DXA is presently favored by some clinicians and researchers for measuring muscle mass [109]. Fundamentally, muscle mass is correlated with body size; i.e. individuals with a larger body size normally have larger muscle mass. Thus, when quantifying muscle mass, the absolute level of total body Skeletal Muscle Mass (SMM) or Appendicular Skeletal Muscle Mass (ASM) can be adjusted for body size in different ways, namely using height squared (ASM/height^2), weight (ASM/weight), or body mass index (ASM/BMI) [142]. There is an ongoing debate about the preferred adjustment and whether the same method can be used for all populations.

An advantage of DXA is that it can provide a reproducible estimate of Appendicular Skeletal Muscle Mass (ASM) in a few minutes when using the same instrument and cut-off points. A disadvantage is that the DXA instrument is not yet portable for use in the community, as needed for care in countries that favor aging-in-place. DXA measurements can also be influenced by the hydration status of the patient.

Bioelectrical impedance analysis (BIA) [131] has been explored for estimation of total or Appendicular Skeletal Muscle Mass. BIA equipment does not measure muscle mass directly, but instead derives an estimate of muscle mass based on whole-body electrical conductivity. BIA uses a conversion equation that is calibrated with a reference of DXA-measured lean mass in a specific population [74, 143–145]. BIA equipment is affordable, widely available, and portable, especially single-frequency instruments. Since estimates of muscle mass differ when different instrument brands and reference populations are used, EWGSOP2 advised the use of raw measures produced by the different devices along with the cross-validated Sergi equation for standardization [144, 146]. BIA prediction models are most relevant to the populations in which they have been derived, and the Sergi equation is based on older European populations. Age, ethnicity, and other related discrepancies between those populations and patients should be considered in the clinic. In addition, BIA measurements can also be influenced by hydration status of the patient. For affordability and portability, BIA-based determinations of muscle mass may be preferable to DXA; however, more study is necessary to validate prediction equations for specific populations [146, 147].

Although anthropometry is sometimes used to reflect nutritional status in older adults, it is not a good measure of muscle mass [148]. Calf circumference has been shown to predict performance and survival in older people (cut-off point <31 cm) [149]. As such, calf circumference measures may be used as a diagnostic proxy for older adults in settings where no other muscle mass diagnostic methods are available.

Physical Performance

Physical performance has been defined as an objectively measured whole-body function related to locomotion. This is a multidimensional concept that not only involves muscles

but also central and peripheral nervous function, including balance [150]. Physical performance can be variously measured by gait speed, the Short Physical Performance Battery (SPPB), and the Timed-Up and Go test (TUG), among other tests. It is not always possible to use certain physical performance measures, such as when a patient's test performance is impaired by dementia, gait disorder or a balance disorder.

Gait speed is considered a quick, safe, and highly reliable test for sarcopenia, and it is widely used in practice [151]. Gait speed has been shown to predict adverse outcomes related to sarcopenia—disability, cognitive impairment, need for institutionalization, falls, and mortality [152–155]. A commonly used gait speed test is called the 4-m usual walking speed test, with speed measured either manually with a stopwatch or instrumentally with an electronic device to measure gait timing [156, 157]. For simplicity, a single cut-off speed ≤0.8 m/s is advised by EWGSOP2 as an indicator of severe sarcopenia.

The *Short Physical Performance Battery* (SPPB) is a composite test that includes assessment of gait speed, a balance test, and a chair stand test [158]. The maximum score is 12 points, and a score of ≤8 points indicates poor physical performance [114, 133].

The *Timed-Up and Go test* (TUG) evaluates physical function. For the TUG test, individuals are asked to rise from a standard chair, walk to a marker 3 m away, turn around, walk back, and sit down again [159].

The *400-m walk test* assesses walking ability and endurance. For this test, participants are asked to complete 20 laps of 20 m, each lap as fast as possible, and are allowed up to two rest stops during the test.

Each of these physical performance tests (gait speed, SPPB, TUG, 400-m walk) can be performed in most clinical settings. In terms of its convenience to use and ability to predict sarcopenia-related outcomes, gait speed was advised by EWGSOP2 for evaluation of physical performance [111]. The SPPB also predicts outcomes [160], but it is more often used in research than in clinical assessment because the battery of tests takes at least 10 min to administer. Likewise, the 400-m walk test predicts mortality but requires a corridor more than 20 m long to set up the testing course [161]. The TUG has also been found to predict mortality [162]. Table 3.5 shows EWGSOP2 sarcopenia cut-off points of these tests as advised by EWGSOP2.

Alternative or New Tests and Tools

A variety of methods are being used or evaluated to determine the quantity and quality of muscle and impact of sarcopenia on the patient's quality of life. These diagnostic measures are being tested for validity, reliability, and accuracy and may play a relevant role in the future. For use in practice, tools need to be cost-effective, standardized and repeatable by practitioners in a variety of clinical settings and across different patient populations [148, 163].

Lumbar Third Vertebra Imaging By Computed Tomography

For patients with cancer, computed tomography (CT) has been used to image tumors and their response to treatment, and this technique has also been shown to give practical and precise measures of body composition. In particular, CT images of a specific lumbar vertebral landmark (L3) correlated significantly with whole-body muscle [155, 165]. As a result, this imaging method has been used to detect low muscle mass, even in patients with normal or high body weights, and it can also predict prognosis [166, 167]. L3-CT imaging is not limited to patients with cancer; this parameter has been used as a predictor of mortality and other outcomes in the intensive care unit [168] and in those patients affected by liver disease [169]. Quantification of lumbar L3 cross-sectional area has also been done by MRI [67]. With ever-increasing needs to quantify muscle and detect sarcopenia in early stages, high-resolution imaging is expected to be more widely used in the

future—initially in research studies, and ultimately in clinical practice.

Mid-Thigh Muscle Measurement

Mid-thigh imaging (by MRI or CT) has also been used in research studies, as it is a good predictor of whole-body skeletal muscle mass and very sensitive to change [164, 166, 170]. Mid-thigh muscle area is more strongly correlated with total body muscle volume than are lumbar muscle areas L1–L5 [131].

Psoas Muscle Measurement with Computed Tomography

CT-based measurement of the psoas muscle has also been reported as simple and predictive of morbidities in certain conditions (cirrhosis, colorectal surgery) [171, 172]. However, because psoas is a minor muscle, other experts argue that it is not representative of overall sarcopenia [173, 174]. Further studies are needed to verify or reject use of this method.

Muscle Quality Measurement

Muscle quality is a relatively new term, referring both to micro- and macroscopic changes in muscle architecture and composition, and to muscle function delivered per unit of muscle mass. Highly sensitive imaging tools such as MRI and CT have been used to assess muscle quality in research settings, e.g. by determining infiltration of fat into muscle and using the attenuation of the muscle [162, 175]. Alternatively, the term muscle quality has been applied to ratios of muscle strength to appendicular skeletal muscle mass [176, 177] or muscle volume [178]. In addition, muscle quality has been assessed by BIA-derived phase angle measurement [163]. As yet, there is no universal consensus on assessment methods for routine clinical practice. In the future, assessments of muscle quality are expected to help guide treatment choices and monitor response to treatment.

Creatine Dilution Test

Creatine is produced by the liver and kidney and is also ingested from a diet rich in meat. Creatine is taken up by muscle cells, where a portion is irreversibly converted each day to phosphocreatine, a high-energy metabolite. Excess circulating creatine is changed to creatinine and excreted in urine. The excretion rate of creatinine is a promising proxy measure for estimating whole-body muscle mass.

For a creatine dilution test, an oral tracer dose of deuterium-labeled creatine (D3-creatine) is ingested by a fasting patient; labeled and unlabeled creatine and creatinine in urine are later measured using liquid chromatography and tandem mass spectrometry [179]. Total body creatine pool size and muscle mass are calculated from D3-creatinine enrichment in urine. Creatine dilution test results correlate well with MRI-based measures of muscle mass and modestly with measures from BIA and DXA [180, 181]. The creatine dilution test is mostly used in research at this time, so further refinement is needed to make this methodology practical for use in clinical settings.

Ultrasound Assessment of Muscle

Ultrasound is a widely used research technique to measure muscle quantity, to identify muscle wasting, and also as a measure of muscle quality. It is reliable and valid and is starting to be used at the bedside by trained clinicians. Ultrasound is accurate with good intra- and inter-observer reliability, even in older subjects [182]. Assessment of pennate muscles such as the quadriceps femoris can detect a decrease in muscle thickness and cross-sectional area within a relatively short period of time, thus suggesting potential for use of this tool in clinical practice, including use in the community [183, 184].

The use of ultrasound has recently been expanded in clinical practice to support the diagnosis of sarcopenia in older adults. The EuGMS sarcopenia group recently proposed a consensus protocol for using ultrasound in muscle assess-

ment, including measurement of muscle thickness, cross-sectional area, fascicle length, pennation angle, and echogenicity [184]. Echogenicity reflects muscle quality, since non-contractile tissue associated with myosteatosis shows hyper-echogenicity [185, 186]. Thus, ultrasound has the advantage of being able to assess both muscle quantity and quality.

A systematic review on the use of ultrasound to assess muscle in this population concluded that the tool was reliable and valid for the assessment of muscle size in older adults, including those with comorbid conditions such as coronary artery disease, stroke, and chronic obstructive pulmonary disease [187]. Ultrasound was shown to have good validity to estimate muscle mass as compared to DXA, MRI, and CT. While data are available for older adults, more research is needed to validate prediction equations for those with varying health conditions and functional status [187–189].

Specific Biomarkers or Panels of Biomarkers

The development and validation of a single biomarker might be an easy and cost-effective way to diagnose and monitor people with sarcopenia. Potential biomarkers could include markers of the neuromuscular junction, muscle protein turnover, behaviour-mediated pathways, inflammation-mediated pathways, redox-related factors, and hormones or other anabolic factors [190]. However, because of the complex pathophysiology of sarcopenia, it is unlikely that there will be a single biomarker that can identify the condition in the heterogeneous population of young and old people [147]. The development of a panel of biomarkers must instead be considered, including potential serum markers and tissue markers [190, 191]. The implementation of a multidimensional methodology for the modeling of these pathways could provide a way to stratify risk for sarcopenia, facilitate the identification of a worsening condition and provide monitoring of treatment effectiveness [191].

SarQoL Questionnaire

From a patient's perspective, it is important to have sarcopenia treatment plans that address quality of life (QoL) issues. To this end, the SarQoL tool is a self-administered questionnaire for people with sarcopenia [192–194]. SarQoL identifies and predicts sarcopenia complications that may later impact the patient's quality of life. SarQoL assists the healthcare provider in assessing a patient's perception of his or her physical, psychological, and social aspects of health. The SarQoL tool has been validated as consistent and reliable, and it can be used in clinical care and in research studies [195]. The sensitivity of SarQoL to patient status changes over time needs validation in longitudinal studies. Once validated, SarQoL may serve as a proxy measure of treatment efficacy. To facilitate widespread use of the SarQoL tool, it has been translated into multiple languages.

How to Diagnose Osteosarcopenia?

In most of the cases, osteosarcopenia is asymptomatic until a catastrophic fracture occurs. Consequently, it is important to screen the patients to identify who might have this disorder. While F-A-C-S (Find-Assess-Confirm-Severity) is a good approach to identify sarcopenia; screening for risk factors such as previous history of recurrent falls and/or fracture(s), or high fracture risk probability in older people should alert general practitioners or the treating health care professional to the presence of osteosarcopenia. Common clinical signs of osteoporosis include kyphosis and decreased height because of pathological fractures of the vertebrae after middle age. Muscle weakness, falls, and decreasing function could indicate sarcopenia. In addition, patients should be screened for nutrition history, cognition, medication review (antipsychotics, benzodiazepines, SSRIs), gait and balance assessment, and environmental assessment.

Figure 3.6 shows the risk factors which should be assessed to identify this patients' cohort. Regular assessment of bone and muscle mass,

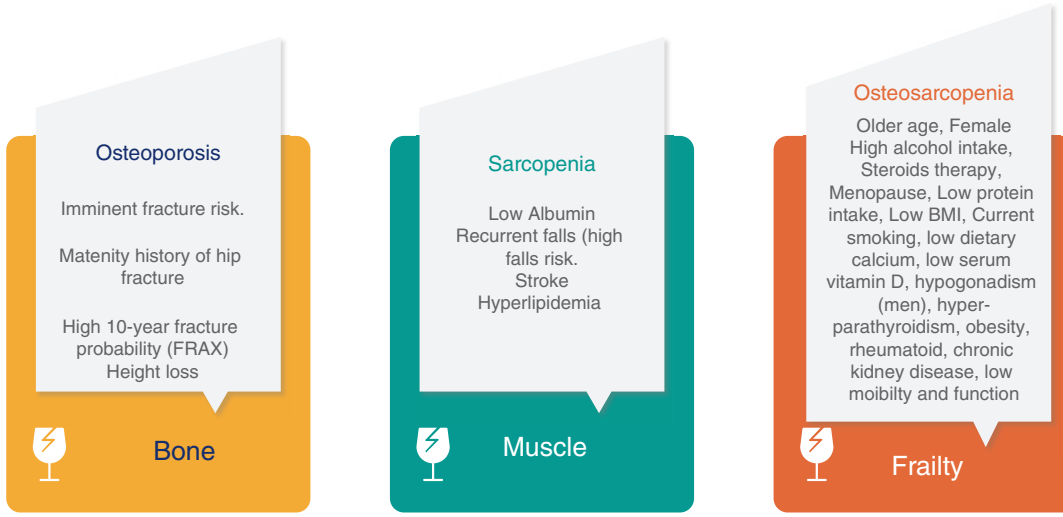

Fig. 3.6 Risk factors for osteosarcopenia

strength as well as function in older people with risk factors for this disease is the next step. Nevertheless, the European Consensus agreed that, even in the absence of imaging or bioelectrical impedance analysis, clinical parameters (gait velocity and grip strength) are reliable enough to diagnose sarcopenia in clinical practice [162]. Table 3.10 shows a list of the risk factors of falling based on the FRAS tool [196], whereas Table 3.11 includes a list of the recommended baseline laboratory investigations indicated to identify metabolic contributors to falls and fractures in older adults [163].

Table 3.11 Recommended laboratory tests to identify metabolic contributors to falls and fractures in older adults

Recommended laboratory tests to identify metabolic contributors to falls and fractures in older adults
Bone profile (calcium, phosphorus, alkaline phosphatase)
Serum 25 $(OH)_2$ vitamin D
Parathyroid hormone (whenever indicated)
Albumin
Creatinine/estimated glomerular filtration rate
Serum testosterone in men

Table 3.10 Falls Screening (FRAS tool) [196]. High risk is considered if the total score is ≥3.5, moderate risk if the total score is ≥2

FRAS: Risk Factor	Points	Total Score
>1 fall in the last 12 months	2	
Slow walking speed/ change in gait	1.5	
Loss of balance	1	
Poor sight	1	
Weak hand grip	1	

Osteosarcopenia in Standard Clinical Practice

Osteoporosis and sarcopenia are chronically deteriorating conditions. Therefore, regular follow-up and education of patients are paramount for successful management. Joined bone health and falls clinics, is the best approach to, on one hand, screen for this disease and identify patients at high risk to develop osteosarcopenia; on the other hand, have the advantage of providing comprehensive care and minimizing the risk of fragmented models of care that evaluate and treat bone health and sarcopenia separately [197].

Therefore, an important part of the osteosarcopenia management in standard clinical practice, involves identifying and referring high-risk patients, those with multiple risk factors for osteoporosis and sarcopenia, or patients who have suffered falls and fractures, to specialized multidisciplinary clinics, which has the facility of

providing combined model of care, assessing these patients for both bone and muscle health and commencing their management [197, 198].

In cases where specialized clinics and services are not available, the patient could still benefit from being assessed by a physiotherapist or exercise physiologist, while also attending community health centres, which often run exercise programs specifically designed for people who are frail and older.

In addition, follow-up with DXA scans is recommended every two years for low-risk patients and once a year for high-risk patients [198]. As changes in muscle mass occur more rapidly than changes in BMD, annual evaluation of lean mass by DXA, combined with a regular clinical assessment of muscle strength and function, is recommended [199]. Figure 3.7 shows a suggested algorithm for assessment for the diagnosis of sarcopenia [200–202].

Categories of Sarcopenia and Sarcopenia-like Conditions

Primary and Secondary Sarcopenia

In some individuals, sarcopenia is largely attributable to aging; however, in many cases, other causes can be identified. Thus, identifying the

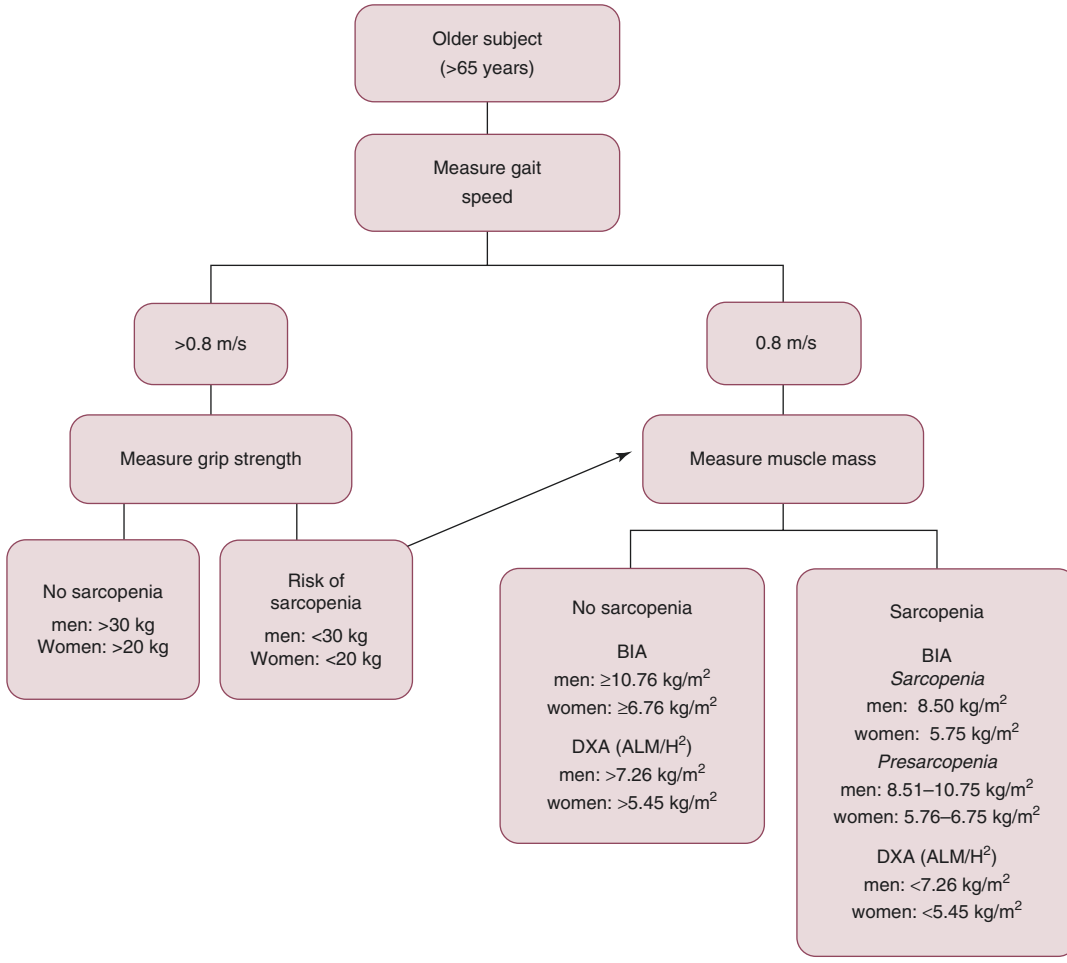

Fig. 3.7 A suggested algorithm for the diagnosis of sarcopenia [2, 91] [Quoted under open access scheme from 2, 200]. ALM/H2 Appendicular lean muscle mass/height (derived from DXA whole body exam), BIA bioelectrical impedance analysis; DXA, dual energy X-ray absorptiometry

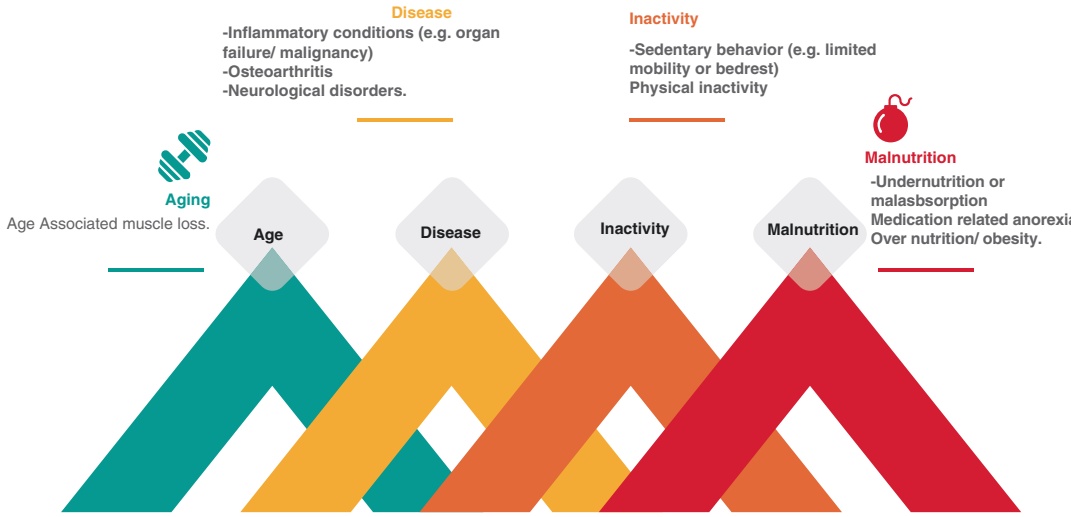

Fig. 3.8 Primary and secondary sarcopenia: Factors that cause and worsen muscle quantity and quality, sarcopenia, are categorized as primary (aging) and secondary (disease, inactivity, and poor nutrition). Because a wide range of factors contribute to sarcopenia development, numerous muscle changes seem possible when these multiple factors interact

categories of primary and secondary sarcopenia may be useful in clinical practice (Fig. 3.8) [2]. Sarcopenia is considered "primary" (or age-related) when no other specific cause is evident, while sarcopenia is considered "secondary" when causal factors other than (or in addition to) aging are evident. Sarcopenia can occur secondary to a systemic disease, especially one that may invoke inflammatory processes, e.g. malignancy or organ failure. Physical inactivity also contributes to development of sarcopenia, whether due to a sedentary lifestyle or to disease-related immobility or disability [203]. Further, sarcopenia can develop as a result of inadequate intake of energy or protein, which may be due to anorexia, malabsorption, limited access to healthy foods, or limited ability to eat.

Acute and Chronic Sarcopenia

EWGSOP2 newly identifies subcategories of sarcopenia as acute and chronic. Sarcopenia that has lasted less than 6 months is considered an acute condition, while sarcopenia lasting ≥6 months is considered a chronic condition. Acute sarcopenia is usually related to an acute illness or injury, while chronic sarcopenia is likely to be associated with chronic and progressive conditions and increases the risk of mortality. This distinction is intended to underscore the need to conduct periodic sarcopenia assessments in individuals who may be at risk for sarcopenia in order to determine how quickly the condition is developing or worsening. Such observations are expected to facilitate early intervention with treatments that can help prevent or delay sarcopenia progression and poor outcomes.

Sarcopenic Obesity

Sarcopenic obesity is a condition of reduced lean body mass in the context of excess adiposity [204]. Sarcopenic obesity is most often reported in older people, as both risk and prevalence increase with age [15]. Obesity exacerbates sarcopenia, increases the infiltration of fat into muscle, lowers physical function, and increases risk of mortality [185, 207]. Sarcopenic obesity is a distinct condition, and there are ongoing initiatives to improve its definition. Sarcopenic obesity is therefore outside the scope of this chapter.

Frailty

Frailty is a multidimensional geriatric syndrome that is characterized by cumulative decline in multiple body systems or functions [185, 186], with pathogenesis involving physical as well as social dimensions [187]. Frailty increases vulnerability to poor health outcomes such as disability, hospital admission, reduced quality of life and even death [187, 188].

The physical phenotype of frailty, described by Fried and co-workers [189], shows significant overlap with sarcopenia; low grip strength and slow gait speed are characteristic of both. Weight loss, another diagnostic criterion for frailty, is also a major etiologic factor for sarcopenia. Treatment options for physical frailty and for sarcopenia likewise overlap—provision of optimal protein intake, supplementation of vitamin D, and physical exercise [190, 191].

Taken together, frailty and sarcopenia are still distinct—one a geriatric syndrome and the other a disease. While sarcopenia is a contributor to the development of physical frailty, the syndrome of frailty represents a much broader concept. Frailty is seen as the decline over a lifetime in multiple physiological systems, resulting in negative consequences to physical, cognitive, and social dimensions. Frailty's diagnostic tools reflect these multiple dimensions, e.g. the Groningen Frailty Indicator, the Frailty Index of Rockwood et al. and others [192–195].

Malnutrition-Associated Sarcopenia

The sarcopenia phenotype is also associated with malnutrition, regardless of whether the malnourished condition is rooted in low dietary intake (starvation, inability to eat), reduced nutrient bioavailability (e.g. with diarrhea, vomiting) or high nutrient requirements (e.g. with inflammatory diseases such as cancer or organ failure with cachexia) [196, 197]. Low muscle mass has recently been proposed as part of the definition of malnutrition [198]. Also, in malnutrition, low fat mass is usually present, which is not necessarily the case in sarcopenia [197, 198]. Table 3.12 shows the core diagnostic criteria to capture major catabolic syndrome: sarcopenia, malnutrition, and frailty.

Table 3.12 Diagnostic criteria of the major catabolic syndromes

Sarcopenia	Malnutrition	Frailty
	Weight loss/ low BMI	Weight loss / low BMI
Loss of strength		Loss of strength
Low muscle mass	Low muscle mass	
Slow gait speed		Gait speed affected
Low grip Strength		Low grip strength
	Low fat mass	Fatigue

Therapeutic Intervention

The advent of patient-centered care has increased attention to the fact that different molecular changes can result in the need to have different therapeutic approaches to similar conditions such as sarcopenia [56, 57]. Sarcopenia can result from a variety of molecular changes resulting in changes in myofiber metabolism and alterations in satellite cell properties. Abnormalities in these pathways can be due to insulin growth factor-1/insulin receptors, activin (myostatin) receptors, tropomysin receptor, kinase C receptors (neurotrophin and G-protein receptors), a variety of cytokines, and testosterone through activation of β-catenin [59–63]. Furthermore, the concurrent link of muscle and bone tissue quality suggests a huge pharmaceutical potential for efficient treatment regimens that act on both tissues simultaneously. Thus, in the long run, the ideal treatment of sarcopenia will involve identification of the aberrant molecular pathway and the possible hormone causing this imbalance.

At present, the treatment of sarcopenia is based on three main pillars: exercise, nutrition, and pharmacotherapy.

Exercise

Exercise is essential for health because it increases muscle mass, reduces body fat, and improves muscle strength, endurance, immune

function, and the cardiovascular system. Accordingly, in sarcopenia, exercise interventions can be effective for increasing appendicular skeletal muscle mass, knee extension muscle strength, normal gait speed and maximum gait speed. However, much remains unclear as to whether this same efficacy, seen in healthy individuals, on muscle strength and physical function will also be shown in patients with sarcopenia. A meta-analysis of seven randomized clinical trials was carried out on skeletal muscle mass data, the basic concept of sarcopenia [15]. Results revealed that most of the randomized clinical trials reported improvement in muscle strength [205–209] as well as physical functions, such as gait, [206, 208, 210] whereas just three of these studies had data showing increased skeletal muscle mass [15, 206, 207]. However, these randomized clinical trials analyzed primarily older individuals residing locally whose conditions were also complicated by frailty, [15]. Therefore, it is not fully clear whether the study conclusions can also be applied to older patients diagnosed with sarcopenia before any intervention.

Exercise interventions administered included a comprehensive training program, including 60-minutes resistance exercises carried out twice weekly for 3 months [210–214]. Comparison against the control group who underwent nutritional intervention or health education. Results revealed that, after the comprehensive training program, there was improvement in the appendicular skeletal muscle mass, normal gait speed, maximum gait speed and knee extension muscle strength. In contrast, no change in grip strength was observed as a result of the comprehensive training program.8 With regard to other exercise interventions, whole body vibration training was found to be ineffective in improving the cross-sectional area of the quadriceps vastus medialis muscle and knee extension muscle strength compared with participants in the control group who did not engage in a training program [215].

Aerobic exercise causes ATP production in mitochondria within skeletal muscle, and improves aerobic capacity, metabolic regulation, and cardiovascular function. Furthermore, it contributes to the inductions of mitochondrial biogenesis and dynamics, to the restoration of mitochondrial metabolism, reduces the expressions of catabolic genes and increases muscle protein synthesis [28, 37].

Resistance exercise is considered an important strategy for preventing muscle wasting because it stimulates muscle hypertrophy and increases muscle strength by shifting the balance between muscle protein synthesis and degradation towards synthesis [216]. It is known regular resistance exercise increases the sizes and cross-sectional areas of muscle fibers, especially fast-twitch fibers (types IIa and IIx) rather than slow-twitch fibers (type I) [217]. Increases in muscle protein synthesis and muscle fibers hypertrophy increase force- generating ability [216], muscle quality, and physical performance. However, resistance exercise has some limitations, notably, its little effect on the expression of mitochondrial proteins or their functions, and these are considered potential causes of age-related sarcopenia. Nonetheless, resistance exercise is a meaningful exercise prescription for sarcopenia in terms of improving muscle mass and function.

The majority of studies on the effects of exercise have focused on either aerobic or resistance exercise. However, while aerobic exercise has a little effect on muscle strength or mass compared with resistance exercise [217, 218]; resistance exercise can increase the risk of injury, reduce participation rates, and induce boredom because of the extent of repetition [217]. Also, resistance exercise can be less effective in older individuals who might have already impaired in muscle protein synthesis [19]. Accordingly, no single type of exercise would seem to address adequately the requirements of therapeutic exercise in age-related sarcopenia, and thus, it has been recommended well-rounded exercise programs consisting of aerobic and resistance exercises should be preferred [218]. For example, a circuit exercise program has been developed that combines these two exercise types [217, 218]. Recently, Lee et al. [217] reported that 12 weeks of circuit program improved walking and balancing abilities and isokinetic muscle functions. Gudlaugsson et al. [219] showed “multimodal training interventions” conducted on 117 elderly

subjects for 6 months improved endurance performance as determined by 6-min walking test. Collectively, these reports indicate regular combined exercise can be utilized to combat age-related sarcopenia. Further research is needed to determine whether combined exercise retards potential molecular mechanisms of age-related sarcopenia.

Nutrition

There is significant interest in the role of dietary patterns and the effects of whole diets in predicting health. The term "diet quality" is broadly used to describe how well an individual's diet conforms to dietary recommendations and to describe how "healthy" the diet is [220, 221]. In some occasions "healthy diet" can be identified using principal component or factor analysis, or includes a-priori-defined patterns, such as the Mediterranean diet. Despite using different assessment methods, there are commonalities across diet quality measures, such as the "healthiness" of the diet. When compared with poorer diet quality, better diet quality is characterized by higher intake of beneficial foods (e.g., fruit and vegetables, whole grains, fish, lean meat, low-fat dairy, nuts, and olive oil), but lower in energy-dense, nutrient-poor foods (e.g., refined grains, sweets and animal products that are high in saturated fats) [220, 222]. Higher diet quality in older adults has been linked with various health outcomes, including to a reduced risk of common age-related diseases and to greater longevity. In general, adherence to diets of better quality, assessed by different dietary indices or a "prudent"/healthy dietary pattern, is associated with beneficial health effects; better quality diets are associated with significantly reduced risk of all-cause mortality, cardiovascular disease, cancer, type 2 diabetes, and neurodegenerative disease, as well as reduced mortality in cancer survivors [223–226].

Less is known about the influence of diet quality on sarcopenia (muscle mass and physical function) in older age, although there is a growing evidence base linking "healthier" diets with greater muscle strength and better physical performance outcomes in older adults [227, 228]. However, much of this evidence is cross-sectional.

There is evidence for a link between differences in nutrient intake and status and the components of sarcopenia, with the most consistent associations found for protein, vitamin D, antioxidant nutrients and long-chain polyunsaturated fatty acids [229].

Protein intake has been recognized as one of the main anabolic stimuli for muscle protein synthesis [227]. Many elderly patients can not adhere to an adequate protein diet. Dietary protein is the key to the occurrence of sarcopenia. The recommended diet for healthy people is 0.8 grams / kg body weight/ day (RDA = recommended diet allowance). However, in the elderly age > 70 years, protein intake drops to be 40% protein less than the recommended diet allowance, which facilitates the occurrence of sarcopenia. Therefore, for elderly patients, the recommended allowance is increased to be 1–1.5 g / kg body weight / day. This should be considered in accordance with increased physical activity and comorbidity(ies) that exist. Muscle formation in addition to exercise requires adequate protein intake. Adequate protein diets and exercise are the main therapies in the management of sarcopenia [230].

Addressing sarcopenic obesity, there have been adjustments in the dietary guidelines to prevent this condition and to help the medical professional in the management of weight loss in the presence of sarcopenic obesity. Sufficient protein intake (25–30 g of protein per meal) is important for optimizing the muscle protein synthetic response [231, 232]. A diet relatively low in carbohydrates may also be advisable as the co-ingestion of carbohydrates has been shown to exert negative effects on muscle protein turnover in the elderly [233, 234].

In inflammatory chronic cardiac diseases, a diet optimization might help the energetic balance, giving as a result an increase in the nonfat tissue mass. Diet changes improve respiratory mechanics and oxygen acquirement and also benefit the function of the immune system [235, 236].

Supplementation with leucine, which is the most potent branched-chain amino acid for increasing protein synthesis, was reported to be helpful for preventing sarcopenia [237]. An association was found between leucine supplementation and increased muscle protein synthesis independently of ingestion of other amino acids in older adults [238]. Leucine is a potent activator of the mammalian target of the rapamycin (mTOR) nutrient and energy-sensing signaling pathway. Furthermore, the leucine supplementation has been associated with a decrease in serum TNF-alpha levels and improved insulin sensitivity [231, 239, 240].

There is growing evidence for benefits of supplementation with vitamin D to preserve muscle mass, strength and physical function in older age and to prevent and treat sarcopenia, and it could be that supplementation with vitamin D in combination with other nutrients might be important [241 original].

Sarcopenia is considered to be an inflammatory state driven by cytokines and oxidative stress; an accumulation of reactive oxygen species may lead to oxidative damage and likely contribute to losses of muscle mass and strength [240–242]. "Healthier diets" are also higher in plant phytochemicals, such as polyphenols, which could have antioxidant and anti-inflammatory effects on muscle mass and function [234–236, 241]. Therefore, the consumption of natural antioxidant supplements (flavonoids and polyphenols) has risen in adults to treat obesity and metabolic syndrome. They have been found to have a role in the reduction of cardiovascular diseases, cancer, and neurodegenerative disorders. Beneficial effects are attributed to their potent antioxidant and anti-inflammatory action, and the activation of a histone NAD^+-dependent deacetylase sirtuin 1 (SIRT 1) [237, 238]. SIRT1 regulates the expression of some antioxidant enzymes and also deacetylates and activates PGC-1, which inhibits muscular atrophy. In this regard, resveratrol and quercetin treatment may be useful for protecting against obesity-induced sarcopenia [238, 239].

Omega-3 LCPUFAs have potent anti-inflammatory properties, and variations in intake could be of importance [240]. Aside from effects on inflammation, these fatty acids could also have direct effects on muscle protein synthesis [242].

Drug Therapy

While different medications are available for management of osteopenia, therapeutic medications for sarcopenia are partially effective, with low evidence level and consequently, weak recommendation level. However, some reports showed that skeletal muscle mass and muscle strength both can increase as a result of some therapeutic medications such as androgen supplementation therapy, but the participants in these studies were men showing decreased gonadal function and postmenopausal women [243–245] rather than older patients with sarcopenia. Therefore, there are not yet licensed treatments for it [246], and so far the only preventive measures consist of an equilibrated diet and the regular practice of exercise during all of the lifespan. These were reported to be able to slow and reduce the decline in muscular mass and function present in sarcopenia [247]. Therapeutic agents studied for treatment of sarcopenia vary according to their mechanism of action and therapeutic targets, these include:

Vitamin D

Levels of vitamin D in the elderly drop up to 4 times low compared to adult age. Vitamin D plays a role in muscle and bone metabolism. Vitamin D bind to the Vitamin D receptor in muscle inducing protein synthesis and increased calcium uptake through cell membranes. Low levels of vitamin D are associated with the occurrence of muscle atrophy facilitating the occurrence of sarcopenia. Low Vitamin D levels are often also associated with muscle weakness with general frailty symptoms in elderly [247 original].

One of the new roles described for vitamin D is the maintenance of muscle mass, as well as insulin sensitivity [248]. Insulin sensitivity either

improves or is unaffected by vitamin D supplementation [249, 250]. Vitamin D supplementation was reported to increase muscle fiber size in immobile older women; however, supplementation in individuals with vitamin D deficiency improved muscle strength, but not muscle mass [250, 251]. In knockout mice for the vitamin D receptor (Vdr), there was reduced muscle size, impaired motor activity, and abnormal muscle development [252, 253]. In addition, Vdr-null mice are leaner, but insulin resistant [254]. The relationship between vitamin D status and frailty is largely mediated by the development of sarcopenia. A minimum serum 25-hydroxyvitamin D level of 75 nmol/L is proposed for frail elderly patients and the doses necessary to reach this target are between 800 and 2000 IU/day [255]. However, the value of vitamin D supplementation therapy to improve physical performance is also still not consistent. Things to watch out for in vitamin D supplements are the occurrence of nephrolithiasis and hypercalcaemia [256, 257].

Sex Hormones

1. Androgens: Testosterone produced by leydig cells in men and thecal ovarian in women will decrease as a result of the aging process. Testosterone is instrumental in forming muscle mass and protein synthesis in muscles. The concentration of Sex Hormone Binding Globulin (SHBG) that binds testosterone in the blood increases with age so that free testosterone levels decrease [247].

   Testosterone increases muscle protein synthesis, and its effects on muscle are modulated by several factors including genetic background, nutrition, and exercise [258, 259]. Obese individuals tend to have lower testosterone levels [260]. In males, levels of testosterone decrease by 1% per year and those of bioavailable testosterone by 2% per year from age 30 [261]. In women, testosterone levels drop rapidly from 20 to 45 years of age [2]. High levels of these anabolic hormones are positively associated with elevated muscle strength and may therefore contribute to muscle improvement in obese individuals [262–265]. In young men, low secretion level of testosterone results in decreased muscle mass and strength, and testosterone replacement therapy increases the sensibility of testosterone receptors, consequently increases muscle mass and restores muscle strength [265, 266]. Sinha-Hikim et al. [267] demonstrated that supra-physiological doses of testosterone can induce increase in muscle size and strength in younger men without concomitant exercise.

   However, hormone therapy with increases muscle mass can help preserve muscle strength but it carries a certain risk, especially when the treated population is unhealthy or when supra-physiologic doses are administered rather than replacement doses [268]. Calculating the correct concentration of hormone per individual considering the appropriate threshold without collateral damage, can be difficult since increases muscle mass may have negative impact on different organs. For example, T replacement has been associated with higher rates of prostate cancer, prostate-specific antigen, erythrocytosis cardiovascular events, acne, oily skin, reduced sperm production, and fertility [269]. Orally administered androgens are known to be hepatotoxic and may promote hepatic steatosis which is associated with dyslipidemia and increased very low density lipoprotein- triglyceride (VLDL-TG) secretion. Also they may induce fluid retention, gynecomastia, and sleep apnea [270]. However, lower increases muscle mass concentrations in older men are associated with higher atherosclerosis and myocardial infarction [271]. The above suggests that the threshold of testosterone concentration used to increase muscle mass is very important to obtain the beneficial effects on metabolic pathways and minimize the negative effects risk attributed to this hormone [185].

   Nevertheless, androgen therapy may also be linked to improved insulin sensitivity [246].

   A selective androgen receptor could be developed in the future that might not have

many of these side effects. Candidate drugs e.g. the selective androgen receptor modulator GTx-024 (enobosarm) and synthetic androgen receptor modulator ligand, S42, were reported in preclinical and phase II trials to have beneficial effects on insulin sensitivity, muscle mass, and strength [269, 272].

Estrogens

Numerous studies have revealed that estrogens mediate the attenuation of infiltration of inflammatory cells, such as neutrophils and macrophages, into skeletal muscles of rats following exercise or injury. It also plays a significant role in stimulating muscle reparation and generative processes including the activation and proliferation of satellite cells. However, the mechanisms by which estrogen exerts influence on damaged muscle and can influence the force generating capacity of skeletal muscle are still unknown [273]. Estrogen reduction is associated with decreased muscle size and a decline in force-generating capacity; this can be prevented using hormone replacement treatment [274]. Lowe et al. showed that estrogen has beneficial effects on muscle strength in postmenopausal women.

Estrogen replacement therapy also has beneficial effects against menopause-related obesity sarcopenia [275].

However, estrogen effects on muscle structure and contractile function in humans are controversial and depend on age, muscle size, and muscular fiber type [276]. For example, testosterone or estrogen are potent skeletal muscle protein anabolic agents in men and women. Administration for 3 weeks in obese but otherwise healthy premenopausal women did not affect plasma lipid kinetics and concentrations [277]. The most important risk that is feared in the use of HRT estrogen is breast cancer that until now has not been tested [278].

The beneficial effects of estrogen therapy was reported to be associated with an increase of pro-anabolic markers, such as MyoD, myogenin, Myf5, and the greater suppression of proteolytic markers, such as FOXO3A, as well as the negative growth regulator, myostatin. These beneficial effects are even more evident when combined with exercise [277].

Insulin and Insulin-Like Growth Factor-1

Insulin and insulin-like growth factor-1 (IGF-1) have predominant metabolic and anabolic effects on muscle, constituting powerful anabolic signals [279]. The activation of phosphoinositide 3-kinase (PI3K) pathway has positive effects on muscle size and metabolism. Insulin significantly stimulates muscle protein synthesis in young but not older subjects.

In sarcopenia, there is a reduced muscle protein synthesis in response to nutrients or insulin and a reduced insulin-mediated suppression of proteolysis, which has been referred to as "anabolic resistance." Elderly individuals of normal muscle mass also show resistance to the anabolic action of insulin, which may precede the physical expressions of sarcopenia [280–282]. Differential insulin resistance with respect to glucose, protein, and lipid metabolism can develop with aging and sarcopenic obesity. Many elderly persons respond to insulin by modifying glucose metabolism, but protein synthesis is not affected by the hormone [283]. When elevated adiposity is present, the effectiveness of high levels of insulin, essential amino acids, and resistance exercise to induce muscle protein synthesis is decreased [284–286]. The insulin-mediated increase of muscle mass is mediated by the activation of p38 mitogen-activated protein kinase (MAPK (p38 MAPK) and mTOR/p70S6 kinase (mTOR/p70S6 is a serine/threonine protein kinase that supports cell growth, cellular metabolism, cell proliferation, cell motility, cell survival, protein synthesis, and transcription such as angiogenesis and autophagy; and stimulation of mRNA translation [281, 287].

Treatment with the insulin-sensitizing thiazolidinedione drug rosiglitazone leads to an improvement in muscle mass. Although impairment of the Akt-mTOR pathway in muscles (the PI3K/AKT/mTOR pathway is an intracellular signaling pathway important in regulating the

cell cycle), does not seem to occur during aging in humans or mice, stimulation by rosiglitazone of PPAR (peroxisome proliferator-activated receptor gamma (PPARγ) ligand) - could also result in the activation of the Akt-mTOR cellular signaling pathways having a beneficial effect upon insulin resistance and muscle mass [288].

Growth Hormone

Growth of multiple target tissues, including skeletal muscle, is regulated by growth hormone, which is a single-chain peptide produced and secreted by the somatotrophs of the anterior pituitary gland [289]. Growth hormone can maintain muscle and bone mass. The role of GH is to stimulate the secretion of IGF-1 as an anabolic hormone from the liver that stimulates the production of muscle cell mass and muscle protein synthesis. After 30 years of age and in aged men, circulating GH levels decline progressively; GH secretion per day is 5- to 20-fold lower in elderly people than the secretion found in young adults [290, 291].

Growth hormone supplementation for the elderly has been tested in a large population; however, it was not effective to treat sarcopenia and it showed minor side effects [291–293]. Its use is not favored by the fact that high circulating levels of free fatty acids, which are present in obesity, inhibit GH production and decrease plasma levels of IGF-1 [294, 295]. A recent study showed that sarcopenic obese subjects had depressed GH secretion when compared to obese persons [296]. Makimura et al. [297] recently reported the effects of a GH-receptor analog that reduced fat mass and increased lean body mass in obese individuals was not associated with abnormalities in glucose homeostasis or other adverse events compared to placebo [298].

Myostatin Inactivation

Myostatin was first discovered during screening for novel members of the transforming growth factor- (TGF- superfamily). Myostatin is a potent negative regulator of muscle growth [299].

Beneficial effects on metabolism, adiposity, and insulin sensitivity have been found with low levels of Myostatin. There was elevated muscle glucose utilization and insulin sensitivity linked to increased lean mass and diminished fat mass in Myostatin-null mice and in mice treated with a soluble receptor to Myostatin, namely activin receptor type IIB (ActRIIB). Myostatin leads to receptor-mediated phosphorylation of Smads 2 and 3, and binds to Smad 4. Increased Smad2/3/4 signaling inhibits the Akt/mTORC1 pathway, thus leading to protein degradation and muscle atrophy (Fig. 3.9) [300–302].

Mutations in Myostatin cause significant hypertrophy and/or hyperplasia in developing animals [299]. The inhibition of Myostatin induced by gene manipulation or neutralizing antibodies improves sarcopenic obesity by increasing skeletal muscle mass and improving glucose homeostasis. Moreover, when Myostatin is inactivated, activation of AMP-activated protein kinase (AMPK), which leads to increased lypolisis, elevated fatty acid oxidation in peripheral tissues, and a high expression of brown adipocyte markers in white adipose tissue [303, 304].

Overexpression of the Myostatin propeptide and sequestration of the active peptide enhances skeletal muscle glucose disposal due to increased muscle mass, implying that additive or synergistic mechanisms are in operation. Although the inhibition of Myostatin activity as a therapeutic approach has not been effective, the use of antisense-mediated destructive exon skipping is being evaluated. It seems to preserve muscle mass in a mouse model of Duchenne muscular dystrophy [305].

Based on the notion that Myostatin interferes with growth hormon in the muscles to facilitate the occurrence of atrophy and sarcopenia. Giving follistatin (myostatin antagonist) is expected to be able to increase protein synthesis in muscle and increase muscle mass. This therapy is very potential for sarcopenia but still needs further research [original]. Another study revealed that Myostatin inhibition induce a reduction of fat in obesity and osteoporosis and has also been suggested for other diseases in which cachexia is present such as cancer, acquired immune deficiency syndrome (AIDS), obstructive chronic pulmonary disease, and renal failure [306].

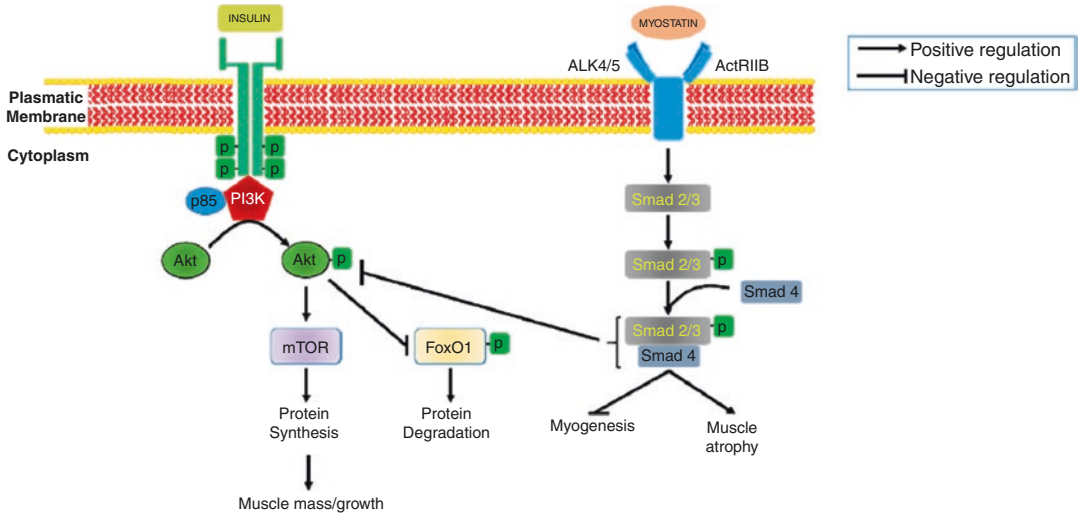

Fig. 3.9 Schematic illustration of myostatin signaling pathway in sarcopenia. Signaling activated by insulin positively regulates muscle mass, downstream of protein kinase Akt and mTOR. Myostatin first binds to the activin receptor (ActRIIB)/Alk 4/5 on skeletal muscle causing phosphorylation of Smad2 and Smad3, and the recruitment of Smad4 into a Smad complex, which leads to muscle atrophy. Second, Smad 2/3/4 complex downregulate the activity of Akt, thereby inhibiting protein synthesis. Akt blocks FOXO1 nuclear translocation to inhibit protein degradation. (Quoted under open access scheme from Rubio-Ruiz et al. [233])

Moreover, there was no amelioration in muscle strength or function in muscular dystrophy patients in one phase I/II trial of a MSTN antibody [307]. In another study which included patients with muscular dystrophy, there were also no important improvements in muscle strength by Myostatin inhibition, although there was an amelioration in muscle function at the cellular level [308].

Urocortins

The central nervous system and peripheral tissues express neuropeptide ligands for the corticotrophin-releasing factor receptor 2 (CRFR2) known as urocortins (Ucns). This family of proteins plays different roles in metabolic functions, including adaptive stress.

Modulation of CRFR2 or its ligands may improve muscle mass and metabolism by activating the hypothalamic–pituitary–adrenal (HPA) axis [309]. Skeletal muscle has high levels of urocortin2 (Ucn2) and CRFR2 [310]. Knockout mice for urocortin2 (Ucn2) or corticotrophin-releasing factor receptor 2 (CRFR2) are resistant to diet-induced obesity and urocortin2 (Ucn2) knockouts have increased muscle mass [311]. Overexpression of urocortin3 (Ucn3) also results in mice with muscular hypertrophy. Short-term overexpression of urocortin3 (Ucn3) in rat muscle increased glucose disposal, elevated levels of glucose transporter expression, and phosphorylation of both AMP-activated protein kinase (AMPK) and insulin signaling molecules. Muscle mass increased afterwards in these mice [312].

Since urocortins (Ucns) or corticotrophin-releasing factor receptor 2 (CRFR2) agonists have potentially beneficial effect in preserving skeletal muscle mass/function in a cachexia state linked to other diseases, such as cancer, there might be a potential in testing their use for the treatment of sarcopenic obesity [313].

Angiotensin 1–7 and Angiotensin-Converting Enzyme Inhibitors

The renin–angiotensin system (RAS) is an important regulator of skeletal muscle mass. Recent advances have improved our understanding of the

renin-angiotensin system (RAS). These have included the recognition that angiotensin (Ang)-(1–7) is a biologically active product of the RAS cascade [314]. The classical renin-angiotensin system "classical RAS axis" involves: angiotensin II, angiotensin converting enzyme (ACE), AT1 receptor, and AT2 receptor; whereas the "nonclassical RAS axis" involves: angiotensin 1–7, ACE2, and Mas receptor. Both axes have been found in skeletal muscle and could play a role in the regulation of muscle function by a differential expression of the biochemical and/or metabolic features of the fibers [315].

The metabolic actions of RAS in skeletal muscle were addressed in earlier studies [248]. Activation of the classical RAS causes deleterious effects in skeletal muscle, including muscle wasting. In contrast, angiotensin 1–7 produces beneficial effects in skeletal muscle by downregulating the catabolic pathway of sarcomere proteins and preventing the atrophic effects induced by TGF-ß [316].

Angiotensin 1–7 treatment, sarconeos which activate the MAS (angiotensin-1) receptor, was able to maintain muscle strength and prevented decreases in muscle diameter and mass by activating IGF-1 and Akt pathways that also might improve insulin resistance in skeletal muscle [317]. Moreover, angiotensin 1–7 had an ameliorating effect on insulin resistance, hypertriglyceridemia, fatty liver, inflammation, obesity, and oxidative stress in metabolic syndrome models [318]. Based on this, it has been suggested to use angiotensin-converting enzyme inhibitors to modulate RAS, favoring the production of angiotensin 1–7, thus contributing to the change in body composition and preventing the development of sarcopenia and simultaneously ameliorating the pathophysiologic parameters [319]. The beneficial effects of ACE-inhibitors on the musculoskeletal system have been attributed to several mechanisms such as anti-inflammatory effects, endothelial function improvement as well as angiogenesis effects which improves muscle circulation (Fig. 3.10). However, few studies have been conducted to determin the musculoskeletal effects of ACE-inhibitors, therefore, larger studies are needed to prove the most promising effect seen in the above mechanism [320].

Selective Androgen Receptor Modulators (SARMs)

The benefits of maintaining lean mass are apparent to the medical community, and significant efforts are being made to explore options for the medical management of sarcopenia.

One direction under investigation is the development of SARMs, which are a synthetic group of compounds that bind to specific areas of androgen receptors on many cell surfaces to activate or inhibit selective functions of the steroid receptors.

This selective activation/inhibition could encourage muscle growth while at the same time prevent some of the unwanted aspects of hormone therapy, such as prostate growth in men, and minimize the virilization effects on women. Similarly, for any SARM to become accepted for clinical use in the treatment of sarcopenia, it must not adversely affect the patient's cardiovascular risk profile [321].

Currently, there are several SARMs in clinical trials. One such example is ostarine, a SARM developed to help with muscle wasting secondary to malignancy. After only 86 days of use, elderly men and women had improved ability to climb stairs and had increased lean body mass. More importantly, men had no increase in prostate-specific antigen levels and women had no increase in hair growth, suggesting the selective androgenic nature of this drug and side effect profiles remain low [322] However, there is always the potential for misuse of new therapies, especially by people for whom the treatment was not intended. While SARMS can help increase muscle tissue in wasting conditions, including sarcopenia and cachexia, there is potential for athletes to utilize these new products to enhance performance. The World Anti-Doping Agency has added SARMs to its list of banned substances in advance of any specific product on the market. Clinical detection mechanisms are already in place to detect these new compounds [323].

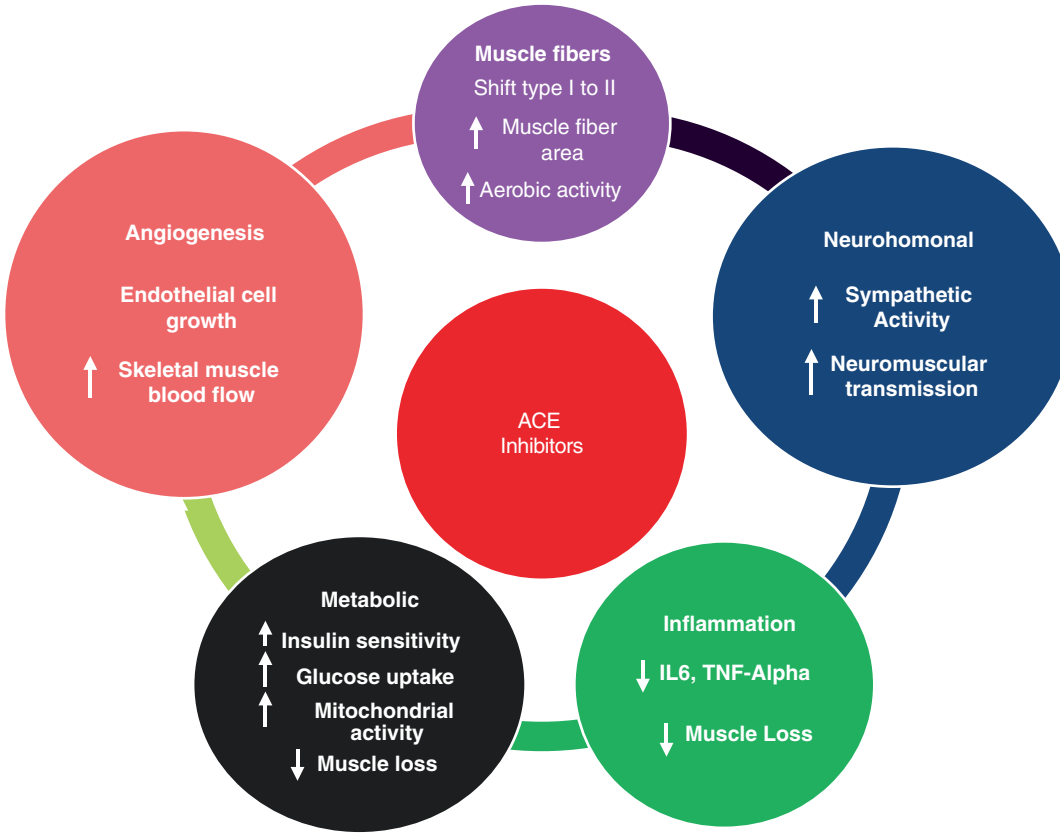

Fig. 3.10 Effects of the ACE inhibitors on the musculoskeletal system

Future Therapies

Other future therapies include Peroxisome-Proliferator-Activated Receptor-δ (PPAR-δ) and Adenosine Monophosphate (AMP) -activated protein kinase. PPAR- δ and AMP-activated protein kinase are proteins that regulate metabolism and muscle contraction. Giving agonist PPAR- δ and AMP-activated protein kinase can improve physical ability and exercise but this is still in animal experiments only [278]. Metformin, a drug that has been used for the treatment of type-2 diabetes, was reported to have anti-inflammatory properties. This was attributed to its ability to stimulate the same metabolic pathways (AMPK), mimicking some of the effects of exercise. However, whether metformin is an effective treatment for sarcopenia is still a matter of debate [279]. There is also interest in the role of beta-blockade. Earlier study revealed that beta-adrenergic blockade attenuated the development and promoted a partial reversal of cachexia in patients with severe chronic heart failure, supporting a role for prolonged sympathetic activation in the genesis of weight loss [324].

Patient-Centered Approach for Sarcopenia Management

The advent of patient-centered care has attracted the attention to the fact that disorders with multifactorial aetiology require different therapeutic approaches tailored to the patients' condition and associated comorbidities. Osteosarcopenia is a good example for such management approach. At present, the treatment of osteosarcopenia is focused on bone protection, calcium and vitamin D supplementation, and resistance exercise. Nutrition and protein supplements are also

another factor which plays an important role particularly in older adults. The use of leucine essential amino acids and/or β-hydroxybutyrate has not been clearly established but would seem a reasonable adjunct in persons with low protein intake.

However, while these measures can help in primary prevention and management of ostesarcopenia, they may not be enough for secondary and tertiary prevention of the condition (Fig. 3.11). Diseases leading to secondary sarcopenia include cancer, COPD, CKD, heart failure, osteoporosis, and others.

Cancer Few reports currently described the results of clinical trial results investigating the impact of improving sarcopenia in conjunction with cancer treatment. Earlier studies revealed that supplementation with vitamin D or β-hydroxy-β-methylbutyric acid in cancer patients is effective for increasing or preventing decreases in muscle mass [325], whereas suitable amounts of exercise have been reported to potentially suppress loss of muscle mass during breast cancer treatment [326]. In addition, in an RCT investigating 57 patients with prostate cancer undergoing androgen suppression therapy for >2 months, the patients were divided into a resistance +aerobic exercise group (29 patients) and a usual care group (28 patients), and were observed over a 12-week period. As a result, patients in the exercise group showed significant increases in skeletal muscle mass, (whole body, lower extremities, upper extremities), increased muscle strength and gait function compared to the usual care group [327].

Respiratory rehabilitation and physical training to improve COPD have been shown to result in increases in bodyweight and skeletal muscle mass, as well as improved motor functions. In a study investigating the impact of amino acid supplementation, 32 patients aged >40 years with severe COPD complicated by sarcopenia were divided into a 4 g/b.i.d. amino acid group (16 patients) or a placebo group (16 patients), after which the degree of change in their conditions after 4 and 12 weeks was examined. As a result, compared with the placebo group, patients in the amino acid group showed a mean increase in

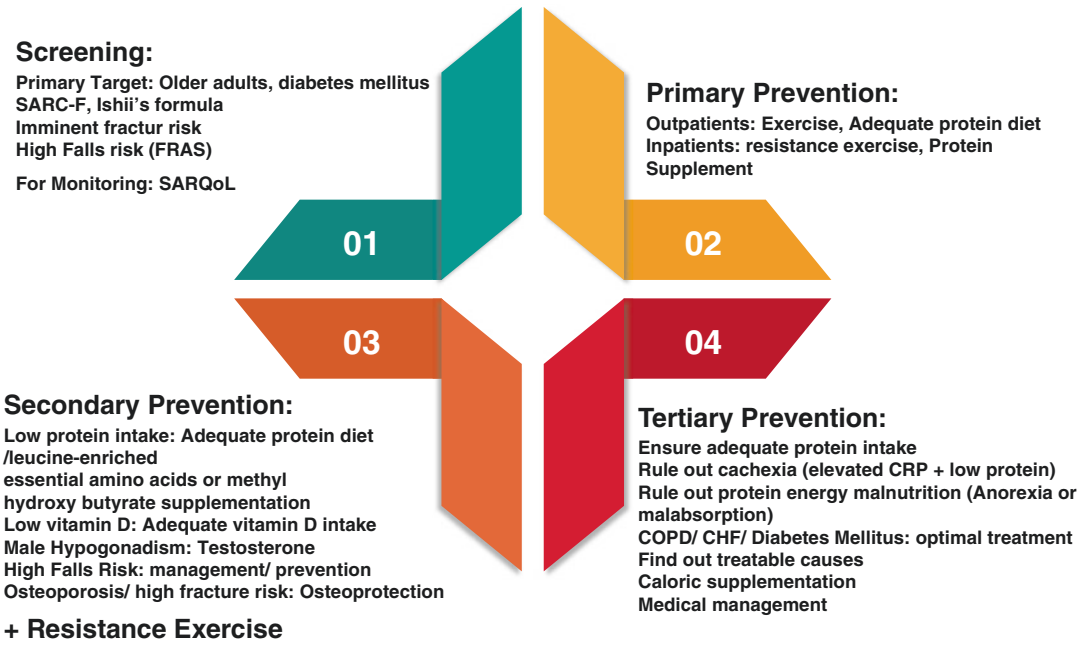

Fig. 3.11 Targeted Management of osteosarcopenia: patient-centered approach

bodyweight of 6 kg, increased physical activity, improved cognitive function and improved overall health [328].

Chronic kidney disease Sarcopenia readily complicates chronic renal impairment and CKD cases, and the prevalence of sarcopenia increases as the severity of CKD progresses to higher stages [329]. Exercise and amino acid as well as vitamin D supplementation are effective for improving inactivity and sarcopenia symptoms in patients with CKD [330]. In support of this observation, in a study which included 119 patients with stage 3 or 4 CKD, patients were randomly placed into a group undergoing exercise training (65 patients) or a usual care group (54 patients). The patients were followed for 12 weeks. Results revealed that the performance on the 6-min walk test improved by 19% in the exercise training group, whereas the performance decreased by 10% ($P < 0.001$) in the usual care group. In addition, the performance on the chair-stand test improved by 29% and 0.7% in the exercise training and usual care groups, respectively ($P < 0.001$). These results suggested that the exercise program was effective for improving the physical capacities and quality of life of patients with CKD [331].

Impaired cardiac function Restriction of physical activity due to diminished cardiac function in patients with chronic heart failure can result in decreased muscle mass and muscle weakness, and sarcopenia occurs as a complication in approximately 20% of older patients with chronic heart failure [332]. Although nutritional supplementation, exercise, and hormone replacement therapy have been proposed as methods for improving sarcopenia and diminished cardiac function [330], others have highlighted the effect of a high-protein diet and/or amino acid supplementation to cause weight gain in patients with chronic heart failure [333], whereas exercise training has been shown to help reduce myostatin and improve aerobic capacity [334, 335]. Although inadequate testosterone in patients with chronic heart failure has been associated with the onset of muscle weakness, such patients have shown improved gait functions and increased muscle strength as a result of testosterone supplementation [336]. Although similar effects have been reported with regard to supplementation with human growth hormone, ghrelin and vitamin D, there is currently insufficient evidence regarding the effects of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and β-blockers in patients with sarcopenia.

Osteoporosis is strongly associated with decreases in muscle mass and muscle strength. In a study of 131 men (mean age 77.1 ± 7.6 years) with a history of bone fractures, low bone density, and low blood testosterone level, the participants were divided into either a group administered 5 mg/day testosterone supplementation or a placebo group, and were then observed for 12–24 months. As a result, femoral cervical and lumbar bone densities increased by 1.4% and 3.2%, respectively, in the testosterone-supplemented group. In addition, although muscle mass increased and body fat decreased in the testosterone supplemented group, no differences in exercise capacity were observed compared with the placebo group [337].

Furthermore, in another study in which 5 mg/day of alendronate and 0.5 μg/day of calcitriol were administered for 6 months to 38 women (mean age 56.0 ± 8.00 years) with decreased bone density, interleukin-6 levels, lumbar vertebral bone density and grip strength decreased by 56.5%, 2.62%, and 33.5%, respectively. These findings clearly show that treatment with 5 mg/day of alendronate and calcitriol were effective for suppressing bone loss and increasing skeletal muscle mass in women presenting with reduced bone density [338, 339].

In conclusion, given its characteristics, osteosarcopenia can be considered as a new geriatric syndrome that describes the co-existence of osteoporosis and sarcopenia, two chronic musculoskeletal conditions associated with aging. This phenotype is associated with a higher risk of falls, fractures, dependence, and health care costs than its individual components. Its aetiology is multifactorial, with mechanical, biochemical, genetic

as well as lifestyle factors all contributing to involution of the "bone–muscle unit." Therefore, understanding its pathophysiology and diagnosis, as well as its nonpharmacological and pharmacological management is a task of great importance. Combined management interventions might be an effective option for sarcopenia. The challenge in addressing this phenotype arises from the tradition of managing sarcopenia and osteoporosis separately. Improved understanding of the interactions between muscle and bone could facilitate the development of new therapeutic agents which target muscle and bone as one. Adopting a patient-centered approach in management would play an important role in the disorder management.

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Bone Health in Women

4

Yasser El Miedany

Introduction

Bone is a living, dynamic tissue that undergoes constant remodeling throughout life. This is necessary to allow the skeleton to increase in size during growth, respond to the physical stresses placed on it, and repair structural damage due to structural fatigue or fracture. This process requires a range of proteins and minerals, which are absorbed from the bloodstream [1]. In childhood, bones grow and repair very quickly, but this process slows down as you get older. Bones stop growing in length between the ages of 16 and 18 but continue to increase in density until late 20s. From about the age of 35, gradually lose bone density. This is a normal part of aging, but for some people it can lead to osteoporosis and osteoporosis is a condition that affects the bones, causing them to become weak and fragile and more likely to break [2]. Before a woman reaches 30 years of age her body gains more bone than it loses. Around age 30, this process balances out. However, for most women, bone mass remains stable until menopause, when the loss of estrogen in conjunction with aging is associated with a decline in bone mineral content. The onset of menopause around 50 years of age may speed up the rate of bone loss. If bone loss becomes severe, a woman may develop osteoporosis [3]. Family history, gender, and race are responsible for the majority of peak bone mass; however, diet and exercise behaviors are responsible for up to 25%.

Risk for osteoporosis is greater for women than men. Established risk factors for women include increased age, Caucasian or Asian ethnicity, postmenopausal status, late menarche or early menopause, low peak bone mass, family history of osteoporosis or fracture, low dietary intake of calcium and vitamin D, lack of physical activity, smoking, excess alcohol consumption, and long-term use of certain medications, such as steroids, anticonvulsants, immunosuppresants, and heparin [4, 5]. Female bone health can be stratified into phases outlined by the woman's age. In postmenopausal women, osteoporosis is usually the result of accelerated bone turnover due to estrogen deficiency, whereas in aging women and men, vitamin D insufficiency and secondary hyperparathyroidism may further contribute to bone loss. In these subjects, osteoporosis is diagnosed when their hip or spine bone mineral density (BMD) is two and a half standard deviations (SD) or more lower than the young adult mean (T-score ≤ -2.5) [6, 7]. Together with prevalent fragility fractures (typically spine or hip), T-scores equal to or below −2.5 are considered as clear indications for osteoporosis therapy, although age and clinical risk factors that modulate fracture probability may also have to be taken into account [9]. In contrast, low bone mass

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in children and adolescents has been defined as an areal bone mineral density (aBMD) more than 2 SD below the age-adjusted mean value (Z-score <−2SD) [8], and it has been recommended that bone fragility should not be diagnosed on the basis of low bone mass alone but requires the presence of fractures due to low trauma [10]. On the other hand, in comparison to childhood and postmenopausal/ elderly subjects, diagnosis and treatment of osteoporosis in young adults, i.e., between 20 and 50 years of age, remain poorly defined. The true difficulty resides in differentiating between those young healthy individuals whose apparently low aBMD reflects low peak bone mass in relation to their body size, pubertal timing, genetic background, and environment during growth [11–13], which does not necessarily represent a pathological condition, and those who may truly have osteoporosis with bone fragility at a young age, resulting from altered bone modeling and/or remodeling during growth and/or thereafter. The latter situation is most commonly associated with a chronic disorder and may also occur as a genetic or idiopathic condition. Distinguishing between these two situations can be difficult base up to 30% of young women and 50% of young men have had fractures during childhood and adolescence, usually traumatic but not uncommonly multiple [14–17]. These fractures are associated with decreased bone mass acquisition and lower peak bone mass in otherwise healthy individuals [16], i.e., without an underlying pathophysiological mechanism. It would, therefore, be inappropriate to investigate for osteoporosis, e.g., perform a DXA examination, and to search for secondary causes of osteoporosis in most young people with prevalent fractures, unless the circumstances (low trauma), frequency (over two fractures), and/or site of fractures (e.g., vertebrae) appear unusual.

This chapter will discuss the physiological and pathological changes in young adult women, pregnancy and lactation, followed by changes in both the pre-menopausal and post-menopausal period and lastly elderly women. The chapter will then discuss the diagnostic criteria for osteoporosis in women. It will also propose a clinical approach to the patients' assessment in standard practice.

Young and Adulthood

Between 8 and 18 years of age, bone mineral content (BMC) more than doubles, whereas the true volumetric bone mineral density (vBMD) barely changes [18]. This bone mass accumulation pertains primarily to an increase in bone size (diameter) and cortical thickness by periosteal apposition (modeling) and, to a lesser extent, to trabecular bone formation and thickening [19]. Meanwhile, endosteal surfaces undergo both modeling and remodeling in order to achieve, approximately by the age of 20, bone mass, geometry, and microstructure of the adult skeleton [20]. In turn, peak bone mass is a major determinant of bone strength and fragility throughout life, hence, the increase in bone diameter and mass in growing females, which occurs at approximately the same rate as in males. However, this increase lasts longer in men leading to a 10–15% greater peak bone mass on average, consequently, it plays an important role in explaining the lesser and later propensity to fractures in aging men compared to women. Nevertheless, as a result of continuous bone remodeling, loss of cortical and trabecular bone starts soon after peak bone mass is achieved in both genders, albeit in variable proportions in weight-bearing and non-weight-bearing bones and accelerates in women after menopause and in aging men [21–24].

Heredity, that is, the additive effects of genes and their polymorphisms, accounts for 50 to 80% of the variation in bone mass and structure among individuals [25] and likely contributes to some of the phenotypic differences between the male and female skeleton [26]. Yet gene expression depends on both the internal and external milieu, i.e., on hormone levels, particularly gonadal steroids (puberty) and the growth hormone (GH)–IGF-1 axis; nutrition, such as calcium and protein intake; physical activity, particularly load-bearing exercise; lifestyle; etc. [19] (Fig. 4.1 shows developmental risk factors for osteoporosis). Therefore, any disorder that might occur during growth that alters one or more of these parameters will exert a negative influence on bone modelling and remodelling; consequently, will affect bone mass acquisition

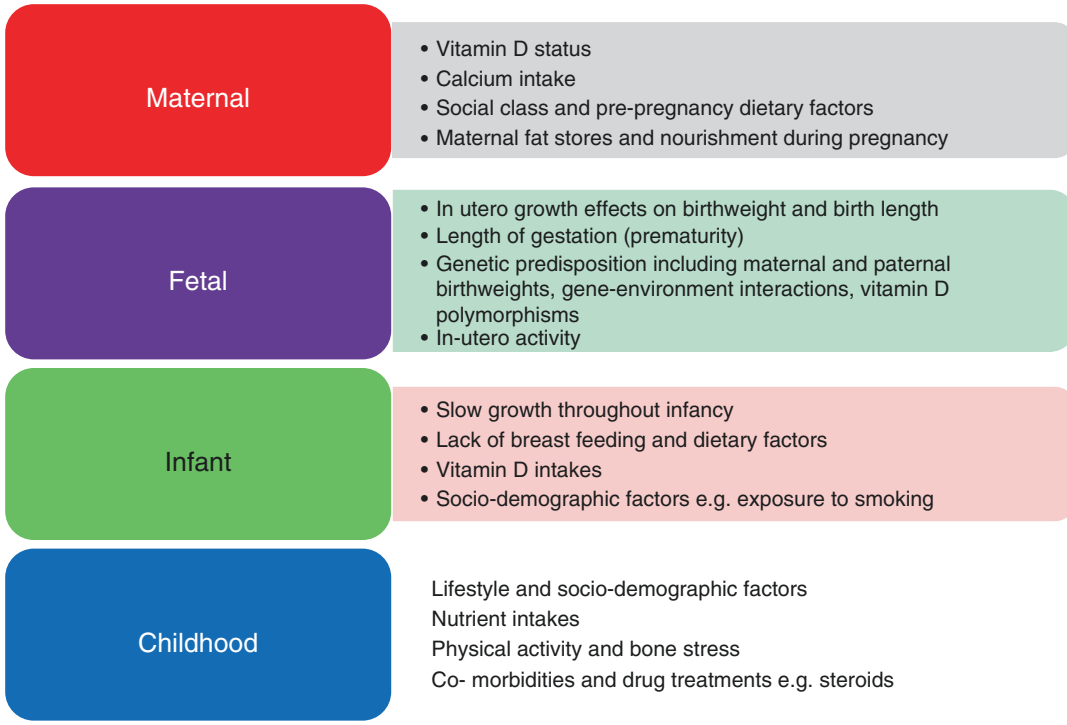

Fig. 4.1 Developmental risk factors for osteoporosis

and its distribution in the cortical and/or trabecular compartment; and could thereby cause bone fragility not only during growth but later on in young adults. Similarly, endocrine, nutritional, and other disturbances appearing during early adulthood will precipitate bone loss at a younger age. A good example would be inflammatory bowel diseases (IBD), particularly Crohn's disease, which impair bone mass accrual and/or accelerate bone loss because of malabsorption and poor nutrient intake; low levels of physical activity; delayed puberty or secondary amenorrhea, in addition to systemic inflammation, and, in many cases, effects of corticosteroid treatment [27]. Another example of the complex pathophysiology of osteoporosis in the young is illustrated by thalassemia major, which causes hormonal deficiencies (GH–IGF-1 and gonadal steroids), expands bone marrow at the expense of bone tissue, interferes with mineralization due to iron overload, and, additionally, defers oxamine treatment that inhibits osteoblastic function [28]. Among numerous pharmacological agents implicated in bone loss (Fig. 4.2), depot progesterone acetate (Depo-Provera), used as a contraceptive agent, has raised huge concerns [29, 30].

Pregnancy and Lactation

A moderate increase of bone turnover (Fig. 4.3) has been reported during pregnancy [31], although it is still uncertain whether significant changes of bone mass occur. A small decrease in aBMD has been observed at the lumbar spine, but in long bones, this might be compensated by endosteal and periosteal appositions [32]. While during pregnancy the mother's intestinal calcium absorption is increased; it returns to normal values during lactation [33], putting further pressure on the skeleton to compensate for the need of calcium associated with breastfeeding. The body adapts by increasing bone resorption and reducing renal calcium excretion, influenced by increase in parathyroid hormone production and hypo-estrogenic state secondary to high prolactin

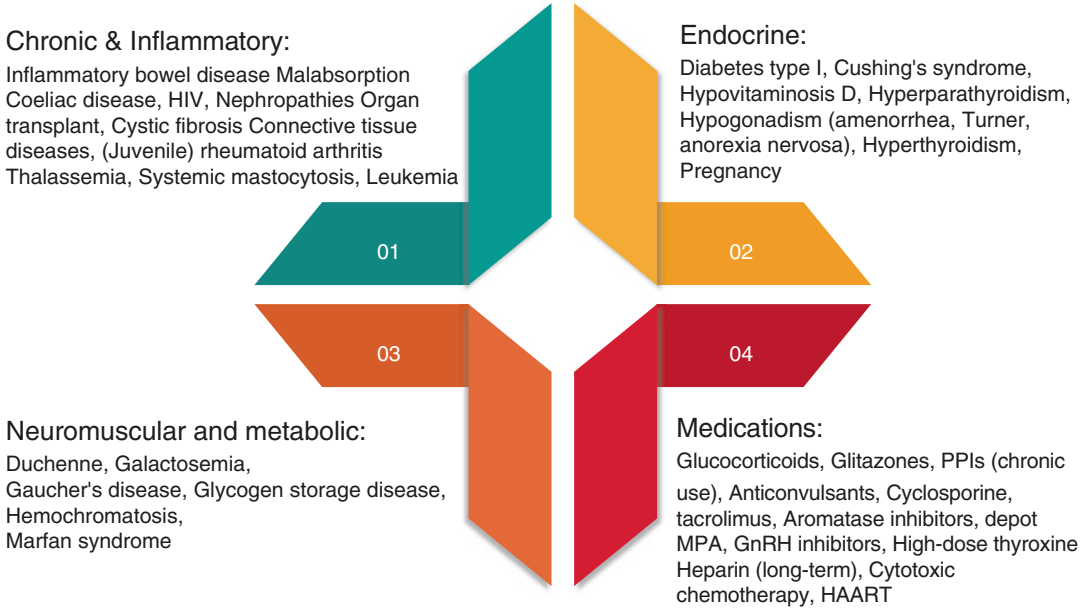

Fig. 4.2 Causes of secondary osteoporosis in the young. (*HIV* human immunodeficiency virus, *MPA* medroxyprogesterone acetate (used as contraceptive), *HAART* highly active antiretroviral therapy, *PPIs* proton pump inhibitors)

levels [32, 34, 35]. The decrease in bone mass, observed mainly in the trabecular compartments of bones, is generally restored 6 to 12 months after weaning [36].

Pregnancy-associated osteoporosis is a rare condition, which can present in the form of spinal osteoporosis or transient osteoporosis of the hip, as well as associated with prolonged heparin use [37]. Transient osteoporosis of the hip is associated with uni- or bilateral hip pain and may be complicated with a fracture, sometimes spontaneous [38]. Post-pregnancy osteoporosis can lead to vertebral fractures, height loss, and severe back pain [39], as well as clinical fractures at other sites. Pre-existing low BMD and high bone turnover during pregnancy and lactation may both play a role [34]. In women of reproductive age with established osteoporosis, it could, therefore, be recommended to avoid breastfeeding. Randomized doubleblind placebo-controlled study on postpartum healthy women revealed that calcium supplementation did not prevent bone loss during lactation and only slightly enhanced gain in bone density after weaning [40].

Premenopausal Women

Osteoporosis is less common in premenopausal women than in postmenopausal women. However, both fractures and low bone mineral density do occur in the premenopausal years, and young women with these conditions require specialized clinical considerations. Osteoporosis in premenopausal women results from either a low peak bone mass, increased bone loss prior to menopause, or both [41]. As noted earlier, peak bone mass is reached by 30 years of age with 90% of the development completed by 18 years of age. For most women, bone mass remains stable until menopause, when the loss of estrogen in conjunction with aging is associated with a decline in bone mineral density. Peak bone mass variations are genetic in 60–70% of cases [42]. The loss of bone results from an imbalance in bone formation by osteoblasts and bone resorption by osteoclasts. Most treatments for osteoporosis aim to adjust this imbalance [43]. In the case of premenopausal osteoporosis, secondary causes are responsible for at least half of cases [41]. Secondary causes are listed in Table 4.1.

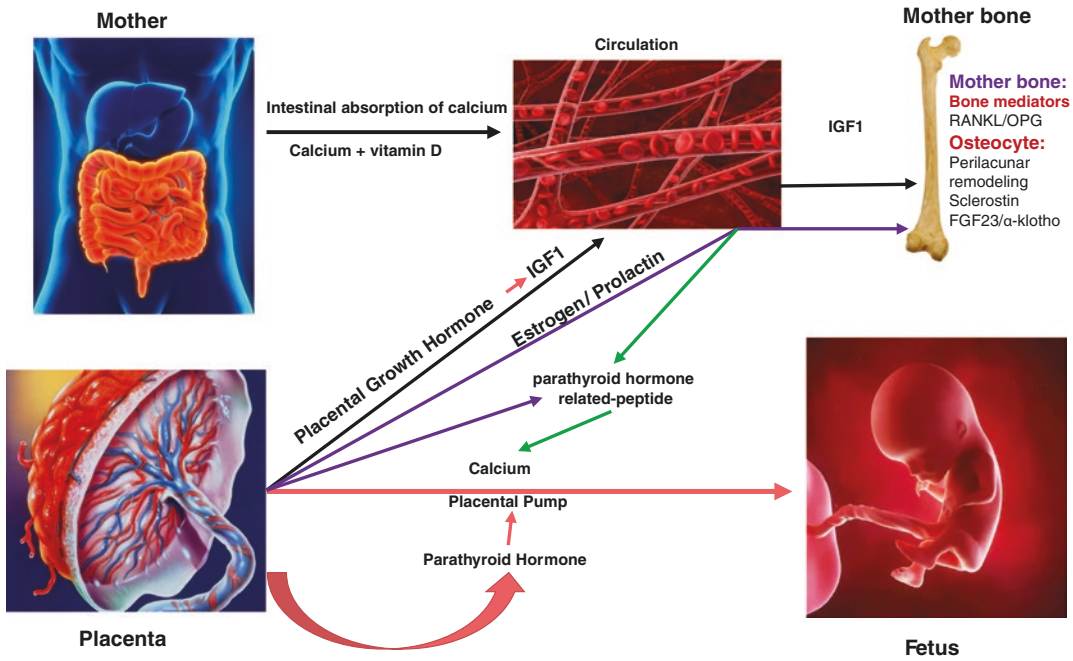

Fig. 4.3 Main changes in the mother and the feto-placental unit to facilitate adequate transfer of calcium to the fetal skeleton. The mother is the main source of calcium transferred to the fetus. Three main domains, mother/ mother bones, placenta, and fetus. The changes in the maternal domain include an increased intestinal absorption of calcium. Further calcium supply is provided via maternal parathyroid hormone related-peptide and by local changes within maternal bone, where receptor activator of nuclear factor kappa B ligand/osteoprotegerin (RANKL/OPG) and osteocytes may participate. The calcium drainage is partly counterbalanced by an increased anabolic process, where IGF1, stimulated by placental growth hormone may be involved. Other potential factors are prolactin and estrogens. Despite the reactive bone formation process, the bone balance seems negative for the mother. The placental calcium gradient is sustained by the placental pump, where fetal parathyroid hormone and parathyroid hormone related-peptide are determinant

Earlier study (the Michigan Bone Health Study), which included over 600 premenopausal women followed for 6 years, revealed varied changes in lumbar spine BMD but a 1.6% decrease in femoral neck BMD starting in a woman's mid 20s [44]. Risk factors for low BMD in premenopausal women include low body weight, amenorrhea, lack of physical activity, smoking, low dietary calcium or vitamin D, personal or family history of fracture, pregnancy, and Caucasian or Asian race [42]. Minimal bone loss is noted during pregnancy and breastfeeding; however, this loss is usually corrected shortly after pregnancy and breastfeeding are complete [45].

Healthy premenopausal women experience a 0.25–1% loss in BMD annually after reaching peak bone mass (commonly at the femoral neck); however, no link has been established between this gradual loss in BMD and fracture risk in healthy women. Low Z-scores (2.5 standard deviations below other age matched females) are seen in 0.5% of premenopausal women [42]. Another study [41] revealed that in Spanish women 20–44 years of age, 0.34% will have osteoporosis at the lumbar spine, and 0.17% will have osteoporosis at the femoral neck based on BMD alone. Overall, 50–90% of premenopausal women have a secondary cause for osteoporosis (e.g., eating disorders or glucocorticoid use, among others), whereas the remaining women were diagnosed with idiopathic osteoporosis [46]. Fracture risk in premenopausal women with osteoporosis remains low due to the small baseline fracture risk in younger women. The incidence of fractures in females under the age of 35 years is more difficult to detect due to the low

Table 4.1 Secondary causes of osteoporosis in premenopausal women

Hormonal
Any childhood disease that has affected puberty and/or skeletal development
Premenopausal amenorrhea (e.g., pituitary diseases, medications, athletic amenorrhea)
Premature menopause (<40 years)
Endocrine
Cushing syndrome
Hypogonadism
Hypopituitarism
Hyperthyroidism
Primary hyperparathyroidism
Diabetes (types 1)
Hyperprolactinemia
Chronic and inflammatory conditions
Vitamin D, calcium,
Inflammatory bowel disease
Cystic fibrosis
Rheumatoid arthritis, SLE, other inflammatory conditions
Malnutrition/malabsorption
Anorexia nervosa
Intestinal bypass/gastrointestinal surgery
Celiac disease
Malabsorption
Primary biliary cirrhosis
Connective tissue diseases
Osteogenesis imperfecta
Marfan syndrome
Ehlers Danlos syndrome
Turner's and Klinefelter's syndromes
Systemic and metabolic
Renal disease
Liver disease
Hypercalciuria
Other rare diseases, including mastocytosis, Gaucher disease, hemochromatosis, hypophosphatasia
Lifestyle changes
High salt intake
Smoking (active/passive)
Alcohol abuse
Immobilization
Low calcium intake
Excess vitamin A
Organ transplantation
Solid organ and bone marrow transplants
Medications (some have not been studied in premenopausal populations)
Glucocorticoids
Immunosuppressants (e.g., cyclosporine)
Antiepileptic drugs (particularly cytochrome P450 inducers such as phenytoin, carbamazepine)
Cancer chemotherapy/aromatase inhibitors
Gonadotropin-releasing hormone (GnRH) agonists (when used to suppress ovulation)
Depo medroxyprogesterone acetate (DepoProvera)
Heparin
Other medications with probable relationships to osteoporosis: Proton pump inhibitors, selective serotonin reuptake inhibitors, low molecular weight heparin

incidence of three fractures per 100,000 patient-years but is noted to increase to 21 per 100,000 patient-years in women aged 35–44 years [41]. Premenopausal fractures are associated with a 1.5- to three-fold increase in the risk of postmenopausal fractures [42]. Fracture risk is doubled or tripled once a loss of 10% in BMD has occurred; however, treatments resulting in a 5% increase in BMD may decrease fracture risk [47].

A third study [48] assessed premenopausal women referred for a bone disease at a tertiary medical center and looked for secondary versus idiopathic osteoporosis. A retrospective review of all premenopausal women referred for fracture or low bone mass over 1 year (n = 61) was conducted, and 39% of the total cohort of patients were found to have idiopathic osteoporosis, while 49% of the 29 women who had a history of low trauma fracture had idiopathic osteoporosis. This is consistent with other measures in premenopausal women. Low trauma fracture was defined as that occurring due to a fall from standing height or less, with the exception of digit or skull fracture. Over half of the women (57%) reported a family history of osteoporosis. Secondary osteoporosis was due to amenorrhea in 34%, anorexia nervosa in 16%, glucocorticoid use in 13%,and celiac disease in 10%. Premenopausal women with secondary osteoporosis had lower BMD at the spine (Z-score: −2.39 vs −1.58; p = 0.001) and hip than those with idiopathic osteoporosis, indicating a greater need for treatment in those women with secondary causes. Of the women referred due to a fracture, 28% did not have a low BMD. Bisphosphonates were used by 47% of women with low BMD, but no history of fracture and by 50% of women with idiopathic

osteoporosis, which may indicate overuse of osteoporosis treatments in this population. Therefore, further insight to clarify the role of osteoporosis treatments in younger, premenopausal women is needed [49].

Postmenopausal Osteoporosis (Type I Osteoporosis)

There is a direct relationship between the lack of estrogen during menopause and the development of osteoporosis. Initially, 2 basic types of osteoporosis have been identified. Type I osteoporosis uses the postmenopausal woman as the prototype (although men also rarely may suffer from the abrupt loss of sex steroids that impact greatly on the retention of bone tissue), and Type II osteoporosis, discussed in the next section, is age-related and typically occurs in both genders in the later decades of life (the causation of Type II is poorly understood, but it accelerates when the musculoskeletal system functions decline). At the bone level, type I and II osteoporosis can also be differentiated. Whereas the accelerated cancellous (trabecular) bone loss caused by estrogen deficiency at menopause (type I) results predominantly from trabecular perforation and loss of connectivity, the later phase of slower bone loss (type II) that occurs in both older women and men primarily affects cortical sites and is associated with a decrease in osteoblast number and bone formation rate (Fig. 4.4). Additionally, bone loss in older men is associated with trabecular thinning rather than perforation [50].

Estrogen deficiency causes loss of bone associated with an increase in the bone remodeling rate, increased osteoclast and osteoblast numbers, and increased resorption and formation, albeit unbalanced. Conversely, estrogens decrease bone resorption, restrain the rate of bone remodeling, and help to maintain a focal balance between bone formation and resorption. These effects are the result of hormonal influences on the birth rate of osteoclast and osteoblast progenitors in the bone marrow, as well as pro-apoptotic effects on osteoclasts and anti-apoptotic effects on mature osteoblasts and osteocytes [50–52]. However, estrogen deficiency can be also closely linked or intercorrelated to the aging process in postmenopausal women. While the onset of cortical bone loss in women is closely tied to estrogen deficiency, attesting to the adverse effect of estrogen deficiency on skeletal homeostasis and its contribution to the age-associated bone loss [53], a significant proportion of trabecular bone loss throughout life is age-related and estrogen-independent [52, 53]. The age-dependent loss of trabecular bone in the spine accelerates after the menopause, as does the rate of fractures at the wrist, spine, and hip. Between menopause and the age of 75 years, women lose approximately 22 percent of their total body bone mineral. It has been estimated that of this, 13.3 percent is due to aging and 7.75 percent is due to estrogen deprivation. In the femoral neck, 14 percent of the loss is "age related" and only 5.3 percent because of estrogen deprivation [54].

The accelerated phase of cancellous (trabecular) bone loss caused by menopause results predominantly from trabecular perforation and loss of connectivity. This phase is followed few years later by a phase of slower bone loss that primarily affects cortical sites. The slower phase occurs in both women and men and is associated with a decrease in osteoblast number and bone formation rate and reduced number of trabeculae. In line with this, decreased wall width, the hallmark of decreased osteoblast work output, is the most consistent histological finding in older women and men with osteoporosis [55–57].

Estrogen deficiency may also contribute to the development of osteoporosis in men [58, 59]. Estrogens derived from androgen aromatization and acting via the estrogen receptor are important for skeletal homeostasis in men, as evidenced by bone abnormalities in men with ER or aromatase mutations, as well as results of short-term clinical experimentation with administration of aromatase inhibitors [60]. In addition, several clinical studies show correlation between a decrease in bioavailable estradiol, but not testosterone, and bone mass in older men [51]. Studies of mouse models with targeted deletion of the ER and the androgen receptor in specific cell types have elucidated that the antiresorptive effects of estrogens

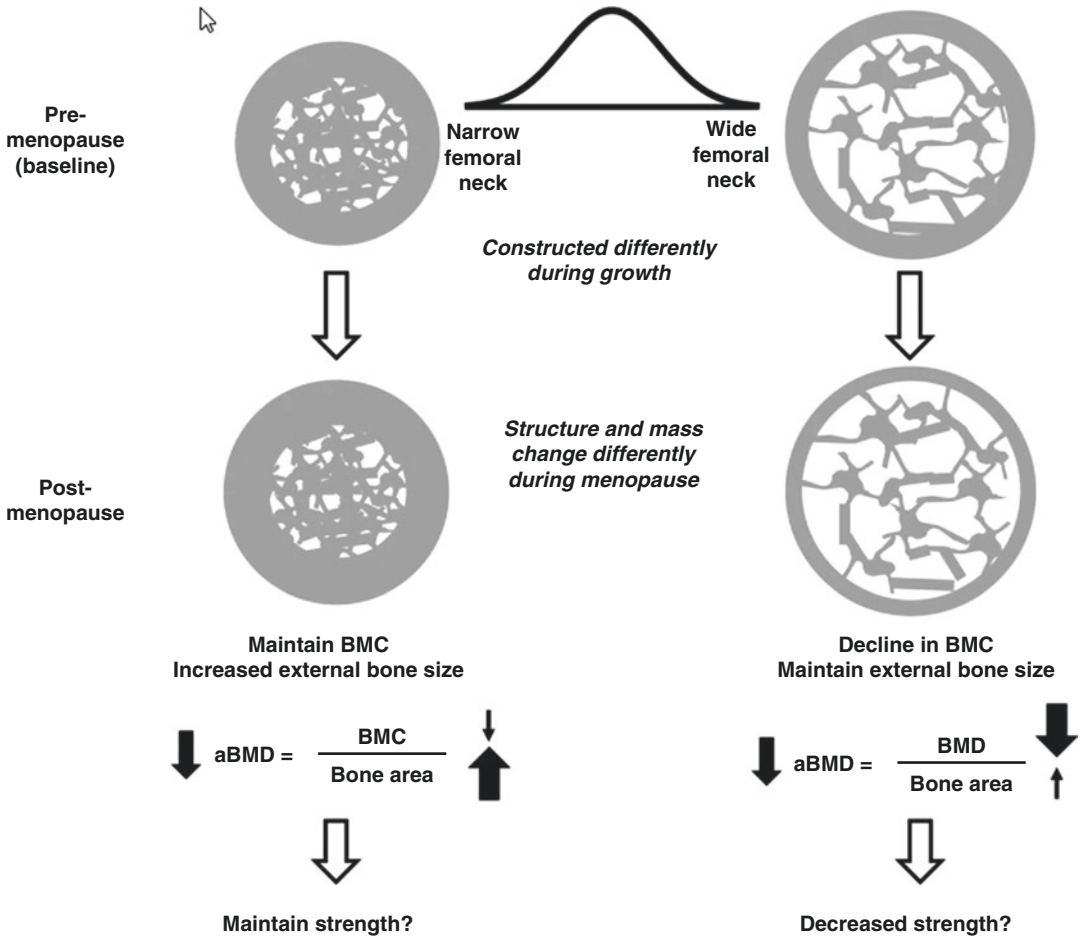

Fig. 4.4 Areal BMD as determined by DXA declines with aging for different reasons. With aging, women with smaller femoral necks tend to increase bone area through an increase in cortical thickness by an increase in periosteal and endosteal bone formation. Since BMD may only decrease slightly but bone area increases more, the result is lower areal BMD as measured by DXA despite likely having little change in bone strength. In the case of women with larger femoral necks, the endosteal cortex undergoes excessive resorption without periosteal expansion resulting in a thinner cortex. The result is a lower BMC without significant change in bone area. The DXA areal BMD decreases and may result in a bone with less strength. (Quoted under open access scheme from Choksi, P., Jepsen, K.J. & Clines, G.A. The challenges of diagnosing osteoporosis and the limitations of currently available tools. Clin Diabetes Endocrinol 2018; 4: 12)

or androgens in the cancellous versus the cortical bone compartment are mediated by different cell types [60–62]. The protective effects of estrogens on the cancellous bone compartment are mediated via signaling through the estrogen receptor-alpha expressed in cells of the osteoclast lineage [63, 64]. On the other hand, estrogen receptor-alpha signaling in cells of the osteoblast lineage is responsible for the protective effect of estrogens against endocortical resorption in females, but it plays no role in their effects on cancellous bone resorption. Whether estrogen receptor-alpha also plays a role on cancellous or cortical bone formation remains controversial [62, 65–68].

Osteoporosis is the most prevalent metabolic bone disease. Approximately 70% of people with osteoporosis are women, hence the importance of postmenopausal osteoporosis. Half of postmenopausal women over 50 will experience an

osteoporotic fracture at some point [45]. The most common fracture locations are the vertebrae (spine), proximal femur (hip), and distal radius (wrist). Most fractures cause pain, many produce lingering disability, and, in the case of hip fracture, it can result in death. Furthermore, osteoporosis exacts a psychological toll on individuals and their families, especially when the discomforts and limitations of fracture lead to depression and loss of independence. On another front, postmenopausal osteoporosis raises a major economic concern, bearing in mind osteoporosis-linked costs attained through acute care admissions, rehabilitation, long-term care, drug costs, and productivity losses, among others [69].

Osteoporosis in Elderly Females

In view of the progressive aging of most of the world's populations, it can be expected that the incidence of age-related conditions will grow and therefore the treatment and management of these individuals will gain increasing priority. Osteoporosis and frailty, which together greatly increase the risk of fracture, are of particular concern. Hip fractures are the most serious osteoporotic fractures, with high risk of mortality. A large proportion of patients (more than 50%) admitted to hospital with hip fracture are over 80 years old [70]. The survivors have a high risk of sustaining another major fracture and face deterioration in their quality of life and risk of dependency. Furthermore, Patients over the age of 80 years are often denied having bone mineral density assessment or osteoporotic treatments because it might be felt that the treatments do not work or they are "too late to treat" [71].

Old age and estrogen deficiency are the two most critical factors for the development of osteoporosis in both women and men. However, it is unknown whether the cellular and molecular events responsible for the imbalance between resorption and formation in old age versus sex steroid deficiency are similar or distinct or whether and how much sex steroid deficiency contributes to the age-dependent involution of the skeleton. Because of the abrupt decline of ovarian function at menopause in women and a slower decline of both androgen and estrogen levels in men with advancing age, the two conditions inevitably overlap, making it impossible to dissect their independent contribution to the cumulative anatomic deficit. However, findings from the mouse model suggest that the adverse effects of old age on the skeleton are independent of estrogens and are due to molecular mechanisms that are distinct from those responsible for the effects of sex steroid deficiency [72–74]. Such bone-intrinsic molecular mechanisms likely include mitochondria dysfunction, oxidative stress, declining autophagy, DNA damage, osteoprogenitor and osteocyte senescence, senescence-associated secretory phenotype (SASP), and lipid peroxidation [75].

In both women and men, the balance between bone formation and resorption becomes progressively negative with advancing age (Fig. 4.3). Age-related bone loss begins immediately after peak bone mass for either sex, but most bone loss occurs after age 65 years. Men, however, are less likely to develop osteoporosis than women for two reasons. First, they gain more bone during puberty, and second, they lose less bone during aging because, unlike women, men do not experience an abrupt loss of estrogens. Older residents in long-term care have the greatest risk. Eighty-five percent of nursing home women over age 80 years have osteoporosis. Hip and nonvertebral fractures in older residents of nursing homes are 2.5 to 3.5 times more common than in the community [76].

Most fractures after age 65 years occur at predominantly cortical sites. High-resolution peripheral quantitative computed tomography (HRpQCT) of the radius and post-mortem femurs of women between ages 50 and 80 years have revealed that most bone loss in old age is the result of increased intracortical porosity (Fig. 4.4) [77]. Importantly, the age-dependent increase in cortical porosity is not captured by dual-energy x-ray absorptiometry (DXA) bone mineral density (BMD) [78].

Besides its effects on bone mass, aging increases the risk of fractures, independently of bone mass, as highlighted by evidence that for the

same BMD, a 20-year increase in age is accompanied by a fourfold increase in fracture risk (Fig. 4.4) [79]. Consistent with this, human cadaveric specimens demonstrate significant declines in whole bone strength with age, with younger specimens being three- to tenfold stronger than older specimens. Furthermore, population-based studies with 3D-QCT imaging have demonstrated significantly greater declines in vertebral compressive strength over life in women than men (−43 versus −31 percent). Declines in femoral strength in a sideways fall configuration are also significantly greater in women than men (−55 versus −39 percent) and exceed the declines in femoral BMD (−26 and − 21 percent for women and men, respectively). In addition, cortical porosity increases by 176 percent and 259 percent from 20 to 90 years of age (Fig. 4.5).

Muscle strength and power decline 10 to 20 percent per decade after age 50 years. These declines obviously impact the risk of falls, and perhaps the severity of falls, but may also influence loads applied to vertebral bodies during daily activities. The influence of muscle strength on vertebral body compressive forces depends on the activity being performed. Vertebral compressive forces may remain unchanged, decrease, or greatly increase with reduced muscle strength.

The aging process is driven at the cellular level by random molecular damage that slowly accumulates with age. Although cells possess mechanisms to repair or remove damage, they are not 100% efficient and their efficiency declines with age. At the bone level, there are several bone-intrinsic molecular mechanisms which impact on bones in older adults. These include:

- *Oxidative stress* – Oxidative stress is a shared mechanism of the pathogenesis of several degenerative disorders associated with aging,

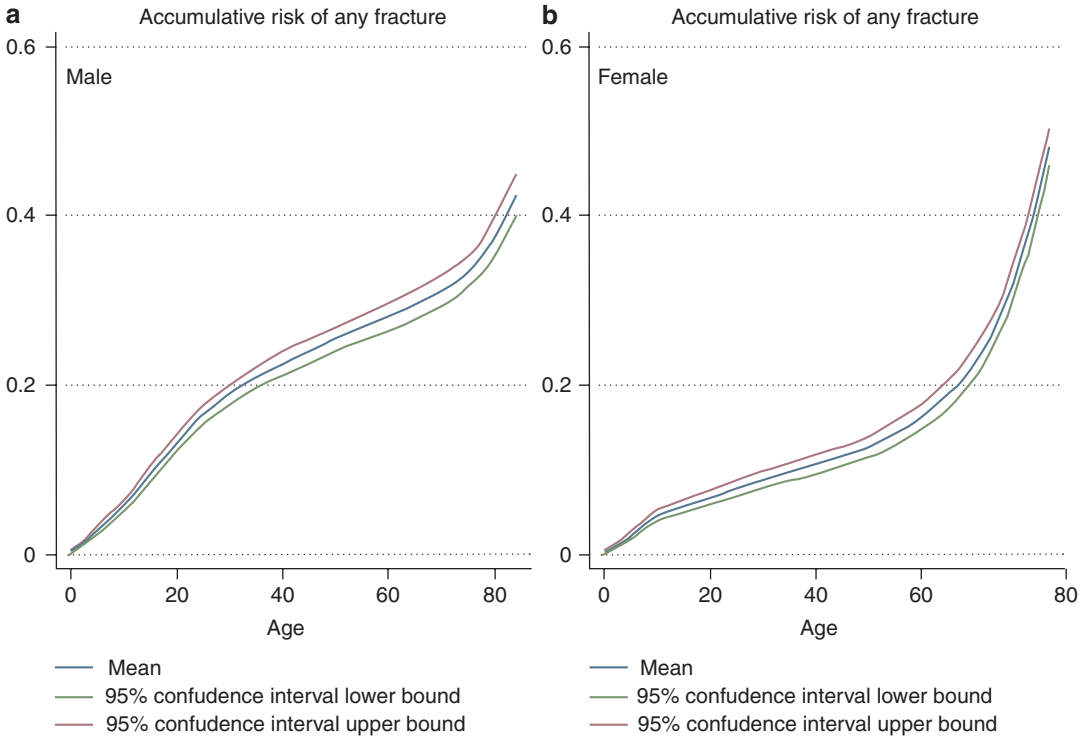

Fig. 4.5 Cumulative risk of having any fracture hospitalization since birth in both men and women. (Quoted under open access scheme under the Creative Commons Attribution License from Liang W and Chikritzhs T. The Effect of Age on Fracture Risk: A Population-Based Cohort Study. Journal of Aging Research. 2016, Article ID: 5071438 (https://doi.org/10.1155/2016/5071438))

including osteoporosis [80, 81]. An increase in reactive oxygen species (ROS) has been implicated in the decreased bone formation associated with advancing age, as well as the increased resorption associated with estrogen deficiency [81]. In line with this evidence, increased reactive oxygen species production in osteoblasts stimulates apoptosis and decreases bone formation. On the other hand, reactive oxygen species, and in particular, H_2O_2, is a critical requirement for receptor activator of nuclear factor kappa-B ligand (RANKL)-induced osteoclast generation, activation, and survival [82].

- *Osteoblast and osteocyte senescence* – Cellular senescence is a process in which cells stop dividing and undergo distinctive phenotypic alterations, including profound chromatin and secretome changes termed senescence-associated secretory phenotype (SASP) [83]. Nonproliferating, terminally differentiated cells also become senescent and exhibit the senescence-associated secretory phenotype (SASP). Cellular senescence is one of the hallmarks of aging in most, if not all, tissues [84]. Osteoblast progenitors as well as osteocytes from old mice exhibit typical features of cellular senescence [85–87]. Furthermore, cellular senescence of osteoprogenitors is associated with a decline in their number by more than 50 percent between 6 and 24 months of age in both female and male mice, as well as increased production of senescence-associated secretory phenotype (SASP)-associated pro-osteoclastogenic cytokines, such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-1-alpha, matrix metalloproteinase 13 (MMP13), SDF1, and RANKL. Senescent osteocytes similarly exhibit senescence-associated secretory phenotype (SASP), including some of the same cytokines found in the osteoprogenitors. Prevention of apoptosis by deleting Bak and Bax, two genes essential for apoptosis, in osteoblasts and osteocytes greatly potentiates the effects of old age on cortical porosity [88]. Notably, attenuation of apoptosis stimulates cellular senescence [89, 90]. Increased production of senescence-associated secretory phenotype (SASP) cytokines by senescent, apoptotic, or dysfunctional osteocytes and probably their affected neighbors (paracrine senescence), stimulate osteoclastogenesis, matrix degradation, focal bone resorption, and cortical porosity.
- *Autophagy* – Autophagy is a major adaptive response to cellular starvation and an essential protein/organelle quality control. Declining autophagy with advancing age is a big component of the loss of proteostasis, another one of the hallmark mechanisms of aging. Attenuation of autophagy in osteocytes, by conditional deletion of the ATG7 gene, recapitulates most of the effects of old age in six-month-old mice, including cortical porosity. Along with several other lines of evidence [91–93], these findings support of the general idea that in line with the seminal role of osteocytes in the choreography of physiologic bone remodeling, in conditions of overwhelming stress, the physiological mechanisms of bone repair are exaggerated and become disease mechanisms [94].

Definition of Osteoporosis

In Young/Premenopausal Females In young age where the peak bone mass has not been achieved, the definition of osteoporosis based on T-score cannot be implemented. Hence, low bone mass in children and adolescents has been defined by a Z-score below −2. This definition could also be extended beyond 20 years of age in those with delayed puberty, as is often the case with chronic diseases from childhood [9, 10].

However, it has to be noted that by extension and considering that in young adults T- and Z-scores are virtually identical, the 2007 International Society for Clinical Densitometry Official Positions has suggested keeping the use of Z-scores to define “low bone mass” in young adult (premenopausal) women [95]. On the other hand, and for the sake of coherence with the WHO operational definition of osteoporosis, the

T-score-based definition of the disease for young adults is also kept, unless it appears that the young adult is still growing. Therefore, in young adults living with a chronic disorder known to affect the bone metabolism, a T-score below −2.5 at spine or hip should be considered as diagnostic of osteoporosis. On another front, it is important to note, that the relationship between aBMD and fracture risk is not well established among young adults and that fracture prediction tools, such as FRAX®, are not valid for the young population. In the absence of secondary causes, occurrence of fragility fractures, in addition to the low T-score, may indicate genetic or idiopathic osteoporosis. Hence, the detection of prevalent vertebral fractures, which in the absence of major back trauma most likely indicate bone fragility, plays an important role in the identification of young adults with osteoporosis. For this purpose, DXA-based vertebral fracture assessment (VFA) tools now appear as major add-ons to aBMD evaluation [96].

According to a T-score ≤−2.5, in theory, only 0.5% of young women aged 30–40 years would fulfill the criteria of osteoporosis and another 15% would be considered as osteopenic (T-score between −2.5 and − 1) in any population [97]. This is corroborated by several observations, including a study of 282 premenopausal healthy women (mean age 34.8 years) without family history or secondary causes of bone fragility, which reported osteopenia in 10.6% of cases [98]. Similar prevalence of low bone mass in 579 Spanish premenopausal women (aged 20–44 years) was observed, with lumbar spine BMD characterized as osteoporosis and osteopenia in 0.3% and 13.1% of the cases, respectively, and in 0.2% and 12.6%, respectively, using femoral neck BMD [99].

Against this background of low prevalence of osteoporosis in healthy young individuals, the prevalence of osteoporosis and/or fragility (vertebral) fractures can reach 15% to 50% in young subjects with inflammatory bowel disease [100–102], celiac disease [103–105], cystic fibrosis [106–108], type 1 diabetes [109–111], rheumatoid arthritis [112], and anorexia nervosa [113–115], among other causes of secondary osteoporosis.

Special considerations are required for interpretation of BMD results in premenopausal women. Dynamics of Peak BMD Accrual BMD in premenopausal women depends primarily upon achievement of peak bone mass. Attainment of peak bone mass varies according to gender [116, 117], ethnicity [118], body size, menarchal age [119, 120], and region of bone. In healthy girls, the peak period of bone mass accrual occurs between ages 11 and 14 [121], and the rate of bone mass accrual slows dramatically by approximately 2 years after menarche [116]. Although at least 90 percent of peak bone mass is acquired by the late teen years [122, 123], studies have documented small additional gains between the ages of 20 and 29 [124]. Moreover, population-based, cross-sectional studies suggest that the timing of peak bone mass accrual may be site-specific [116], with women reaching peak bone mass at the proximal femur in their 20s and at the spine and forearm around age 30 [125]. When interpreting BMD measurements in premenopausal women, the possibility that peak bone mass has not yet been achieved must always be considered.

Physiologic Changes in the Bone Mass in Association with Pregnancy and Lactation

The majority of epidemiological studies in humans suggest that the net effect of the loss and regain of bone mass during and after lactation does not affect postmenopausal bone mass or long-term fracture risk [126–128]. However, other studies show that multiparity and longer periods of lactation are associated with decreased bone mineralization [129–134]. Additionally, studies performed in Turkey, China, and Mexico suggest that there may be an impact of lactation history on postmenopausal BMD in some populations [130, 135, 136]. Differences in population age, stature, parity, socioeconomic conditions, study duration and design, analysis techniques, and covariates included must be taken into account when interpreting these differing results.

Because of these physiologic bone mass changes associated with reproduction, interpretation of BMD results in premenopausal women must take into account the timing of any recent pregnancy or lactation. Based on available data, BMD at the lumbar spine is likely to have returned to that individual's premenopausal baseline by 12 months post-weaning [137].

Pregnancy- and Lactation-Associated Osteoporosis In some women, premenopausal osteoporosis may first present with low trauma fracture(s), usually at trabecular sites such as the vertebrae, occurring in the last trimester of pregnancy or during lactation [136–139]. Given the physiologic bone mass changes described above, pregnancy and lactation may represent particularly vulnerable times for the premenopausal woman's skeleton, particularly if low bone mineral density is present before pregnancy.

However, premenopausal fractures, including those associated with pregnancy and lactation, remain quite rare, suggesting that additional factors contribute to bone fragility in women who present with fractures during this time. Women with low trauma fractures sustained during pregnancy and/or lactation require the same thorough evaluation for secondary causes as do young women with fractures that are not associated with reproductive events. We have included women with pregnancy- and lactation-associated osteoporosis, in whom no cause is found after extensive evaluation, in cohorts defined to have idiopathic osteoporosis [140, 141].

Post-Menopausal and Elderly Women Several clinical groups have been involved in the diagnosis and recommendations concerning the treatment of osteoporosis in postmenopausal women. Two of these, the National Osteoporosis Foundation (NOF) in the USA [148]and the National Osteoporosis Guideline Group (NOGG) in the UK [143], have provide an interesting contrast in views with respect to their use of FRAX as a tool for patient identification and decisions on intervention (Table 4.2). While NOF suggests that a FRAX calculation is warranted when the BMD indicates elevated fracture risk, the decision to treat rests mainly on BMD; NOGG suggests that FRAX should be used in a case-finding exercise and the BMD should be performed in cases where the risk estimate is in a borderline zone [144].

Table 4.2 Xomparison between NOF and NOGG regarding guidelines for intervention in osteoporosis, with a focus on older individuals

	NOF	NOGG
BMD testing	Women aged ≥65 years Men aged ≥70 years Initiate therapy in those with T-scores ≤2.5 (at femoral neck, total hip or lumbar spine)	If suggested by FRAX case-finding analysis
Vertebral Imaging	Women aged ≥70 years Men aged ≥80 years	Not mentioned
	Its use is warranted in patients with low femoral neck BMD. Noted that using FRAX in patients with low BMD at the lumbar spine with relatively normal levels at the femoral neck leads to an underestimation of fracture risk	Case finding using FRAX in all post-menopausal women and men aged ≥50 years Initiate therapy following discussion of risk with patient

NOF National Osteoporosis Foundation (USA) [142]
NOGG National Osteoporosis Guideline Group (UK) [143]

In cases where the diagnostic threshold is crossed (i.e., elevated risk), additional clinical data might be sought to determine whether treatment should be initiated. This could be BMD (as suggested by NOGG), if not already done. Biomarker analysis might also be of potential interest, since high levels of bone turnover markers are associated with increased fracture risk in post-menopausal women [145]. One of the goals of this risk analysis exercise is to improve the targeting of anti-osteoporosis medication to ensure that the individuals who need to be treated are identified and presented with their therapeutic options.

The guidance of NOF concerning the intervention thresholds for treatment (while focusing on men and women 50 years and older) is to treat

if T-score ≤ −2.5 at femoral neck or if the T-score is between −1.0 and − 2.5 and the 10-year probability of fracture (on FRAX) is ≥3% for hip or ≥ 20% for a major fragility fracture. The guidance of NOGG is to treat when the age-related fracture probability exceeds the intervention threshold given by FRAX (where the FRAX threshold is the risk equivalent to a woman with a prior fragility fracture). The age-dependent intervention threshold favored by NOGG is designed to avoid under-prescription of treatment in eligible younger patients as well as the over-prescription in older age groups that could arise from a fixed threshold.

The FRAX defined intervention threshold therefore corresponds to "severe osteoporosis," i.e., the presence of at least one fragility fracture [146]. Other definitions of severe osteoporosis or high-risk patients could include that used in the GLOW study (Global Longitudinal Study of Osteoporosis in Women) [147], of patients having an age ≥65 years and a prior fracture or at least 2 other FRAX risk factors (parental hip fracture, current smoker, less than or equal to three alcoholic drinks/day, rheumatoid arthritis, current corticosteroid use, body mass index (BMI) <20 kg/m^2, or secondary osteoporosis).

Clinical Approach to Patient Identification and Diagnosis

Young/Premenopausal Females

Identifying individuals prone to have osteoporosis in the standard clinical practice represents the cornerstone in their management process. Young individuals suffering from a chronic disease (Table 4.1) and/or presenting with a low trauma fracture, particularly in the vertebrae (>20% loss of the vertebral height), and/or multiple low force long bone fracture (more than two) should be targeted for the possibility of having osteoporosis. The evaluation process starts with thorough medical history and examination (Table 4.3). Medical history should include full personal as well as family history (bearing in mind the genetic causes for osteoporosis) of bone fragility and/or endocrine, metabolic, and inflammatory disorders. Also, it should include past and present medications, age of menarche and/or history of amenorrhea, food intolerance, abdominal pain and bowel movements, urticaria, timing of recent pregnancies and lactation, as well as dietary and exercise patterns. Physical examination should particularly seek signs of Physical examination should seek signs of: nutritional deficiency or eating disorder, Cushing syndrome, thyroid hormone excess, connective tissue disorders (e.g., osteogenesis imperfecta, Ehlers Danlos syndrome, Marfan syndrome), and inflammatory conditions (e.g., rheumatoid arthritis, SLE) [148].

Table 4.3 Clinical approach of osteoporosis in the young / premenopausal females rely mainly on the patient's history and clinical assessment. Many secondary causes can be identified by a detailed history and physical examination

Medical history should include information on
Adult and childhood fractures
Adult and childhood illnesses and medication exposures
Menstrual history
Timing of recent pregnancy or lactation
Dieting and exercise behavior
Gastrointestinal symptoms
Nephrolithiasis
Family history of osteoporosis and/or nephrolithiasis
Physical examination should pursue signs of
Low height and/or BMI
Abdominal tenderness
Cutaneous signs of allergy (urticaria)
Hyperpigmentation or decreased pilosity (hypogonadism)
The presence of kyphosis
Limb deformities
Joint inflammation
Hyperlaxity
Blue sclerae
Poor dentition

Laboratory assessment: In addition to clinical assessment, lab tests are carried out to screen for the most common bone and mineral disorders (Table 4.4). Basic osteoporosis blood profile should be carried out for all patients. This aims to identify the common causes of bone thinning, including vitamin D deficiency, primary hyperparathyroidism, thyroid dysfunction, diabetes, renal impairment and hepatic dysfunction, systemic inflammation, and in men, hypogonadism

Table 4.4 Laboratory evaluation of young patients prone to have osteoporosis. The laboratory evaluation should aim to identify conditions such as vitamin D and/or calcium deficiency (and laboratory evidence that may distinguish osteomalacia from osteoporosis), hyperthyroidism, hyperparathyroidism, Cushing syndrome, early menopause, renal or liver disease, celiac disease, as well as other forms of malabsorption and idiopathic hypercalciuria

Basic osteoporosis blood profile	Specific laboratory evaluation
Complete blood count Electrolytes, renal function Serum calcium, phosphate Serum albumin, transaminases, total alkaline phosphatase Serum TSH Serum 25-hydroxyvitamin D PTH 24-hour urine for calcium and creatinine	Estradiol, LH, FSH, prolactin Screening for Cushing syndrome: 24 hour urine for free cortisol (or dexamethasone suppression test) Celiac screen (serologies) Serum/urine protein electrophoresis ESR or CRP Vitamin A/retinol level Specific testing for other rare conditions (e.g., mastocytosis, Gaucher disease, hypophosphatasia, hemochromatosis) If genetic diseases such as Gaucher disease, hypophosphatasia, or osteogenesis imperfecta are considered, genetic testing may be pursued Bone turnover biomarkers Transiliac crest bone biopsy

(particularly in the presence of other clinical signs). It is particularly important to exclude the possibility of vitamin D deficiency ($25(OH)_2$ vitamin D <10 ng/ml or 25 nmol/L), as this may affect bone mineralization and be translated into low aBMD, without being osteoporosis (Osteomalacia). Bearing in mind the secondary causes of osteoporosis in this cohort of patients, some patients might require specific laboratory tests. It is worth noting that celiac disease (prevalence 1%) may present in occult form, particularly since most adults will change their diet to avoid food intolerance/bowel symptoms, and should be suspected especially in the presence of low 25-hydroxyvitamin D. An elevated titer of antiendomysial or antitissue transglutaminase antibodies has an excellent positive predictive value for this disease [149]. In patients suffering from inflammatory bowel disease (IBD), Crohn's disease and ulcerative colitis are commonly delayed up to 2 years after the appearance of the first digestive symptoms. Hence, patients with low bone mass/bone fragility and abdominal symptoms/signs who test negative for antitissue transglutaminase Ab (and who may have inflammatory markers) should be assessed for fecal calprotectin and referred to a specialist for further intestinal investigations.

An additional set of selected diagnostic tests can be applied particularly when the clinical and/or baseline laboratory results orient towards a specific condition. Although systemic mastocytosis (SM) is a rare (0.3/10,000) condition, it is diagnosed in 0.4 to 1% of bone biopsies referred for the investigation of osteoporosis [150]. It becomes clinically manifest as urticaria pigmentosa in 60% of the patients, gastrointestinal manifestations in 40%, and idiopathic anaphylactoid reactions in 20%. However, all of these symptoms can be absent and the skeletal manifestation can be the sole presentation, with osteoporosis reported in up to 30% of patients with systemic mastocytosis [58, 59]. An elevated serum tryptase (>20 ng/ml) has a positive predictive value of 98% for systemic mastocytosis [151].

Besides bone alkaline phosphatase isoenzyme (BALP), it can be assessed in patients presenting with persistently elevated alkaline phosphatase level. If elevated, after growth is completed, it can orient toward osteomalacia (together with low 25(OH) vitamin D levels), Paget's disease, or bone neoplasia; and if low, it raises the possibility of hypophosphatasia.

The utility of bone biomarkers—that is, procollagen peptides (N and C terminals, PINP, and PICP, respectively) for bone formation and telopeptide cross-links of collagen type I (N and C terminals, NTX, and CTX, respectively), deoxypyridinoline/pyridinoline, and tartrate-resistant acid phosphatase for bone resorption—in the investigation of osteoporosis in the young remains controversial [152–154]. So far, the predictive role of bone biomarkers for fracture risk in secondary osteoporosis has not been fully documented, although they have been correlated with BMD changes in some diseases

(inflammatory bowel disease) [155]. Several examples have been reported to show such poor association. Firstly, bone biomarkers are correlated to the level of 25(OH) vitamin D, IGF-1, physical activity, etc. [156–159]; and in the case of a chronic disorder, bone biomarkers can be elevated, normal, or low depending on the nature of the underlying disease, its severity and relapses, past and current therapy, as well as the subject's mobility and nutrition. Secondly, in premenopausal women with idiopathic osteoporosis, bone turnover may also be high, normal, or low [160]. Furthermore, bone biomarkers have been negatively correlated with HbA_1C in type 1 diabetes, i.e., were lower with poor glucose control [161]. In contrast, when the achievement of peak bone mass is delayed, as is often the case with chronic disorders starting during childhood or adolescence, bone biomarkers may remain elevated into young adulthood (between 20 and 25 years of age) as a reflection of the ongoing physiological bone modeling/remodeling state rather than a catabolic state. In addition, a recent fracture may also cause an elevation of biomarkers for several months. Furthermore, patients with osteogenesis imperfecta, levels of PINP, and ß-CTX are normal or low, whereas osteocalcin is normal or high, reflecting the alterations in collagen metabolism on one side and bone turnover on the other side [162].

Despite these difficulties in interpreting bone biomarkers, normal bone biomarkers in a young adult with low aBMD would argue for an acquired low peak bone mass, whereas high bone biomarkers would point toward an ongoing process of bone loss, as seen, for instance, in anorexia nervosa compared to constitutionally lean women. Taken together with a low T-score and some evidence of bone fragility, elevated bone biomarkers could, therefore, prompt further investigations for an underlying cause and could be useful for therapeutic guidance [163]. On the other hand, low bone turnover has been observed in a subset of young women with idiopathic osteoporosis in association with a more pronounced deficit in bone microarchitecture and stiffness [160].

All patients suspected to have osteoporosis should have a DXA (ideally combined with VFA) scan. For those individuals with a T-score < −2.5 and/or fragility fractures but no known secondary cause, a search for underlying disorders and/or medications potentially associated with osteoporosis should be initiated (Fig. 4.5). Low aBMD alone and/or together with bone and muscle pain (and weakness in the latter) can be due to vitamin D deficiency, eventually osteomalacia, i.e., not necessarily osteoporosis. Moreover, when vitamin D levels are adequate, low aBMD without fragility fractures, including the absence of vertebral crush fractures as evaluated by VFA and/or lateral X-rays, does not necessarily represent a pathological situation, particularly in subjects of small body size [24]. Investigations in this case should be limited in the absence of symptoms and/or signs of a chronic disorder.

Postmenopausal Females

Identifying postmenopausal women at risk of osteoporosis/ osteoporotic fracture relies primarily on population screening. At present, there is no universally accepted policy for pop-

Table 4.5 Clinical risk factors used for the assessment of fracture probability

Risk factors for osteoporosis/osteoporotic fracture
Age
Sex
Low body mass index
Previous fragility fracture, particularly of the hip, wrist, and spine including
Morphometric vertebral fracture
Parental history of hip fracture
Glucocorticoid treatment (by mouth for 3 months or more)
Current smoking
Alcohol intake of 3 or more units daily
Secondary causes of osteoporosis include
rheumatoid arthritis
untreated hypogonadism in men and women
inflammatory bowel disease
prolonged immobility
organ transplantation
type I diabetes
thyroid disorders
chronic obstructive pulmonary disease

ulation screening; however, in most cases, the patients are identified opportunistically using a case-finding strategy on the finding of a previous fragility fracture or the presence of significant risk factors. The risk factors that are used for clinical assessment are summarized in Table 4.5. Algorithms that integrate the weight of clinical risk factors for fracture risk with or without information on BMD have been developed—FRAX™. The FRAX™ tool (www.shef.ac.uk/FRAX) computes the 10-year probability of hip fracture or a major osteoporotic fracture (clinical spine, hip, forearm and humerus fracture) [164]. Probabilities can be computed for several countries, categorized for different levels of risk.

Similar to young females, the same approach should be undertaken in all patients with osteoporosis. However, the range of clinical and biological tests depend on the severity of the disease, age at presentation, and the presence or absence of vertebral fractures [165]. The aims of the clinical history, physical examination, and clinical tests (Table 4.6) are to:

- Exclude diseases that mimic osteoporosis (e.g., osteomalacia, myelomatosis).
- Identify the cause of osteoporosis and contributory factors.
- Assess the risk of subsequent fractures.
- Select the most appropriate form of treatment.
- Perform baseline measurements for subsequent monitoring of treatment.

Table 4.6 Routine procedures proposed in the investigation of postmenopausal osteoporosis

Basic osteoporosis profile
History and physical examination
Blood cell count, sedimentation rate, serum calcium, albumin, creatinine, phosphate, alkaline phosphatase, vitamin D, and liver transaminases
Lateral radiograph of lumbar and thoracic spine
Bone densitometry (dual energy X-ray absorptiometry)
Other tests
X-ray—Vertebral fracture assessment
Markers of bone turn over (when available/appropriate)

Approach 1: Quantitative Assessment

The diagnosis of osteoporosis relies on the quantitative assessment of bone mineral density (BMD), usually by central dual energy X-ray absorptiometry (DXA). Bone mineral density at the femoral neck provides the reference site. It is defined as a value for BMD 2.5 SD or more below the young female adult mean (T-score less than or equal to −2.5 SD). Severe osteoporosis (established osteoporosis) describes osteoporosis in the presence of 1 or more fragility fractures [164].

However, diagnostic thresholds differ from intervention thresholds for several reasons. Firstly, the fracture risk varies markedly in different countries and at different ages, even with the same T-score. Other factors that determine intervention thresholds include the presence of clinical risk factors, high indices of bone turnover, and the cost and benefits of treatment as well as presence of other comorbidities [166].

In addition to the bone mineral density assessment, assessment for falls should also be carried out particularly among elderly women. Several tools are available to assess for the falls risk in standard practice that vary between using for research or standard clinical practice [167].

Approach 2: Probability-Based Assessment

Women with a prior fragility fracture should be considered for treatment. In the presence of other clinical risk factors, the 10-year probability of a major osteoporotic fracture (clinical spine, hip, forearm, or humerus) should be determined using FRAX™ (www.shef.ac.uk/FRAX). Women with probabilities below the lower assessment threshold can be reassured (Fig. 4.6). Women with probabilities above the upper assessment threshold can be considered for testing with BMD and their fracture probability reassessed. Women with probabilities above the intervention threshold should be considered for treatment. The intervention threshold at each age is set at a risk equivalent to that associated with a prior fracture

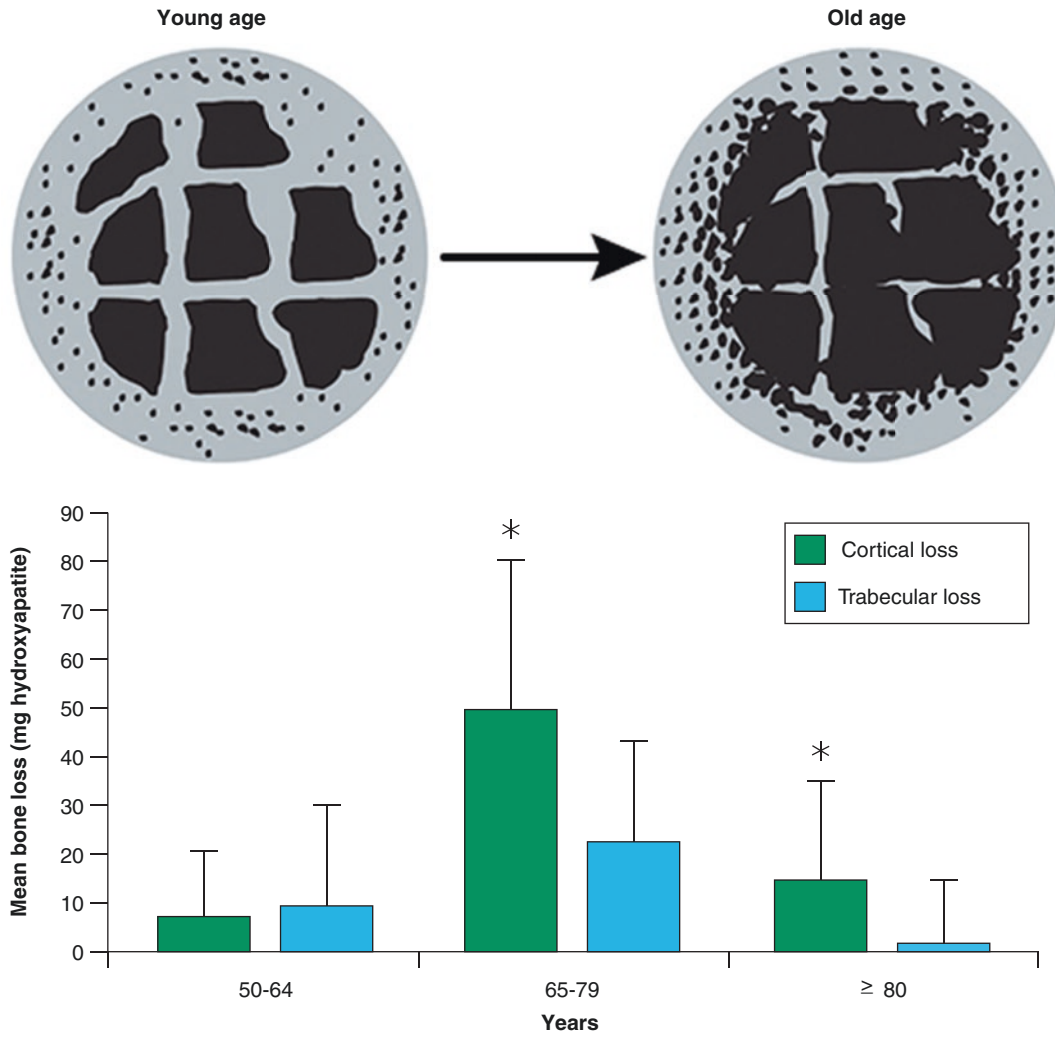

Fig. 4.6 The mg of hydroxyapatite lost with age was measured using high-resolution peripheral CT of the distal radius in a cross-sectional study of 122 white women with a mean age of 62.8 (range 27 to 98) years. Please note that most bone lost after the age of 65 was cortical. Cortical porosity was measured using scanning electron microscopy of postmortem specimens of femora from 24 women with a mean age of 69 (range 29 to 99) years and is depicted in a schematic fashion. (*CT* Computed tomography. *$p < 0.0001$. Reproduced from: Zebaze et al. [83]. Illustration used with the permission of Elsevier Inc. within the STM permissions guidelines. Figure 4.5: Assessment threshold for BMD testing (left) and treatment threshold (right))

and therefore rises with age. But the proportion of women in the UK potentially eligible for treatment rises from 20 to 40% with age.

Without computer access, the following management algorithm can be used. Women with a prior fragility fracture should be considered for treatment. In the presence of other clinical risk factors, BMD should be measured at the femoral neck. The chart (Fig. 4.7) gives average fracture probabilities according to BMD T-score and the number of clinical risk factors. The chart is color coded. Green denotes that an individual's risk lies below the intervention threshold, i.e., treatment is not indicated. Red denotes that the fracture probability is consistently above the upper assessment threshold, irrespective of the mix of clinical risk factors, so that treatment can ordinarily be strongly recommended. The intermedi-

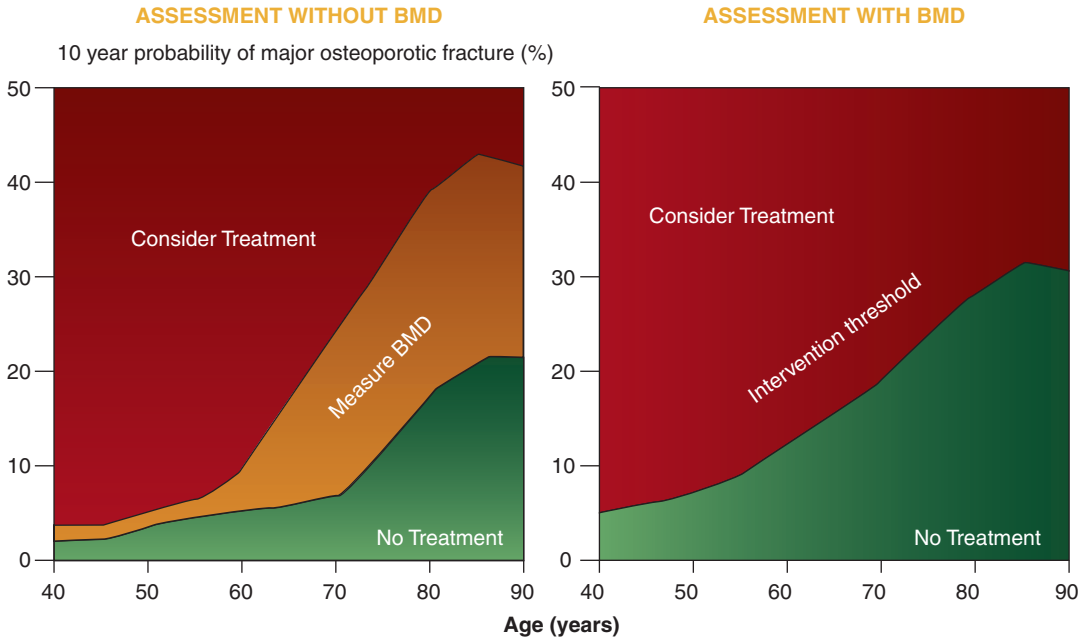

Fig. 4.7 Assessment and treatment thresholds in the absence of a BMD test (left) and with a BMD test to compute fracture probability (right) for men and women. (Quoted from nogg National Osteoporosis guideline Group. JA Kanis, J Compston, A Cooper, C Cooper, R Francis, D Marsh, EV McCloskey, D Reid, P Selby and M Wilkins, on behalf of the National Osteoporosis Guideline Group (NOGG). Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. https://iofbonehealth.org/sites/default/files/PDFs/National%20Guidelines/nogg_pocket_guide-healthcare_professionals.pdf (Accessed on 18th October 2020))

ate category (orange) denotes that probabilities lie between these limits and that treatment can be recommended in those with the stronger risk factors. Smoking and alcohol are weak risk factors, glucocorticoids and secondary causes of osteoporosis are moderate risk factors, and a parental history of hip fracture is a strong risk factor. However, it has to be noted that the only secondary cause of osteoporosis that should be used with BMD is rheumatoid arthritis [166] (Fig. 4.8).

Specific Clinical Situations

Idiopathic Osteoporosis in the Young

In some cases of low trauma fracture in premenopausal women, no known secondary cause can be found after extensive evaluation. These women are said to have idiopathic osteoporosis (IOP). Based on current guidelines, the term IOP applies only to those with a history of low trauma fractures, and not to those with low BMD and no history of fractures [148].

Idiopathic osteoporosis has been reported in premenopausal women, but its pathophysiology is less well understood. A recent bone biopsy study in 45 premenopausal women with fragility fractures, 19 with low aBMD and 40 controls, indicated that the group with idiopathic osteoporosis has significantly thinner cortices and trabeculae, and a lower mean wall thickness, i.e., a bone formation deficit [168]. Other studies, utilizing central quantitative CT, peripheral high-resolution CT, and microCT of transiliac bone biopsy samples, demonstrated similar findings with markedly thinner cortices, fewer, thinner, widely separated, and heterogeneously distributed trabeculae and lower estimated stiffness in IOP women compared to normal controls. Studies

Fig. 4.8 Assessment of men and assessment of women with no previous fracture according to body mass index (BMI) and the number of clinical risk factors (CRFs). (Quoted from nogg National Osteoporosis guideline Group. JA Kanis, J Compston, A Cooper, C Cooper, R Francis, D Marsh, EV McCloskey, D Reid, P Selby and M Wilkins, on behalf of the National Osteoporosis Guideline Group (NOGG). Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. https://iofbonehealth.org/sites/default/files/PDFs/National%20Guidelines/nogg_pocket_guide-healthcare_professionals.pdf (Accessed on 18th October 2020))

of biochemical and bone remodeling characteristics suggest that the pathogenesis of IOP is heterogeneous, with some women exhibiting evidence of low bone turnover while others have evidence of high bone turnover [168, 169].

Therefore, pathogenesis is likely to be diverse; etiologies including excess urinary calcium excretion and IGF-1 axis abnormalities have been implicated [137]. However, bone turnover and indices of bone remodelling are extremely heterogenous in these women. Only in a subgroup with low bone formation rate and more severely disrupted microarchitecture were serum IGF-1 levels elevated, suggesting a resistance against this growth factor. In another study, young women with idiopathic osteoporosis were reported to have lower free estradiol levels and higher bone turnover than normal [170]. It should be noted that hypercalciuria may be present in premenopausal women with idiopathic osteoporosis [171].

Premenopausal Women with Fractures or Low BMD Related to Known Secondary Causes.

In premenopausal women with low BMD or low trauma fractures and a known secondary cause of osteoporosis, the first goal of management should be to address the underlying cause. Bone density benefits have been shown in the context of intervention for several such secondary causes in premenopausal women:

- Estrogen replacement for those with estrogen deficiency [172–174].
- Discontinuation of medications, for example, depot medroxyprogesterone acetate (Depo Provera) [175, 176].
- Gluten-free diet for celiac disease [177–179].
- Nutritional rehabilitation and weight gain for anorexia nervosa [180].
- Parathyroidectomy for primary hyperparathyroidism [181].

Although thiazides are used for idiopathic hypercalciuria, and appear to have beneficial effects on BMD in men64, few data are available in young women. Continuing or severe effects of the secondary cause may lead to a necessity for pharmacological therapy.

In conclusion, bone health in females is an important topic that requires careful consideration. Most premenopausal women, with low trauma fracture(s) or low BMD have a secondary cause of osteoporosis or bone loss. Women who present with unexplained fractures or low BMD should have a thorough clinical and laboratory evaluation to search for known causes of fractures and/or bone loss. Post-menopausal and elderly women are highly prone to develop fractures. Where possible, treatment of the underlying cause should be the focus of management. Women with an ongoing cause of bone loss and those who have had, or continue to have, low trauma fractures may require pharmacological intervention.

An example is given in Fig. 4.7 for a woman with rheumatoid arthritis aged 60 years on oral glucocorticoids with a BMD T-score of −1 SD (i.e., two clinical risk factors). The chart gives an average10-year fracture probability of 12% for any combination of 2 CRFs and is coded orange. With the 2 moderate risk factors in this woman, the probability is close to the average (11%) and exceeds the treatment threshold. With weak risk factors (e.g., smoking and alcohol), the probability would be lower (6.8%) and fall below the treatment threshold. The range (6.7–12%) is not a confidence interval but, because the weight of different risk factors varies, is a true range.

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Bone Health in Men

5

Yasser El Miedany

Introduction

Osteoporosis is characterized by a reduction in bone density, associated with skeletal fragility and an increased risk of fracture after minimal trauma. Osteoporosis is often thought of as a women's disease, as it is particularly common after menopause. The reality is osteoporosis also affects men. Up to 20% of symptomatic vertebral fractures and 30% of hip fractures occur in men [1]. The number of men presenting with these fractures is rising, because of increasing life expectancy and a doubling of the age-specific incidence of fractures over the past three decades.

The key challenge facing healthcare professionals and policymakers is to ensure that men, who are clearly at high risk of suffering fragility fractures, get the care they need. A gender-specific approach to screening, diagnosis, and treatment should reduce the morbidity and mortality of the disease, particularly in men over 70. Therefore, screening for men who have already suffered a fragility fracture would be the first step. A broken bone is a very clear signal of elevated future fracture risk—nevertheless osteoporosis assessment and treatment rates among these men are very low—being mostly under 20%. A report from the "international osteoporosis foundations" [2], reported that there is a near universal absence of secondary fracture prevention systems for men who have already suffered fragility fractures. Similar poor attention to bone health is evident among men receiving androgen deprivation therapy for prostate cancer or glucocorticoid treatment for many other conditions, the most common causes of secondary osteoporosis in men.

To avert this calamity, a concerted international effort is required to improve the awareness of osteoporosis in men among both doctors and the community and to implement systems of care to prevent fragility fractures. In this regard, there is good news. There are a range of therapies now available that have proven effective in the treatment of osteoporosis in men. These treatments have been shown to work against the various types of osteoporosis which can affect men, including primary (or idiopathic) osteoporosis and when secondary causes are responsible for bone loss (e.g., glucocorticoids or low sex hormone levels).

After analyzing why bone health in men is important, this chapter will present the epidemiology of osteoporosis in men as well as bone development in different stages of the man's life from childhood through to older adult phase. The chapter will expand to discuss pathogenesis of osteoporosis in men and the role of hormones, causes of osteoporosis in men, as well as criteria for the diagnosis. The chapter will conclude with

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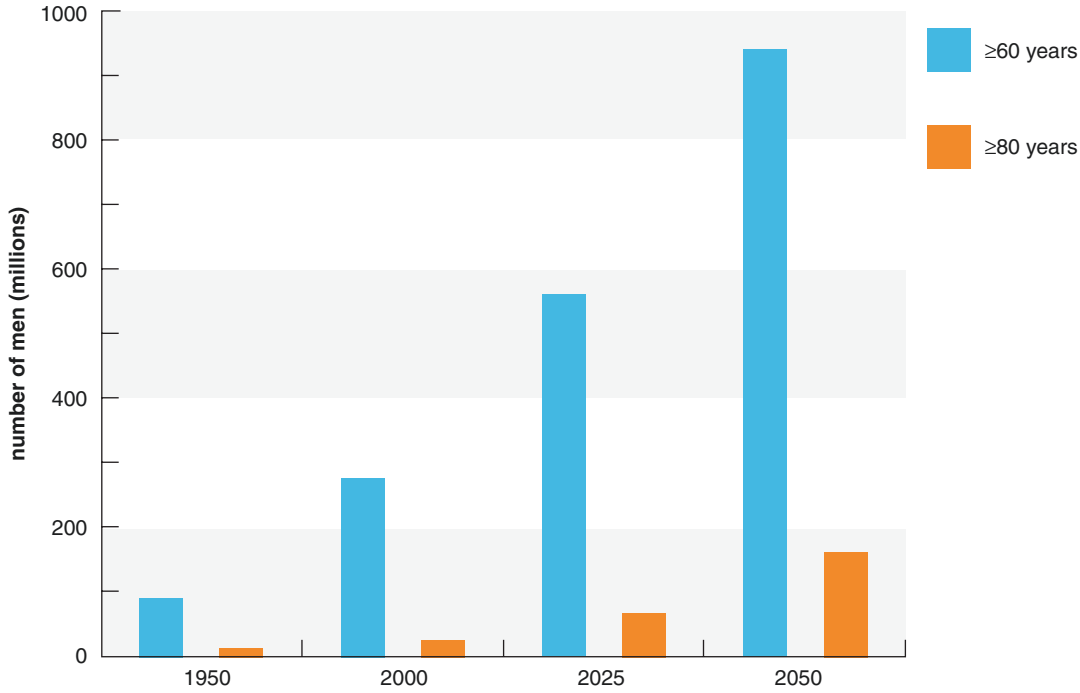

Fig. 5.1 the ageing of the world's male population 1950–2050 [3]

a clinical approach to assessment of men at risk of osteoporosis in the standard clinical practice.

Why Bone Health in Men Is Important?

The world's men are ageing fast; by 2050 the number of men aged 60 years or over will increase ten-fold (Fig. 5.1) [3]. Consequence of aging is the reduced functional capacity, due to malfunctions of the body systems, which reflects negatively on the individual autonomy and independence. The rate of decline of functional capacity depends on intrinsic factors such as the existence of diseases, as well as environmental factors including social and economic factors. Frailty and disability belong to geriatric syndromes and affect the quality of life and older people's functionality. Disability is defined as the inability of the older adult to perform everyday life activities, to self-handling and to be independent. Frailty is a common geriatric syndrome that affects nervous, musculoskeletal, endocrine, and immune system. These people have an increased risk of fall, fractures, hospitalization disability, and mortality [4, 5].

Osteoporotic fractures are associated with substantial morbidity in both men and women. There is considerable disability after hip fracture in men; only 21% are living independently in the community a year later, whereas 26% are receiving home care and 53% are living in an institution [2]. Men with symptomatic vertebral fractures commonly complain of back pain, loss of height, and kyphosis but also have significantly less energy, poorer sleep, more emotional problems, and impaired mobility compared with age-matched control subjects [6].

On another front, although the overall prevalence of fragility fractures is higher in women, men generally have higher rates of fracture related mortality [7, 8]. For example, while the mortality rate in men after hip fracture, as in women, increases with age and is highest in the year after a fracture, over the first 6 months, the mortality rate in men approximately doubled that in similarly aged

women [9]. Vertebral crush fractures are also associated with excess mortality of about 18% at 5 years, due mainly to coexisting conditions associated with osteoporosis rather than the fracture itself [10].

It is estimated that the residual lifetime risk of experiencing an osteoporotic fracture in men over the age of 50 is up to 27%, higher than the lifetime risk of developing prostate cancer of 11.3% [11, 12]. Furthermore, the combined lifetime risk for hip, forearm, and vertebral fractures coming to clinical attention is around 40%, equivalent to the risk for cardiovascular disease [13]. On another front, osteoporosis takes a huge personal and economic toll. In Europe, the disability due to osteoporosis is greater than that caused by cancers (with the exception of lung cancer) and is comparable or greater than that lost to a variety of chronic noncommunicable diseases, such as rheumatoid arthritis, asthma, and high blood pressure-related heart disease [14].

Epidemiology

Worldwide, osteoporosis causes more than 8.9 million fractures annually, resulting in an osteoporotic fracture every 3 seconds [13]. By 2050, the worldwide incidence of hip fracture in men is projected to increase by 310% and 240% in women, compared to rates in 1990 [15]. The prevalence of fracture spine or hip in men is about one-third that in women [16]. In men, there seems to be a lag period, such that an exponential increase in fracture incidence begins 10-years later in men than in women [17], coinciding with the phase of accelerated bone loss after the age of 70 [18]. Although women have a higher overall prevalence of fracture, the increase in fracture risk for each standard deviation decrease in bone mineral density (BMD) seems to be higher in men. Moreover, mortality associated with hip fracture is two or three times higher in men that in women [19, 20].

It is estimated that the residual lifetime risk of experiencing an osteoporotic fracture in men over the age of 50 is up to 27% [11]. The following observations illustrate the magnitude of the problem in men:

- Worldwide, 39% of annual osteoporotic fractures occur in men [21, 22].
- A 60-year-old man has an approximately 25% chance of having an osteoporotic fracture during his lifetime [23].
- By the age of 90 years, one of every six men will have a hip fracture. The prevalence of vertebral or hip fracture in older men is approximately one-third that in women (5 to 6% versus 16 to 18%) and Colles' fracture one-sixth as common (2.5 versus 16%) [24].
- The mortality rate associated with hip fractures, as well as vertebral and other major fractures, is higher in men than in women. In addition, men are even less likely than women to be evaluated or receive antiresorptive therapy after a hip fracture (4.5 versus 49.5%, respectively) [25].

Although low BMD confers increased risk for fracture, most fractures occur in postmenopausal women [26–28] and elderly men [29] at moderate risk. This is of significant epidemiological impact as fragility fractures are more prevalent among older adults. Considering fragility fractures, men fare particularly badly and are the "weaker sex." A national registry study [30] from Denmark published in 2010 echoed the findings of previous studies [31–34]: Hip fractures in men are associated with greater mortality compared with women, with rates as high as 37% in the first year following fracture. In addition, mortality is increased after most fragility fractures in men, not only following hip fractures [35].

Bone Development and Loss in Men

Childhood through to Young Adulthood

While many factors influence the growth of the human skeleton and maintenance of its bone mass throughout life, changes in bone mass pass in different stages of development (this was

reviewed in an article published by the international osteoporosis foundation [2]). Up to the age of 10–12 years, there are no significant differences in bone mass between boys and girls. However, at the onset of puberty, the bone mass increases more in males, and both males and females attain peak bone mass between ages 20 and 30 years [36] (Fig. 5.2).

Why does this occur? Accrual of bone mass during childhood and adolescence is controlled by sex steroids and the growth hormone/insulin-like growth factor 1 (IGF-I) axis of the endocrine system [36]. A study of young men from Gothenburg sought to establish whether androgens increase the size of cortical bone and whether estrogens have the opposite effect [37]. Levels of free testosterone and estradiol were measured and correlated with the size of cortical bone. The results supported the notion that androgens increase, whereas estrogens reduce, cortical bone size. Consequently, during puberty, boys develop larger bones than girls and so accrue greater bone mass. The size of bones and the thickness of their cortex are major determinants of bone strength, and thus men generally have larger bone size and greater bone strength than women.

The importance of normal sex steroid production in the acquisition of peak bone mass is illustrated by the findings of low bone mass in young men with idiopathic hypogonadotropic hypogonadism (IHH) [38]. Because idiopathic hypogonadotropic hypogonadism is almost always a congenital abnormality due to gonadotropin-releasing hormone (GnRH) deficiency, this disorder provides a valuable model to assess the effects of hypogonadism on pubertal bone development (i.e., the attainment of peak bone mass). Both cortical and trabecular bone density (Fig. 5.3) are markedly decreased in these men [39]. Osteoporosis can be detected even before the attainment of skeletal maturity, suggesting that it is due to inadequate pubertal bone accretion rather than post-maturity bone loss.

Although the observation that peak BMD is reduced in men with congenital hypogonadism illustrates the importance of gonadal steroids in bone development, those findings do not indicate whether androgens, estrogens, or both are primarily responsible for the pubertal increase in

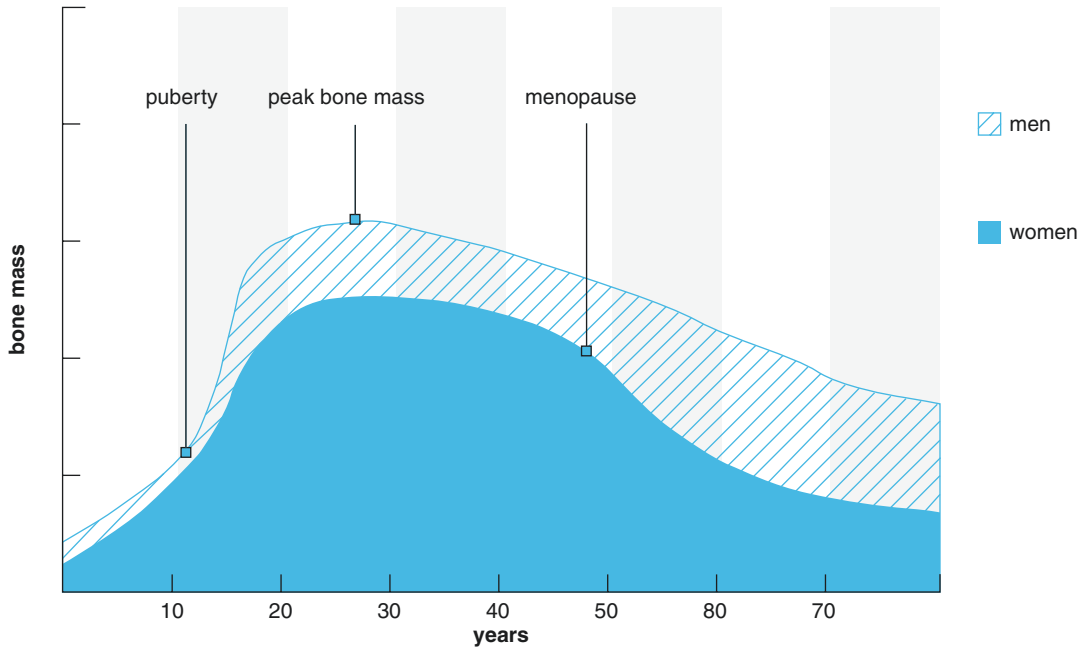

FIG. 5.2 Bone mass throughout the life cycle [61, Springer is the publisher; do we need permission or just put the reference?]

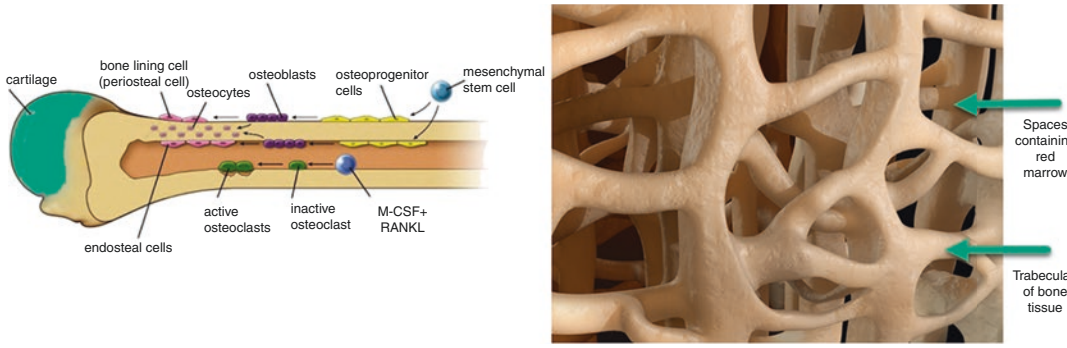

Fig. 5.3 Cortical and Trabecular bone. (M-CSF: Macrophage colony-stimulating factor, RANKL: receptor activator of nuclear factor κβ ligand)

BMD and the attainment of peak bone mass. Reports that BMD is markedly reduced in men with null mutations in the estrogen receptor-alpha, so that responsiveness to estrogen is essentially absent, or in men with null mutation in the aromatase gene, so that synthesis of estradiol is virtually absent, strongly suggest that estrogens provide the primary hormonal stimulus to the attainment of peak bone mass [40].

Another important determinant of peak bone density is the timing of puberty. In adult men with history of constitutionally delayed puberty, BMD of the radial shaft, lumbar spine, and proximal femur is significantly lower than in age-matched normal men, and it does not appear to improve with time [40, 41]. Similar findings have been reported in adolescent boys with delayed puberty [42]. These observations suggest that there is a critical time period during which the skeleton is responsive to sex steroids.

Achieving one's genetic potential for peak bone mass during childhood and adolescence is the primary objective during this first stage of the skeleton's life cycle. The consequence of not doing so has been illustrated by computer modelling developed to predict the relative influences of peak bone mineral density (BMD), menopause, and age-related bone loss on the development of osteoporosis in women [43]. A 10% increase in peak BMD was predicted to delay the development of osteoporosis by 13 years.

Important influences on peak bone mass for young males include as follows.

Exercise In a report published by Australia's "Building healthy bones throughout life strategy" [44], it was stated that "Childhood and adolescence may represent the optimal window of opportunity in which exercise can improve bone strength and protect against osteoporosis and associated fragility fractures in old age, assuming the gains achieved are maintained in later life." Systematic literature review has reported beneficial effects on BMD for children participating in moderate to high impact weight-bearing physical activities [45]. Long-term follow-up from the Australian Schools Health and Fitness Survey conducted in 1985 suggests that higher levels of fitness as a child are predictive of greater peak bone mass at age 30 years [46].

Calcium intake: approximately 40% of adult peak bone mass is acquired during the two years around puberty [47]. Accordingly, ensuring adequate dietary calcium intake during this period of growth is essential. In this regard, it is of great concern that a multinational study of calcium intakes in adolescent boys reported levels of only 60% of country-specific requirements [48].

Vitamin D Levels The association between vitamin D deficiency and rickets is well documented and understood. Consequently, it is expected that the impact that vitamin D deficiency in childhood has on bone health at the population level is also likely to be significant [49]. Reports from Europe [50–55], the Middle East [56], North America [57], and Oceania [58–

61] suggest that low levels of vitamin D in children are a cause for concern throughout the world. The Institutes of Medicine report on dietary intakes of vitamin D and calcium defined the adequate intake of vitamin D of infants (0–12 months old) to be 400 IU and the recommended dietary allowance of vitamin D for children aged 1–18 years to be 600 IU/day [62].

Protein Intake Proteins can be considered as building blocks and, subsequently, help to maintain strong bones. Conversely, low protein intake is associated with impaired skeletal growth thereby influencing peak bone mass [63]. Proteins positive effect on bone and muscle may be medicated through hepatic production of insulin-like growth factor I (IGF-I) [64]. Serum levels of IGF-I are closely related to growth, increasing from birth to puberty. Furthermore IGF-I is considered as a major factor for bone longitudinal growth, stimulating chondrocyte from the growth plate and stimulating the production of active form of vitamin D (1,25 dihydroxyvitamin D) in the kidney. Dairy products, fish, meat, nuts, and legumes are a good dietary source of proteins. Both animal and plant proteins sources appear to favor strong bones.

Other factors which can adversely affect peak bone mass and BMD in young males include delayed puberty [65], smoking [66–68], alcohol consumption [66], and certain childhood diseases such as acute lymphoblastic leukemia [69], and medications such as glucocorticoids [70] and anti-epileptic drugs [71].

Ages: 20–60 Years

During these decades of adulthood, the primary objective is to avoid premature bone loss and maintain a healthy skeleton. On account of the muscular system being the generator of the strongest mechanical forces applied to bones [72], avoiding loss of muscle mass (sarcopenia) is also of paramount importance in this stage of life. Accordingly, as for younger males, regular exercise has an important role to play. Recommendations for building healthy bones in healthy adults [43, 73, 74] provide an illustration of the type and frequency of activities that current knowledge suggests will be of benefit (Table 5.1).

Bone loss appears to start soon after young men reach peak bone mass. A study from Sweden investigated changes in BMD in men aged between 17 and 26 years [75]. A significant year-on-year loss of BMD at the hip was observed from age 19 years, when peak bone mass had occurred. Analysis of bone density data from these young men's fathers suggested that 25% of BMD at the hip may be lost by 50 years of age and that bone remodelling may be regulated differently at the hip than at other sites.

There are important differences between the ways in which bone loss occurs with aging in men as compared with women. To appreciate these differences, the basics of bone biology must be firstly considered.

Table 5.1 Recommendations for building healthy bones in healthy adults

Form of physical activity	
Weight bearing	Participating regularly in moderate impact weight-bearing physical activity is highly recommended. This can be in the form of high impact training (e.g. 50–100 jumps) or related impact loading sports for at least 30 minutes 3–5 days per week
Muscle-strengthening exercises	Muscle-strengthening exercises should be practiced regularly on at least 2 days per week. To achieve maximum benefits, the program should be high intensity (60–80% of peak capacity), become progressively more challenging over time, and, in particular, target the major muscles around the hip and spine
Multi-modal exercise regimen	Participation in a multi-modal exercise regimen, where possible, is recommended (inclusive of weight bearing/high impact/high intensity resistance exercise) at least three times per week
Calcium and vitamin D intake	Men should aim to comply with the relevant international/ national calcium and vitamin D intake recommendations

Bone is a living tissue able to impart tremendous strength to support the human bodies, yet simultaneously must also have the capacity to be flexible to absorb shock without breaking. As illustrated in Fig. 5.3, bone comes in two major forms, the cortical bone, which forms the casing or outer shell, and the trabecular bone—also known as spongy or cancellous bone—which forms a honeycomb-type mesh within the cortex. The trabecular bone provides structural support when loads are applied and enables the entire bone to be flexible.

Bone is in a perpetual state of remodelling throughout life, with the entire skeleton being replaced every 10 years [76]. One group of cells—osteoclasts—are drawn to sites of microdamage to remove old bone (bone resorption). Once the osteoclasts have completed their task, bone forming cells—osteoblasts—deposit new bone to fill the gap created. This process is known as the bone remodelling cycle and is represented in Fig. 5.4 for a healthy young adult. For bone mass to remain constant, the amount of bone being resorbed by the osteoclasts needs to be equivalent to the amount of bone being formed by the osteoblasts.

As men age, the rate of bone resorption by osteoclasts on the inside surface of cortical bone increases (known as endocortical resorption). At the same time, new bone is being deposited on the outer surface of the cortex (known as periosteal apposition). These concurrent processes lead to an increase in the circumference of bones, which serves to increase the bone size and moves the cortex further away from the center of the bone. From a biomechanical perspective, both of these changes result in greater bone strength. However, the cortex also becomes thinner which reduces bone strength. So, in men aged younger than 70 years, there is a degree of balance between these two competing processes.

In postmenopausal women, there is evidence to suggest that the rate of endocortical resorption is such that periosteal apposition cannot serve as a sufficient compensatory mechanism to prevent bone fragility [77–80]. The change in cross-sectional structure of bone for men and women with ageing is illustrated in Fig. 5.5. These seemingly subtle differences in the way that our bones change with aging contribute to our understanding of why fracture rates increase in women to a greater extent than in men.

Another aspect whereby men differ from women is in the mechanisms underlying age-related trabecular bone loss. In men trabecular, thinning occurs and may be associated with decreases in IGF-1, whereas in women, there is resorption and loss of trabeculae, particularly horizontal trabeculae, associated with estrogen deficiency at the time of menopause [81]. This is another reason why skeletal fragility is higher in women.

Bone wise, after attainment of peak bone mass, men lose approximately 30 percent of their trabecular bone and 20 percent of their cortical bone during their lifetimes. Trabecular bone loss appears

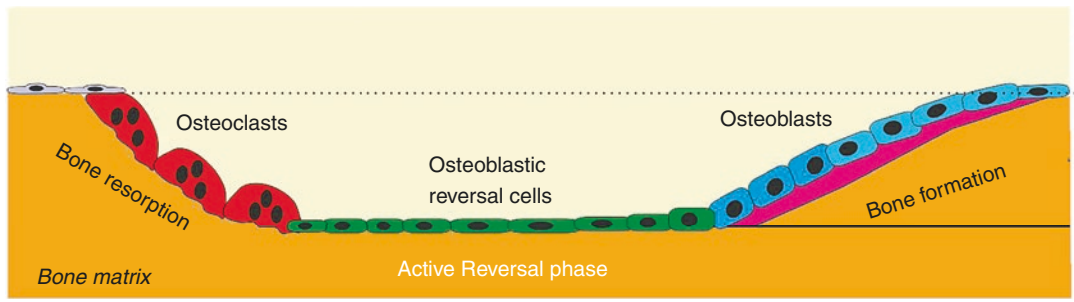

Fig. 5.4 Balanced and coupled bone remodelling. Bone resorption begins when osteoclasts remove a portion of the bone to be replaced later by the action of osteoblasts. This is a vital step for signaling bone formation. Osteoblasts lay down collagen and mineral deposits over the area previously remodelled by osteoclasts. Osteoblast activity is vital for maintaining bone mineral density and bone strength

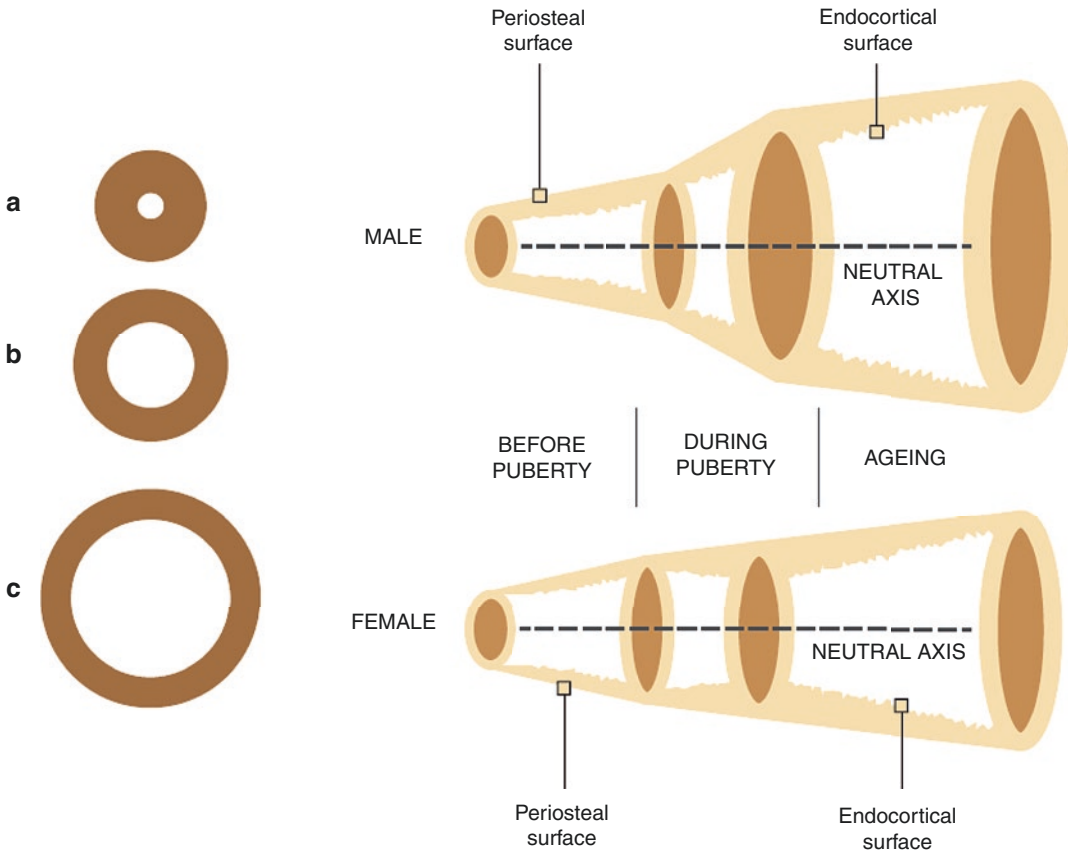

Fig. 5.5 The influence of bone geometry on bone strength105. (IOF: osteoporosis in men). LEFT: For the same areal BMD, bone C has progressively greater bending strength and axial strength than bone B and bone A because the mass of bone C is distributed further away from the center—adapted from Bouxsein [106]. RIGHT: Sex and aging differences in periosteal apposition and endocortical resorption in tubular bones. Adapted from Seeman [107]

to start in young adult life, whereas cortical bone loss is either less pronounced or begins later in life [81]. In some studies, the decline in femoral neck density began shortly after attainment of peak bone mass [82, 83], and the rate of femoral neck bone loss increased with aging [84]. One study reported that bone mineral content of the proximal and distal radius declined at a rate of approximately 1% per year after the age of 30 years, whereas another study found that cortical BMD remained stable until later in life [81, 85].

Patterns of change in spine BMD vary depending upon the measurement technique. When measured by quantitative computed tomography (QCT), which assesses only vertebral body trabecular BMD, spine BMD declines more rapidly than hip or radius BMD [86]. When spine BMD is measured by dual-energy X-ray absorptiometry (DXA) in the posterior-anterior projection, it often appears to increase in older men [87, 88], likely due to degenerative changes in the posterior spinous elements [87]. Thus, posterior-anterior DXA should be interpreted cautiously when assessing bone density of the spine in older men.

Age 70 Years and Onwards

Longitudinal studies suggest that in men bone loss accelerates after the age of 70 years [89]; rapid bone loss is more common with deficient

testosterone or estradiol levels [90]. In contrast to bone loss in women, who lose trabeculae with age due to increased bone resorption; in men bone loss due to trabecular thinning is secondary to reduced bone formation [91]. The preservation of trabecular numbers in men may help explain their lower lifetime risk of fractures. In long bones, bone loss in the marrow cavity is not compensated by bone deposition on the periosteum, which results in loss of cortical bone [92]. A systematic review established that men aged over 70 years were 50% more likely to suffer a fragility fracture than younger men [93].

Other than secondary causes, similar to women, aging is a primary cause of bone loss in men; it induces bone loss through hormonal changes and age-related osteoblast dysfunction.

1. *Hormonal Changes During Aging.*

Hormonal changes during aging are responsible for bone loss; in particular, decreased levels of sexual steroid and relative increase in cortisol negatively influence bone remodeling.

It is widely accepted that the decrease in sex steroid concentrations with age is associated with decreased bone density and increased fracture risk in men [94–96]; nevertheless, the decline of testosterone in men is gradual and not common to all the aged population. In fact, the decrease in bioavailable estradiol more than in testosterone appears to be the cause of bone loss in old men [97].

Excess of glucocorticoids both endogenous and exogenous is known to be detrimental for bone; glucocorticoids affect bone mainly by decreasing osteoblast function [98]. Glucocorticoid action is dependent upon the expression of 11 beta-hydroxysteroid dehydrogenase isozymes, which interconvert active cortisol and inactive cortisone. Bone tissue is able to convert cortisone into active cortisol thanks to this enzyme, whose expression increases with aging [99]. Thus, old persons are more sensible to endogenous and exogenous glucocorticoid; this results in a relative hypercortisolism and possibly in bone damage.

2. *Age-Related Osteoblast Dysfunction.*

In old persons, osteoblasts' dysfunction with a consequent decrease in bone formation has been proposed as one of the underlying mechanisms of osteoporosis in the elderly. Analysis of age-related changes in osteoblasts recruitment, differentiation, and function was carried out. It is known that osteoblasts are derived from the differentiation of skeletal mesenchymal stem cells. The ancestral mesenchymal stem cells are able to differentiate in vitro into osteoblasts, adipocytes, or chondrocytes [100] and to self-renew [101]. It has been suggested that a reduced ability of mesenchymal stem cells to differentiate into osteoblasts may play a role in aging-related bone loss [102–108]. The ability of mesenchymal stem cells to differentiate into osteoblasts has also been studied and a recent work done in mice suggests that age impairs this ability [109, 110]. Thus, this could be one of the mechanisms explaining reduction in bone formation with age.

Moreover, osteoblasts may modify their environment by acquiring a typical senescent secretory phenotype involving inflammatory cytokines, growth factors, and proteases [111, 112], thus contributing to increased osteoclasts activity and bone loss.

3. *Vitamin D Deficiency*.

It is well known that vitamin D plays an important role in regulating calcium metabolism and that its deficiency leads to bone demineralization and increased fracture risk [37]. More than 80% of vitamin D derives from cutaneous synthesis, whereas only 20% comes from diet; cholecalciferol is converted into its active form 1,25-dihydroxyvitamin D3 [1,25$(OH)_2$D3] by two hydroxylations in the liver and in the kidney. Kidney cells hydroxylate vitamin D thanks to the enzyme 1-alpha hydroxylase that is under parathyroid hormone control. 1,25$(OH)_2$D3 binds its nuclear receptor (VDR) and contributes to calcium and phosphorus homeostasis; in the small intestinal cells, the activation of vitamin D receptor (VDR) increases calcium absorption and maintains appropriate calcium levels thus

Table 5.2 Serum 25-Hydroxyvitamin D [25(OH)D], cutoff points for vitamin D serum levels (insufficiency/ deficiency / optimum) and health status (as reported by Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press, 2010)

Serum vitamin D status	Nmol/L*	Ng/mL**	Health status
Deficiency	<30	<12	Associated with vitamin D deficiency, leading to rickets In infants and children and osteomalacia in adults
Insufficiency	30 to <50	12 to <20	Generally considered inadequate for bone and overall health In healthy individuals
Optimum	50–75	20 to 30	Generally considered adequate for bone and overall health In healthy individuals
Normal	75 to 125	30 to 50	Adequate for bone and overall health In healthy individuals
High	>125	>50	Emerging evidence links potential adverse effects to such High levels, particularly >150 nmol/L (>60 ng/mL)

(Serum concentrations of 25(OH)D are reported in both nanomoles per liter (nmol/L) and nanograms per milliliter (ng/mL). ** 1 nmol/L = 0.4 ng/mL)

improving bone mineralization [38]. If the calcium intake is reduced, parathyroid hormone rises and more vitamin D is converted into $1,25(OH)_2D3$; this active form of vitamin D increases calcium level by stimulating osteoclasts activity, thus increasing bone resorption with calcium and phosphorus release in the blood stream [38, 39].

Hypovitaminosis D (Table 5.2) was reported to be largely prevalent among adult population of both genders. The incidence of hypovitaminosis D in older adults has been attributed not only to changes in lifestyle but also to decreased cutaneous synthesis [45]. For the important role vitamin D plays in bones as well as calcium homeostatis, hypovitaminosis D has been considered in the diagnostic processes of male osteoporosis in the elderly, and a correct vitamin D supplementation has to be guaranteed in order to ensure maximum benefit of treatment. Table 5.3 shows the recommended calcium and vitamin D intakes as advised by the Food and Nutrition Board, Institute of Medicine, National Academy of Sciences, 2010.

Pathogenesis: The Role of Hormones

Although gonadal steroids appear to play a crucial role in the attainment of peak bone mass, whether they play a significant role in age-related bone loss is less clear. Unlike women, the rate of age-related gonadal steroid decline is less abrupt in men, and thus, the skeletal impact of these more subtle declines are unclear. However, gonadal levels at the extremes of deficiency have been associated with low BMD and bone loss in older men. Numerous epidemiologic studies have reported associations between gonadal steroids and BMD or fractures [112–116]. These associations are weak, however, as might be expected when studying different populations and relating a single hormone measurement to complex endpoints like bone density and fracture.

Testosterone Some studies have reported significant associations between testosterone, free testosterone, and/or bioavailable testosterone and BMD, rates of bone loss, and prevalent fragility fractures [112–114]. As an example, in the Osteoporotic Fractures in Men Study (MrOS), a cross-sectional and longitudinal study of 2447 men over age 65 years, the prevalence of osteoporosis in the hip or rapid hip bone loss was threefold higher in men whose total testosterone levels were <200 ng/dL (6.9 nmol/L) compared with >200 ng/dL [112].

Estrogen In general, associations of bone density with estrogens have been slightly stronger than associations with androgens [115]. In the MrOS study, the prevalence of osteoporosis in the hip (T-score < −2.5) increased progressively as total or bioavailable estradiol levels fell [112].

Table 5.3 Recommended Calcium and Vitamin D Intakes (as reported by the Food and Nutrition Board, Institute of Medicine, National Academy of Sciences, 2010. [https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/])

Life stage	Calcium (mg/day)		Vitamin D IU (mcg)		Total upper intake level	Pregnancy	Lactation
	Men	Women	Men	Women			
0–12 months	200	200	400 (10mcg)	400 (10mcg)	0–6 months: 1000 IU 7–12 months: 1500 IU		
1–13 years old	1–3 years: 700 4–8 years: 1000 9–18 years: 1300	1–3 years: 700 4–8 years: 1000 9–18 years: 1300	600 (15mcg)	600 (15 mcg)	1–3 years: 2500 4–8 years: 3000 9–18 years: 4000		
14–18 years	1300	1300	600 (15mcg)	600 (15 mcg)	4000	Calcium:1300 Vitamin D: 600 IU	Calcium:1300 Vitamin D: 600 IU Tolerable upper intake: 4000 IU
19–50 years	1000	1000	600 (15mcg)	600 (15 mcg)	4000	Calcium: 1000 Vitamin D: 600 IU	Calcium: 1000 Vitamin D: 600 IU Tolerable upper intake: 4000 IU
51–70 years	1200	1200	600 (15mcg)	600 (15 mcg)	4000		
>70 years	1200	1200	800 IU (20mcg)	800 IU (20mcg)	4000		

In addition, low serum estradiol levels have been associated with an increased risk of future hip fracture in men [116]. Fracture risk appears to be even greater in men with low serum estradiol and testosterone concentrations [115, 116].

Estrogen Versus Testosterone Several studies have evaluated the relative contributions of sex steroids in the regulation of bone resorption and formation (as measured by urinary and serum markers as well as BMD) in adult men [117–119]. Estrogen appears to have the dominant effect on bone resorption and formation. In one physiologic study of induced hypogonadism, 198 healthy men (ages 20 to 50 years) were treated with a GnRH agonist (to temporarily suppress endogenous sex steroid production) and were then randomized to receive 0 (placebo), 1.25, 2.5, 5, or 10 grams of a testosterone gel daily for 16 weeks [119]. A second group of 202 healthy men received the same agents plus anastrozole (to suppress aromatization of testosterone to estradiol). By comparing changes in bone turnover markers, BMD by DXA, and BMD by QCT between men who did and did not receive anastrozole; the study demonstrated that increases in bone resorption and decreases in BMD in hypogonadal men were largely due to estrogen deficiency. The risk of developing hypogonadal bone loss appeared to be small until serum estradiol levels fell below 10 pg/mL and/or serum testosterone levels fell below 200 ng/dL.

Complete Androgen Insensitivity Subjects with complete androgen insensitivity provide a valuable model to assess whether the sexual dimorphism in peak bone density is genetically or hormonally determined. In these subjects, who are genetic males but phenotypic females, radial shaft density is lower than that of normal men but similar to that of normal women. In contrast, lumbar spine density is lower than expected for either men or women of the same age [120–122]. These findings suggest that androgen action con-

Table 5.4 Secondary causes of osteoporosis in men

Causes	Clinical/lab clues
Common causes	
Corticosteroids	At least 5 mg prednisone daily for >3 months
Family history	Family history of minimal-trauma fracture, genetics
Lifestyle	Smoking; high alcohol consumption (i.e., >2 drinks/units daily)
Primary or secondary hypogonadism	Primary or secondary hypogonadism (serum testosterone levels <300 ng/dL); medication use (e.g., corticosteroids, opioids, androgen deprivation therapy)
Vitamin D deficiency and low calcium intake	Serum 25-hydroxyvitamin D <30 ng per mL [74.88 nmol per L]; after correction for renal disease, urinary calcium <50 mg daily suggests inadequate calcium and/or vitamin D intake. Inadequate calcium intake (<600 mg per day)
Less common	
Antiepileptic drugs	Use of phenytoin, phenobarbital, primidone, or carbamazepine
Chronic liver or kidney disease	Elevated creatinine; elevated liver enzymes or other abnormalities of liver function tests
Cushing syndrome	24-hour urine for free cortisol; consider testing in men with clinical signs of Cushing syndrome and unexplained vertebral fractures
Eating disorders	Low body mass index (<20 per m^2); preoccupation with weight; hypotension; electrolyte abnormalities
Endocrine disease	Type I diabetes mellitus, thyrotoxicosis, primary hyperparathyroidism
Inflammatory	Rheumatoid arthritis, inflammatory bowel disease, ankylosing spondylitis
Immobilization	Prolonged bed rest/ chronic illness/neurological deficit
HIV infection	Positive HIV antibodies; treatment with protease inhibitors
Hypercalciuria	High urinary calcium (>250 mg daily) may suggest excessive intake of calcium or vitamin D or impaired renal retention of calcium
Malabsorption (e.g., celiac disease)	Low levels of serum 25-hydroxyvitamin D and/or urinary calcium; positive tissue transglutaminase antibodies
Multiple myeloma or other monoclonal gammopathies	Anemia; renal insufficiency; elevated calcium and erythrocyte sedimentation rate; abnormal immunoglobulin protein (M protein) on serum and urine protein electrophoresis
Organ transplantation	Use of immunosuppressive agents (e.g., cyclosporine, tacrolimus)
Osteomalacia	Serum 25-hydroxyvitamin D may be very low (<15 ng per mL [37.44 nmol per L]); high-normal or elevated alkaline phosphatase and low-normal or low serum calcium or phosphorous
Rare	
Mastocytosis	Fractures, unexplained osteoporosis, and bone pain; high serum tryptase levels (Tryptase levels of 11.5 ng/mL or greater are indicative of either mast cell activation (as in anaphylaxis) or increased total mast cell levels (as in mastocytosis)
Osteogenesis imperfecta	Fractures; hearing loss; positive collagen type I genetic test

tributes to the normal sexual dimorphism in cortical bone density and that the Y chromosome, per se, is not sufficient to guarantee the higher cortical density of normal men. Insufficient replacement of estradiol after gonadectomy, however, cannot be excluded as a reason for these results. As an example, in one study, noncompliance with estrogen replacement therapy after gonadectomy correlated with lower lumbar spine bone density [121].

Other Hormones Other hormonal changes that may be associated with age-related bone loss include higher serum parathyroid hormone (PTH) concentrations and lower serum 25-hydroxyvitamin D and insulin-like growth factor-1 (IGF-1) concentrations [123–125]. Suppression of gonadal steroids in older men with a GnRH agonist increases the skeletal responsiveness to pharmacologic doses of exogenous parathyroid hormone, an observation that might help to explain bone loss in men with hypogonadism [126].

Causes of Osteoporosis in Men

There are two main types of osteoporosis: primary and secondary. In cases of primary osteoporosis, either the condition is caused by age-related bone loss (sometimes called senile osteoporosis)

or the cause is unknown (idiopathic osteoporosis). The term idiopathic osteoporosis is typically used only for men younger than 70 years old; in older men, age-related bone loss is assumed to be the cause.

Male osteoporosis is often secondary and the majority of men with osteoporosis have at least one (sometimes more than one) secondary cause. Epidemiological surveys suggest that causes or contributing factors for osteoporosis can be identified in 40 to 60% of men who have osteoporotic fractures [127–129]. In cases of secondary osteoporosis, the loss of bone mass is caused by certain lifestyle behaviors, diseases, or medications. Some of the most common causes of secondary osteoporosis in men include exposure to glucocorticoid medications, hypogonadism (low levels of testosterone), alcohol abuse, smoking, gastrointestinal disease, hypercalciuria, and immobilization [130, 128–132]. Table 5.4 shows list of the disorders that have been linked to osteoporosis in men.

Additional testing for secondary causes is based on clinical or routine laboratory evaluation. Initial laboratory testing should include complete blood count; liver function test; and thyrotropin (TSH), serum testosterone, 25-hydroxyvitamin D, calcium, and creatinine levels (consider measuring 24-hour urine calcium and creatinine.

Some of the common causes for osteoporosis in men include as follows.

Hypogonadism

Hypogonadism refers to abnormally low levels of sex hormones. It is well known that loss of estrogen causes osteoporosis in women. In men, overt hypogonadism causing reduced levels of sex hormones have been recognized as a possible cause of osteopenia or osteoporosis [133, 134].

Although it is natural for testosterone levels to decrease with age, in contrast with women, there should not be a sudden drop in this hormone level that is comparable to the drop of estrogen levels experienced by women at menopause. However, medications such as glucocorticoids, cancer treatments (especially androgen depletion therapy used for prostate cancer), and many other factors can affect testosterone levels (Table 5.5). In addition to inducing bone loss directly, corsticosteroids may act indirectly by causing hypogonadism. A dose-dependent decrease in serum testosterone is thought to result from both suppression of hypothalamic gonadotropin-releasing hormone secretion and direct effects on testicular testosterone production [135].

Bone turnover increases and bone density decreases in men with serum testosterone levels that are below approximately 200 ng/dL, likely due to a concomitant decline in serum estradiol levels to below 10 to 15 pg/mL [43]. Research suggests that estrogen deficiency may also be a cause of osteoporosis in men. For example, estrogen levels are low in men with hypogonadism and may play a part in bone loss. Osteoporosis has been found in some men who have rare disorders involving estrogen. Therefore, the role of estrogen in men is under active investigation. Furthermore, the low bone density does not appear to be due to dihydrotestosterone deficiency, as men treated with finasteride, which inhibits conversion of testosterone to dihydrotestosterone, do not have accelerated bone loss [136].

Osteoporosis has also been reported in hypogonadal men with hemochromatosis [137, 138] and anorexia nervosa [139]. In these men, it is difficult to determine whether the osteopenia is due to concomitant liver disease and nutritional deficiencies or to hypogonadism. There have been few longitudinal studies of men at risk for osteoporosis as a result of hypogonadism. However, bone density decreases in young men who are castrated for sexual delinquency [140] and in older men with advanced prostate cancer who undergo androgen ablation therapy [141–144].

Testosterone replacement therapy may be helpful in preventing or slowing bone loss. Its success depends on factors such as age and how long testosterone levels have been reduced. Also, it is not yet clear how long any beneficial effect of testosterone replacement will last. Therefore, doctors usually treat the osteoporosis directly,

Table 5.5 Causes of hypogonadism

Primary hypogonadism (testicular pathology)	Secondary hypogonadism (hypothalamus or pituitary gland pathology)
Genetic/chromosomal disorders (Klinefelter's syndrome XXY)	*Idiopathic:*
Anorchia (congenital or post-orchidectomy)	Kallmann syndrome (anosmia and hypogonatrophic hypogonadism)
Cryptorchidism (a condition in which one or both of the testes fail to descend from the abdomen into the scrotum)	*Functional*
Chemotherapy (alkylating agents), radiotherapy	Excessive exercise, weight change
Orchitis (mumps, HIV, autoimmune)	Low BMI
Testicular trauma or torsion	Systemic or intercurrent illness
Medications (glucocorticoids, colchicine)	*Structural*
Alcohol	Pituitary or hypothalamic tumor, prolactinoma
Chronic liver or kidney disease	Infiltration (sarcoidosis, hemochromatosis, histiocytosis X, lymphoma)
Hemochromatosis	Cranial irradiation, surgery, head trauma
	Medications/iatrogenic
	Androgen deprivation therapy for treatment of prostate cancer
	Opioids, marijuana
	Exogenous administration of androgens

Table 5.6 Causes of osteoporosis in men

Endocrine diseases	*Connective tissue diseases*
Hypogonadism	Osteogenesis imperfecta
Primary	Ehlers-Danlos syndrome
Secondary	Marfan syndrome
Delayed puberty	Homocystinuria
Estrogen deficiency	*Drugs*
Hypercortisolism	Alcohol
Hyperthyroidism	Heparin
Hyperparathyroidism	Glucocorticoids
Vitamin D deficiency	Thyroxine-suppressive therapy
Growth hormone deficiency	Anticonvulsant drugs
Diabetes mellitus (type 1 and 2)	Gonadotropin-releasing hormone analogs
Gastrointestinal diseases	Cyclosporine
Malabsorption syndromes (e.g., celiac disease, postoperative states)	Chemotherapy
Inflammatory bowel disease	HIV medications (e.g., tenofovir)
Cirrhosis	*Miscellaneous causes*
Hematologic disorders	Eating disorders (e.g., anorexia nervosa)
Multiple myeloma	Hypercalciuria
Chronic hemolytic anemia	Immobilization
Systemic mastocytosis	Rheumatoid arthritis
	Renal disease
	Hepatic disease
	Tobacco

using medications approved for this purpose (Table 5.6).

Steroids

Glucocorticoids are steroid medications used to treat diseases such as asthma, inflammatory arthritic conditions, as well as autoimmune diseases. Bone loss is a very common side effect of these medications. The bone loss these medications cause may be due to their direct effect on bone, muscle weakness or immobility, reduced intestinal absorption of calcium, a decrease in testosterone levels, or, most likely, a combination of these factors.

Glucocorticoids induce the apoptosis of osteocytes. Osteocytes have a role in the repair of bone micro-damage. Loss of osteocytes by the apoptosis of bone cells interrupts osteocyte-canaliculi network used to obtain nutrients from the blood supply and communicate among themselves and other cells on bone surfaces. As a result, it causes failure to detect signals that normally occur in case of processes associated with the replacement of damaged bone. Disruption of this network system can interrupt fluid flow with the network affecting changes in bone remodeling. Glucocorticoids affect the function of osteocytes, by modifying the elastic part which surrounds osteocytic lacunae to cause osteoporosis in men [145].

Glucocorticoids also enhance the activation of osteoclasts. Glucocorticoids enhance the expression of Interleukin-6, an osteoclastogenic cyto-

kine, and suppress the expression of interferon-beta, an inhibitor of osteoclastogenesis. Those drugs decrease the apoptosis of osteoclasts. As a result, there is increased number of osteoclasts, and the enhanced and prolonged bone resorption is observed in glucocorticoid-induced osteoporosis in men.

When glucocorticoid medications are used on an ongoing basis, bone mass often decreases quickly and continuously, with most of the bone loss in the ribs and vertebrae. Therefore, people taking these medications should be considered for having a bone mineral density test. Men should also be tested to monitor testosterone levels, as glucocorticoids often reduce testosterone in the blood.

A treatment plan to minimize loss of bone during long-term glucocorticoid therapy may include 1. consider discontinuing the medication, 2. use the minimal effective, or 3. administer it through the skin or locally (e.g., intra-articular), if possible. Adequate calcium and vitamin D intake is important, as these nutrients help reduce the impact of glucocorticoids on the bones. Other possible treatments include testosterone replacement and/ or osteoporosis medication [130].

Alcohol Consumption

There is a wealth of evidence that alcohol abuse may decrease bone density and lead to an increase in fractures. Low bone mass is common in men who seek medical help for excessive alcohol consumption.

Alcohol consumption can disrupt the balance of calcium level through hormones, vitamins, and local growth factors which impacts negatively on the bone status. In their study, Laitinen and colleagues [146] reported that each person who receives approximately 5 to 11 standard drinks has increased parathyroid hormone (PTH) levels in their bloodstreams which results in loss of bone mass.

In cases where bone loss is linked to alcohol abuse, the first goal of treatment is to help the patient stop, or at least reduce, his consumption of alcohol. More research is needed to determine whether bone lost to alcohol abuse will rebuild once drinking stops, or even whether further damage will be prevented. It is clear, though, that alcohol abuse causes many other health and social problems, so quitting is ideal. A treatment plan may also include a balanced diet with lots of calcium- and vitamin D-rich foods, a program of physical exercise, and smoking cessation.

Smoking

Bone loss is more rapid, and rates of hip and vertebral fracture are higher, among men who smoke, although more research is needed to determine exactly how smoking damages bone. Tobacco, nicotine, and other chemicals found in cigarettes may be directly toxic to bone, or they may inhibit absorption of calcium and other nutrients needed for bone health.

Several theories have been suggested to explain the negative impact of smoking on human bones. One of the mechanisms is that smoking induces the production of nitric oxide (NO). Nitric oxide is a free radical involved in the regulation of many physiological processes, such as vascular relaxation, platelet aggregation, and immune regulation. During the last decade, it has become apparent that nitric oxide has also an influence on bone cell function [147]. Nitric oxide free radical causes oxidative stress, which presumably increases with age. Continuous oxidative stress in the body normally damage cells, organs, and hormones involved in keeping bones healthy or causes an imbalance between the production of free radicals and the ability of the body to eliminate their harmful effects through neutralization by antioxidants [148]. Oxidative stress caused by free radicals are involved in osteoblastogenesis, in apoptosis of osteocytes and osteoblasts and in osteoclastogenesis, which results in bone resorption as shown in animal and in vitro studies [149].

Another effect of smoking in the body is to increase serum cortisol level. Lewis [150] stated that called smoking, a “stressor,” and described

it as an unwelcomed guest in the body. Smoking has multiple impacts on hormone secretion including the hypothalamic-pituitary-adrenal (HPA) axis. The hypothalamic-pituitary-adrenal axis plays an important role in how the body responds to physical and mental stress. When the body is on stress such as smoking, the cerebral cortex recognizes physiologic stressor and activates limbic system to stimulate hypothalamus, which in turn stimulates the sympathetic nervous system leading to excess production of cortisol in the adrenal gland. Earlier research also reported that small, but persistent, increases in cortisol are associated with reduced bone mineral density.

Quitting is the ideal approach, as smoking is harmful in so many ways. However, as with alcohol, it is not known whether quitting smoking leads to reduced rates of bone loss or to a gain in bone mass [151].

Diabetes-Related Osteoporosis

The link between type 1 diabetes mellitus and osteoporosis has been recognized decades ago [152]. While a number of cellular mechanisms have been postulated to mediate this association, it is now established that defects in osteoblast differentiation and activity are the main culprits underlying bone fragility in type 1 diabetes mellitus. Other contributing factors include an accumulation of advanced glycation end products and the development of diabetes complications (such as neuropathy and hypoglycemia), which cause further decline in bone mineral density, worsening geometric properties within bone, and increased fall risk. As a result, patients with type 1 diabetes mellitus have a 6.9-fold increased incidence of hip fracture compared to controls. Despite this increased fracture risk, bone fragility remains an underappreciated complication of type 1 diabetes mellitus and is not addressed in most diabetes guidelines. There is also a lack of data regarding the efficacy of therapeutic strategies to treat osteoporosis in this patient population [153].

Hypercalciuria

Hypercalciuria is a disorder that causes too much calcium to be lost through the urine, which makes the calcium unavailable for building bone. Idiopathic hypercalciuria (IH) is defined as urinary excretion of calcium >4 mg/kg/day in women and >4.5 mg/kg/day in men without any underlying metabolic cause. There is an association between hypercalciuria and low BMD, and the prevalence is increased among Ca-containing stone formers [154]. This is consistent with studies that report a four-fold increased risk of vertebral fracture observed among urolithiasis patients compared with healthy controls [154]. The deleterious skeletal effects of hypercalciuria in the absence of stone formation is not as well established as in stone formers, and consideration should be given to a radiographic evaluation for asymptomatic stones in osteopenic patients, as this could alter management decisions [155]. Clearly bone loss needs to be aggressively addressed in stone-forming idiopathic hypercalciuria, and the significance of increased urinary Calcium in the absence of stone formation needs to be determined by the clinician on a case-by-case basis. Decreased BMD is even seen in children with idiopathic hypercalciuria and is associated with decreased 25-(OH)D3 levels [156].

The precise mechanism of bone loss in idiopathic hypercalciuria remains incompletely understood despite recent advances. Bone histomorphometry studies have consistently documented decreased osteoblastic activity, mineralization rates, and osteoid surfaces [154]. Idiopathic hypercalciuria is characterized by increased intestinal calcium absorption, increased bone resorption, and decreased renal tubular calcium reabsorption [157]. In 40%–60% of hypercalciuric stone formers, elevated circulating 1,25-dihydroxyvitamin D3 ($1,25(OH)_2D3$) levels are found, as well as increased monocyte expression of vitamin D receptor (VDR) [158, 159]. Animal studies have confirmed role of $1,25(OH)_2D3$ in urinary calcium concentration and decreased BMD [160,

161]. The significance of these findings needs to be determined in humans, but they begin to provide insights into potential pathogenic mechanisms of idiopathic hypercalciuria-related bone disease.

Immobilization

Weight-bearing activity is essential for maintaining healthy bones. Without it, bone density may decline rapidly. Prolonged bed rest (following fractures, surgery, spinal cord injuries, or illness) or immobilization of some part of the body often results in significant bone loss. It is crucial to resume weight-bearing activities (such as walking, jogging, and dancing) as soon as possible after a period of prolonged bed rest. If this is not possible, all efforts should be made to minimize other risk factors for osteoporosis.

Gastrointestinal Disorders

Several nutrients, including amino acids, calcium, magnesium, phosphorous, and vitamins D and K, are important for bone health. Induced by their impaired absorption of these nutrients, disorders of the stomach and intestines can lead to bone disease. In such cases, treatment for bone loss may include taking supplements to replenish these nutrients.

Calcium and vitamin D: In observational studies, vitamin D deficiency is associated with osteoporosis, poor physical performance, and an increased risk of fractures [162]. Evidence supporting the benefit of calcium and vitamin D supplementation in men with osteoporosis comes largely from prospective, randomized, placebo-controlled trials [163, 164]. Although a number of trials have reported a beneficial effect of calcium or calcium plus vitamin D on bone density in postmenopausal women and older men [163–167], the data on fracture rates are more variable [81]. This topic is reviewed in detail separately.

Idiopathic Osteoporosis

The 40 to 60% of men with osteoporosis in whom a cause cannot be identified are said to have idiopathic osteoporosis. Histomorphometric studies suggest that many have diminished bone formation [168–170], but some have increased bone resorption [171]. Many of these men probably have a genetic predisposition to osteoporosis [172].

Serum insulin-like growth factor-1 (IGF-1) concentrations are low in some men with idiopathic osteoporosis. Approximately 2 to 3% of men have a history of delayed puberty, which could be a precursor of idiopathic osteoporosis. Estrogen deficiency may also be responsible for otherwise unexplained osteoporosis in some men.

Diagnosis

Worldwide, a lack of awareness of the threat that osteoporosis poses to men, is evident among men themselves, healthcare professionals responsible for their care and the policymakers determining priorities within health systems. Until recently, the diagnosis of osteoporosis in men was based on the development of fractures after minimal trauma. Osteoporosis can be effectively treated if it is detected before significant bone loss has occurred. A medical workup to diagnose osteoporosis can include a complete medical history, X-rays, and urine and blood tests.

In contrast to fractures, which may be the initial presentation in most men with osteoporosis causing significant pain, disability, and functional impairment; men may present with asymptomatic loss of height (measurement of bone mineral density (BMD) should be considered in men who have lost more than 1.5 inches in height). The most common fracture sites in men are the hip, vertebrae, forearm, and humerus [173].

In the clinical setting, important information includes medications used, chronic diseases, alcohol or tobacco abuse, falls and/or fractures as an adult, as well as family history of osteoporo-

sis. Physical examination should assess patient height in comparison to maximum height, kyphosis, balance, mobility, overall frailty, as well as evidence of causes of secondary osteoporosis. These include testicular atrophy, signs of hyperthyroidism, and evidence of chronic obstructive pulmonary disease. Men for whom bisphosphonate therapy is considered should have an examination of the teeth.

The introduction of dual-energy X-ray absorptiometry for the measurement of bone density has stimulated interest in the diagnosis of osteoporosis before fractures occur. The World Health Organization (WHO) has defined osteoporosis as a BMD 2.5 standard deviations or more below the mean value for young adults (T score equal or less than −2.5), but this has been established only for women. Studies show a similar relationship between absolute bone density measurements and the risk of fracture in both sexes [174]. Furthermore, work from the USA demonstrated that the prevalence of a T-score less than −2.5 at the hip, spine, or forearm in men over the age of 50 year is broadly similar to the lifetime risk of fractures at these sites [175]. This suggests that the WHO criteria may be applicable to the diagnosis of osteoporosis in men and women.

Recent epidemiologic data suggest that for any given absolute bone mineral density value at the spine or hip, the risk of fracture is similar among men and women of the same age. Nevertheless, the average bone mineral density in men who fracture a hip is higher than in women, suggesting that other factors (bone microarchitecture or trauma) may contribute to the risk of fracture more in men than in women. For diagnostic purposes, this discrepancy is addressed by use of a sex-specific T-score, but this practice remains controversial [176].

Using male-specific cutoffs for hip bone mineral density, the National Health and Nutrition Examination Survey III study showed that 6% of US men who were 50 years of age or older had osteoporosis and 47% had osteopenia, as compared to corresponding prevalence in women of 18% and 50%, respectively. If female reference ranges were used in men, the prevalence of osteoporosis and osteopenia would be reduced by two thirds.

Bone densitometry is recommended in men 70 years of age or older—or earlier in men with major risk factors for osteoporosis. Measurements of bone mineral density at the femoral neck are preferable to spinal measurements. Patients should be assessed routinely for risk factors for osteoporosis and for clinical signs of secondary causes.

FRAX®, the WHO fracture risk assessment tool, is used to predict the absolute ten-year fracture risk with or without BMD [177]. It includes key risk factors for osteoporosis such as:

- A prior fragility fracture.
- Parental history of hip fracture.
- Current tobacco smoking.
- Long-term use of oral glucocorticoids.
- Rheumatoid arthritis.
- Other causes of secondary osteoporosis.
- Daily alcohol consumption of three or more units.

Secondary causes of osteoporosis should be sought in men presenting with fragility fractures and/or low BMD by careful history taking, physical examination, and appropriate investigation. Investigations should include full blood count, erythrocyte sedimentation rate, biochemical profile, thyroid function tests, serum testosterone, sex hormone-binding globulin, and gonadotrophins, together with serum and urine electrophoresis in men with vertebral fractures [7]. Prostate-specific antigen should also be measured in men with vertebral fractures and symptoms of prostatism or evidence of sclerosis on X-rays. In elderly men with osteoporosis, serum 25-hydroxyvitamin D, and intact parathyroid hormone measurements may exclude vitamin D insufficiency and secondary hyperparathyroidism, but these are probably unnecessary if calcium and vitamin D supplementation is planned.

Clinical Approach

Men with osteoporosis usually present with low-trauma fractures or radiographic osteopenia discovered incidentally during evaluation for

musculoskeletal pain (e.g., back pain). Osteoporosis should be suspected in men with diseases or treatments known to be associated with bone loss such as hypogonadism, inflammatory bowel disease, or glucocorticoid therapy. The same disorders that cause osteoporosis in women can cause osteoporosis in men, including endocrine diseases, gastrointestinal disorders, connective tissue diseases, drugs, and hematologic conditions. Most osteoporotic men have secondary causes of bone loss, especially alcohol abuse, excess glucocorticoid therapy and hypogonadism [178]. One of the most important causes of severe hypogonadism is androgen deprivation therapy for prostate cancer. Those with idiopathic disease can present at any age but are most dramatic in younger men.

Male patients should be screened for risk factors for osteoporosis. The clinical approach to the diagnosis of male osteoporosis is as follows [179]:

- Screen male patients routinely for risk factors.
- Look for clinical signs of secondary causes.
- Perform a FRAX® calculation.
- Perform a BMD test if the male patient is more than 70 years old, or younger with major risk factors.

Risk factor for osteoporosis in men:

- Past fracture at the of 50 years or older.
- Family history of minimal trauma fracture.
- Physical inactivity.
- High risk of falls, recurrent falls.
- Use of sedatives.
- Low body mass index.
- Smoking.
- Excessive alcohol consumption.
- Taking one of the osteoporosis induced medications.
- Has one of the secondary causes of osteoporosis in men.

Advised Lat Tests Baseline osteoporosis blood profile include measuring serum calcium, phosphate, creatinine (with estimated glomerular filtration rate), alkaline phosphatase, liver function, 25-hydroxyvitamin D [25(OH)D], total testosterone, complete blood count, and 24-h urinary calcium (creatinine and sodium) excretion, in men being evaluated for osteoporosis or considered for pharmacological treatment with bone-active agents.

If history or physical examination suggests a specific cause of osteoporosis, further testing should be done. Depending on the findings of the history and physical examination, such testing may include (but is not limited to) calculated free or bioavailable testosterone (using measurements of SHBG), serum protein electrophoresis with free κ and λ light chains and/or urine protein electrophoresis, tissue transglutaminase antibodies (for celiac disease), thyroid function tests, and parathyroid hormone levels.

In men with low bone mass (osteopenia) or osteoporosis who might have previously undiagnosed vertebral fractures, vertebral fracture assessment (VFA) is recommended, using DXA equipment. If vertebral fracture assessment (VFA) is not available or is technically limited, lateral spine radiographs should be considered.

DXA Scan Interpretation

Interpretation of BMD measures in men has been controversial. Data suggesting that the risk of fracture is similar in men and women at the same absolute level of BMD has led some to recommend that the definition of osteoporosis based on T-scores be the same for both sexes [180]. However, this approach results in fewer men over age 50 being identified as at risk. The ISCD Position Development Conference held in July 2003 reviewed this controversy and recommends using a combination of risk factors and T-scores [181]. However, the 2019 ISCD Official Positions on adult osteoporosis reported that in men age 50 and older, T-scores should be used and osteoporosis diagnosed if the T-score is −2.5 or below the young normal mean for men. Below age 50 years old, T-scores may be used and osteoporosis diagnosed if both the T-score is

equal to or less than −2.5 and other risk factors for fracture are identified. Men at any age with secondary causes of low BMD may be diagnosed clinically with osteoporosis supported by findings of low BMD. The diagnosis of osteoporosis in men under age 50 years should not be made on the basis of densitometric criteria alone. The diagnosis in men under age 50 must be made on clinical grounds. Longitudinal studies are needed to better define the BMD-fracture risk relationship in men [182].

When spine BMD is measured by dual-energy X-ray absorptiometry (DXA) in the posterior-anterior projection, it often appears to increase in older men [183–186] /31,34,35], likely due to degenerative changes in the posterior spinous elements (Fig. 5.4) [185] /34]. Thus, posterior-anterior DXA should be interpreted cautiously when assessing bone density of the spine in older men.

Laboratory Tests

Further testing is strongly indicated to rule out secondary causes in men whose z score is below −2.0 (2 SD below the age-specific mean) on bone densitometry. Routine tests include measurements of serum calcium and creatinine levels, liver function tests, measurement of the thyrotropin level, and a complete blood count. If clinically indicated, serum protein electrophoresis and tests for urinary Bence Jones protein (to check for monoclonal gammopathy), antitissue transglutaminase antibodies (to check for celiac disease), 24-hour urinary cortisol or calcium, and human immunodeficiency virus antibodies should be performed.

Since hypogonadism is often difficult to detect; on the basis of the patient's history and the physical examination alone, measurement of the total testosterone level is recommended in all men with osteoporosis. Sex hormone-binding globulin levels may provide additional information in some cases (e.g., in men with insulin resistance or obesity, in whom low levels of sex hormone-binding globulin may complicate interpretation of total testosterone levels).

Serum levels of 25-hydroxyvitamin D should also be measured. Levels below 30 ng per millilitre (75 nmol per liter) should be treated. There are limited data relating markers of bone turnover to the risk of fracture among men [187]. These markers show high biologic variability, and their measurement has not been shown to improve outcomes in men with osteoporosis, so their routine use in practice cannot currently be recommended. However, they may be useful for men in whom no apparent cause of osteoporosis can be detected on other tests and for men with very low bone mineral density to detect low levels of bone formation [188].

Vertebral Fracture Assessment

A history of a minimal trauma fracture after the age of 50 years is the strongest clinical risk factor for fracture [189]. Recognition of fractures is important for risk stratification, particularly in men with osteopenia. Among minimal trauma fractures, vertebral fractures are most common and are often clinically silent. Spinal radiography is useful for diagnosis, but it involves a relatively high dose of radiation [190]. Assessment of vertebral fracture is also possible with dual-energy X-ray absorptiometry [191], with high sensitivity and specificity for moderate fractures (height loss, 30 to 40%) and severe fractures (height loss, more than 40%), but spinal radiographs remain the gold standard [192].

The finding of mild vertebral deformities with the use of dual-energy X-ray absorptiometry is less specific and should be differentiated from non-osteoporotic short vertebral height (height loss, 15% or less, without central endplate compression), a common finding on spinal radiographs [193].

Figure 5.6 shows a clinical approach to men clinical approach to men at risk of having osteoporosis in standard clinical practice.

In conclusion, osteoporosis and consequent fracture(s) are not limited to postmenopausal women. There is increasing attention being paid to osteoporosis in men, particularly older adults. Men suffer osteoporotic fractures about 10 years

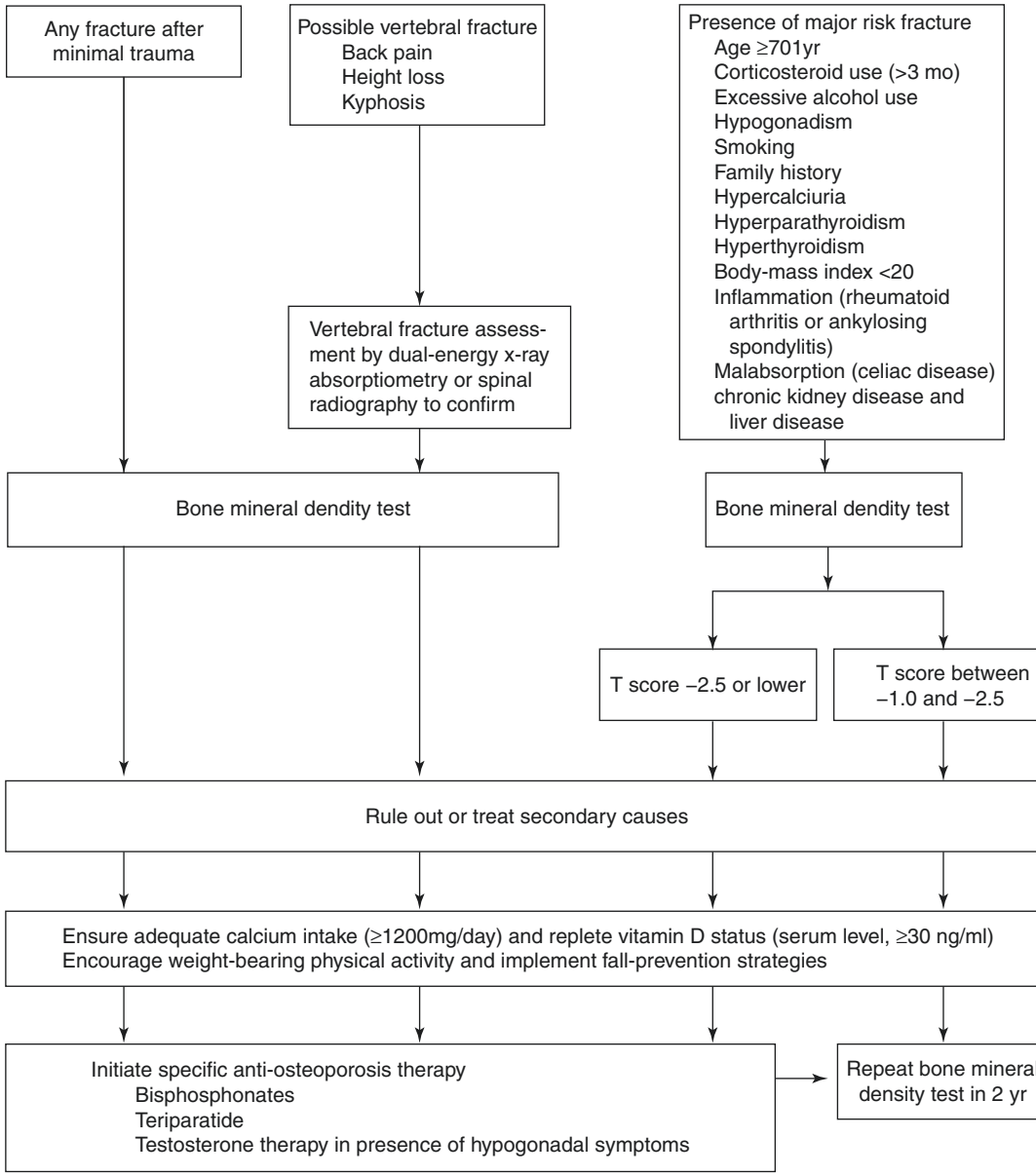

Fig. 5.6 Clinical approach to men at risk of having osteoporosis in standard clinical practice. Excessive alcohol use is defined as 18 oz. (533 ml) or more of full-strength beer, 7 oz. (207 ml) or more of wine, or 2 oz. (59 ml) or more of spirits per day

later in life than women. However, as life expectancy for men is getting longer, this makes men live long enough to fracture. This finding is of utmost importance, as the fracture consequences are greater in men than in women, with men having about twice the 1-year mortality rate after hip fracture, compared to women. Men at high risk for fracture include those men who have already had a fragility fracture, men on oral glucocorticoids, or those men being treated for prostate cancer with androgen depletion therapy. Beyond these high risk men, there are many other risk

factors and secondary causes of osteoporosis in men. Evaluation includes careful history and physical examination to reveal potential secondary causes, including many medications, a short list of laboratory tests and bone mineral density testing by dual energy X-ray absorptiometry (DXA) of spine and hip. International organizations have advocated a single normative database for interpreting DXA testing in men and women. There are several choices of therapy for osteoporosis in men, with most fracture reduction estimation based on studies in women.

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Bone Health in the Transgenders

6

Yasser El Miedany

Introduction

The United Nations human rights defined "gender identity" as a term which refers to a person's experience of their own gender. The term "transgender" people or "gender nonconforming" refers to subjects who have a gender identity that is different from the sex that they were assigned at birth [1]. In another way, the term "transgender" describes a population experiencing incongruence between their physical sex characteristics (assigned gender) and their gender identity (the extent to which people experience themselves to be like others of one gender) [2]. In some instances, as a result of the incongruence between assigned gender and gender identity, an individual can suffer distress (gender dysphoria), which may be accompanied by physical or mental health issues [3]. A transgender or trans person may identify as a man, woman, transman, or transwoman, or as a non-binary person (Table 6.1). Gender identity is different from sexual orientation, trans people may have any sexual orientation, and, therefore, they can be heterosexual, lesbian, gay, bisexual, asexual or pansexual (attracted to a person of any sex or gender identity).

In the past, being transgender was defined as a mental illness concern and was categorized as such by the World Health Organization in the international Classification of Diseases-10. The recognition of the biologic underpinnings to gender identity has resulted in a major framework shift. Indeed, the latest International Classification of Diseases 11, launched in 2018, changed the term to "gender incongruence" and reclassified it under conditions related to sexual health [4].

The current literature on the number and proportion of transgender people is highly heterogenous. The reported proportions of people self-identified as transgender ranged from 100 to 2000 per 100,000 or 0.1% to 2% among adults. The corresponding range among school children was 1.3% to 2.7%. Causes of heterogeneity may include diverse cultural and legal population-specific contexts as well as how transgender people are perceived and treated in a society [5].

Achieving gender reassignment is not often easy. Psychological implications should be considered carefully and are always addressed as part of the individual assessment. The transitioning process may take several years, usually started by seeking a diagnosis, following which the implications can be discussed and treatment plan is agreed. The implications discussed include:

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Table 6.1 Terminology related to sex and gender

Terminology	Definition
Gender identity	Internal sense of being male, female, neither, or along the Spectrum
Sex assigned at birth	Biological characteristics including anatomic phenotype and/ Or chromosomal makeup (usually assigned at birth or shortly thereafter)
Cisgender	Gender identity and expression congruent with sex assigned at birth
Gender dysphoria	Distress that may accompany the incongruence between Experienced or expressed gender and sex assigned at birth
Transgender	A persistent gender identity that differs from sex assigned at birth
Non-binary gender identity	Describes gender identities that are not exclusively masculine Or feminine and therefore outside the "gender binary" of male and female. It may mean the individual feels he/she has no gender
Transgender man (transman)	Sex-assigned female at birth, with masculine Identity
Transgender woman (transwoman)	Sex-assigned male at birth, with feminine Identity
Transvestite (cross-dress)	People who cross-dress are usually comfortable with their assigned Gender and do not wish to change it. (trans people who cross-dress enjoy wearing clothes associated with the opposite sex, often for relatively short periods of time, for personal comfort and pleasure)
Sexual orientation	Gender or genders a person is attracted to
Gender-affirmative healthcare	Include any single or combination of a number of social, psychological, behavioral, or medical (including hormonal treatment or surgery) interventions designed to support and affirm an individual's gender identity

1. Making decisions about whether the person want to commence hormone therapy and be considered for surgery.
2. The need to change the individual's name and gender marker on documentation and explore financial implications.
3. How the person will begin living in the affirmed gender is discussed.

Treatment plan comprises hormone treatment and if the individual has surgery, probably this will involve more than one operation. After surgery, the subject will probably require long-term hormone therapy and regular monitoring for possible side effects.

Studies of mortality and somatic well-being after sex-reassignment surgery of transgenders revealed elevated somatic morbidity as well as mortality in this cohort of people. Long-term follow-up study [6] of individuals undergoing sex-reassignment revealed that 23.1% had somatic morbidity after the reassignment surgery and that of 98% of all transsexuals who officially underwent transgender surgery in Denmark from 1978 through 2010 (total number 104 individuals), one in three had somatic morbidity and approximately 1 in 10 had died. No significant differences in somatic morbidity or mortality were found between male-to-female and female-to-male individuals. The list of somatic morbidities included cardiovascular, cancer, musculoskeletal and bone health, pulmonary, as well as liver diseases. This chapter will focus on bone health in transgenders, the role of sex hormones on bone health, as well as the bone mass effects of cross-sex hormone therapy in transgender people. The chapter will review on the current data available regarding bone health in adult transgender men and women as well as adolescents. It will expand to discuss guidelines for transgender hormone treatment, osteoporosis risk in transgender individuals, as well as approaches toward screening for osteoporosis in transgender individuals. It will conclude by discussing clinical implications for bone health management of transgender people in standard clinical practice.

Sex Hormones and Bone Health

Sex steroids are major determinants of bone homeostasis. In boys, during puberty, testosterone stimulates periosteal apposition, leading to increased bone width and size compared to girls, despite the similar cortical thickness [7]. In turn, estrogen plays a main regulatory role in bone metabolism in both women and men, acting on bone remodeling and keeping it within physio-

logical limits. Estradiol acts on the lifespan of osteoblasts, decreasing apoptosis and increasing the functional capacity of individual osteoblasts. In osteoclasts, estradiol induces apoptosis and decreases cellular differentiation [8]. Estrogen deficiency is associated with an imbalance between bone resorption and bone formation that is linked to osteoblast apoptosis, oxidative stress, and osteoblastic NF-κB (RANKL) activity [9].

Although the importance of sex steroids in bone health is widely accepted, the differential effects of estrogen and testosterone individually remain a topic of discussion. In the late 1990s, Riggs et al. [10] described a pivotal role for estrogen in the female and male skeleton. Recent research, assessing bone architecture, has questioned this model. Cortical bone loss still seems related with estrogen deficiency, but trabecular bone loss occurs earlier in adulthood, in both men and women, in the presence of normal sex steroid status, indicative that trabecular bone loss is either (partly) estrogen-independent or requires higher levels for its preservation [11–13]. Hence, quantitative computed tomography (QCT) and visualizing bone geometry is a valid tool which can be used for unravelling the interactions of sex steroid with trabecular and cortical bone.

Sex steroids also influence bone size: men develop larger periosteal (outer) and endosteal (inner) circumference than women, partly due to the interplay of sex steroids, mechanical loading, and the growth hormone (GH)/ insulin-like growth factor 1 (IGF1)-axis during puberty [14–16]. In adulthood, periosteal apposition continues, but at a slower rate in women than in men [17]. Sex steroid reversal, as encountered in transmen on testosterone treatment, may shed light on the role of individual contributions of sex steroids in the sexual dimorphism in bone geometry.

Bone Mass Effects of Cross-Sex Hormone Therapy in Transgender People

Animal studies have helped elucidate the role played by estrogen as well as testosterone in bone health. In male mice, estrogen receptor deletion in osteoblasts causes a delay in cortical bone mass accrual during puberty. However, in contrast to female mice, this effect is transient; a few months later, male mice develop normal bone mass, suggesting that androgen action via androgen receptor has a compensatory effect. Interestingly, androgen receptor deletion in osteoblasts and osteocytes has no effect on cortical bone, suggesting an indirect action of androgens. Androgens may also exert anabolic actions via paracrine mechanisms by acting on muscle fibroblasts [18, 19]. In fact, muscle mass is one of the main triggers of periosteal apposition, leading to larger periosteal circumference [20]. It is important to keep in mind that DXA scanning does not provide information on bone volume and that men have larger bones than women, which gives them greater resistance even with similar densities. Volume changes associated with the treatment would not be detected by DXA. However, the use of peripheral quantitative computed tomography, a technique that allows assessment of bone size, has shown increased volumetric BMD in transgender men [21, 22], with larger endosteal and periosteal bone circumference [21] after androgen therapy.

In humans, transmen have a female birth sex but identify as, or desire to be, a member of the male gender. In the case of gender dysphoria, this incongruence causes discomfort or distress often leading to the choice for testosterone treatment and/or sex reassignment surgery (including hysterectomy/salpingo-oophorectomy and mastectomy). A substantially higher muscle mass and a larger periosteal and endosteal circumference, higher trabecular volumetric bone mineral density (vBMD), and lower cortical vBMD was reported earlier in a cross-sectional study using peripheral QCT (pQCT) in adult transmen after long-term testosterone treatment (10 years) and transgender surgery compared with age-matched control women. This larger bone size was probably mostly explained by the higher androgen-induced muscle mass in transmen [23–27]. These data may, at least in part, provide a mechanistic basis for the evidence generated by this meta-analysis regarding the impact of cross-sex hormone therapy on preserving bone mass in transgender men.

Transwomen, conversely, receiving estrogen therapy may lose lean mass in association with androgen deprivation, which over time can lead to smaller bones and higher prevalence of low bone mass. Recent study revealed a prevalence of 18.3% of low bone mass in transwomen after long-term cross-sex hormone therapy, whereas no cases were observed in male or female controls [23, 24]. Also, Lapauw et al. [28] found a prevalence of 35% of low bone mass after a mean of 96 months of estrogen therapy. The studies reporting osteoporosis or low bone mass prevalence >25% included transwomen followed for 5 [29, 30] to 6.3 years [31] after the procedure.

Practical Guidelines for Transgender Hormone Treatment

Both the World Professional Association for Transgender Health (WPATH) and the Endocrine Society have created transgender-specific guidelines [32] to help serve as a framework for providers caring for gender minority patients. These guidelines are mostly based on clinical experience from experts in the field. Guidelines for hormone therapy in transgender men are mostly extrapolations from recommendations that currently exist for the treatment of hypogonadal natal men and estrogen therapy for transgender women is loosely based on treatments used for postmenopausal women.

In the past, the guidelines for hormone therapy initiation recommended that all patients undergo a "real-life test" prior to starting medical therapy. This test required patients to live full-time as their self-affirmed gender for a predetermined period of time (usually 12 months) before starting cross-sex hormones. The recommendation was intended to help patients transition socially. However, both abovementioned societies have recognized that this step is unreasonable for many patients as social transition can be very challenging if there is incongruence between an individual's self-affirmed gender and their physical appearance. As a result, the updated guidelines do not require this step, and instead, the societies recommend that patients transition socially and with medical therapy at the same time [32].

WPATH recommends that hormone therapy should be initiated once psychosocial assessment has been completed, the patient has been determined to be an appropriate candidate for therapy, and informed consent reviewing the risks and benefits of starting therapy has been obtained. Per WPATH, a referral is required by a qualified mental health professional, unless the prescribing provider is qualified in this type of assessment. The criteria for cross hormone therapy include: (1). persistent well-documented gender dysphoria (a condition of feeling one's emotional and psychological identity as male or female to be opposite to one's biological sex) diagnosed by a mental health professional well versed in the field; (2). capacity to make a fully informed decision and to consent for treatment; (3). age of majority; and (4). good control of significant medical and/or mental comorbid conditions [32, 33].

This fourth criterion can sometimes be the most challenging to interpret. Many patients may have concurrent mood disorders related to their gender dysphoria, and experienced providers may have success alleviating the severity of these symptoms by allowing the patient to begin the medical transition process. This is a key concept and should be considered when patients are being evaluated for hormone therapy initiation. Patients with comorbid psychiatric conditions should be closely monitored, and mental health support remains paramount for these patients. Table 6.2 shows hormone options available for transgender men and women, whereas Table 6.3 shows Surveillance recommendations for transgender men on testosterone as well as transgender women on estrogen [34].

There are no unanimous recommendations for the use of anti-androgens. Options are listed in Table 6.2. Spironolactone is one of the most common medications used to suppress endogenous testosterone in transfemale patients. The biggest risk associated with spironolactone is hyperkalemia, and this should be closely monitored. Other options include 5α-reductase inhibitors such as finasteride, but these can be associated with liver

Table 6.2 Hormonal options for transgender men and women

Transgender men			Transgender women		
Route	Formulation	Dose	Route	Formulation	Dose
Oral	Testosterone undecanoate	160–240 mg/day	Oral	Estradiol	2–4 mg daily
Parental (subcutaneous, intramuscular)	Testosterone enanthate, cypionate	50–200 mg/week 100–200 mg/10–14 days	Parental (subcutaneous, intramuscular)	Estradiol valerate	5–30 mg every 2 weeks
Implant (subcutaneous)	Testopel	75 mg/pellet	Transdermal	Estradiol	0.1–0.4 mg twice weekly
Transdermal	Testosterone gel (1%) testosterone patch	2.5–10 g/day 2.5–7.5 mg/day	Anti-androgens	Progesterone Medroxyprogesterone acetate GnRH agonist (leuprolide) Histrelin implant Spironolactone Finasteride	20–60 mg PO daily 150 mg IM every 3 months 3.75–7.5 mg IM monthly 50 mg implanted every 12 months 100–200 mg PO daily 1 mg PO daily

Table 6.3 Surveillance recommendations for transgenders on hormone therapy

Surveillance recommendations for transgender men on testosterone	Surveillance recommendations for transgender women on estrogen
Monitor for virilizing and adverse effects every 3 months for the first year, then every 6–12 months Obtain baseline hematocrit and lipid profile and monitor at follow-up visits Obtain baseline bone mineral density if a patient is at risk for osteoporosis; routine screening after age 60, or earlier if sex hormone levels consistently low Monitor serum estradiol during the first 6 months and thereafter until uterine bleeding has ceased Monitor serum testosterone at follow-up visits; target 300–1000 ng/dL Peak levels for parenteral testosterone measured 24–48 hrs after injection Trough levels for parenteral testosterone measured before injection	Monitor for feminizing and adverse effects every 3 months for the first year, then every 6–12 months Obtain baseline hematocrit and lipid profile and monitor at follow-up visits Obtain baseline bone mineral density if a patient is at risk for osteoporosis; routine screening after age 60, or earlier if sex hormone levels consistently low Obtain prolactin at baseline, at 12 months after initiation of treatment, biennially thereafter Monitor serum testosterone during the first 6 months until levels are <55 ng/dL Monitor serum estradiol at follow-up visits; target 100–200 pg/mL

toxicity and may not be as effective as spironolactone [33]. Gonadotropin-releasing hormone (GnRH) agonists can be very expensive and are not always a good option for patients. Progestins are used by some providers, but should be used with caution as there is a theoretical risk of breast cancer associated with long-term exogenous progesterone use [35].

Osteoporosis Risk in Transgender Individuals

There is a broad spectrum of transgendered persons, not all of whom choose to become transsexual by transitioning physically to the opposite sex. Therefore, many transgendered individuals, from a biological perspective, conform to their

natal sex. Of those who have chosen transition, some may be either taking or may have taken sex hormones surreptitiously and self-regulated, whereas others may be undergoing or may have completed medically supervised hormonal and surgical therapy. Surgical therapies include either male orchiectomy or female oophorectomy. In addition to this, there is a high prevalence of exposure to modifiable risk factors for osteoporosis among transgender individuals. Smoking is highly prevalent among transgender individuals [36]. A national survey revealed that 30.7% of transgender individuals smoke and many work in smoke-filled bars resulting in significant exposure levels to passive smoking. An estimated 25% of transgender individuals misuse alcohol or drugs to cope with the discrimination they face because of their gender identity or expression [37].

Like the cisgender population, transgender individuals experience these modifiable risk factors as part of their multiple, interacting, and cumulative lifestyle habits [38]. These risk factors along with transgender individuals use of cross-sex hormones may put them at increased risk for osteoporosis. In addition, because of the complex interactions between the sex hormones and bone metabolism, both in the achievement of peak bone mass leading up to skeletal maturity and then in the subsequent loss of bone with aging, as well as the increased risk behavior; the risk of developing osteoporosis varies widely among transgendered persons.

On another front, transgender individuals often delay accessing healthcare, placing them at risk for poor short- and long-term health outcomes [39]. The World Professional Association for Transgender Health Standards of Care emphasizes access to evidence-based healthcare as a right for transgender individuals. In concordance, the American Academy of Nursing published a position statement on healthcare services for transgender individuals [40]. Although there has been an abundance of research addressing bone health and osteoporosis prevention, the individuals' knowledge and health beliefs for carrying out health behaviors; there is no research on transgender individuals' knowledge, health beliefs, or osteoporosis preventing behaviors in this disparate cohort of population who are often using self-administered cross-sex hormones. Therefore, it would be a logical step to consider examining these variables in transgender individuals.

Use of cross-sex hormones is the most common body modification that transgender individuals can access to bring endocrine and psychological systems into balance [40], but this can potentially affect one's bone mineral density (BMD). The stigma surrounding transgenders has led to growing numbers of individuals obtaining hormones and hormone blockers via the Internet and self-medicating [40, 41]. Self-treatment with cross-sex hormones therapy may increase the risk for developing osteoporosis [42]. The research is limited on the use of non-physician, unprescribed cross-sex hormones [43]. Without medical advice and knowledge required to minimize health risks from self-prescribed use of cross-sex hormones, transgenders may develop misperceptions and inaccurate health beliefs that may lead to unhealthy behaviors with severe risks that include cardiovascular complications, altered bone health, and osteoporosis. There are no randomized controlled trials on the use of long-term cross-sex hormones, and little is known about the long-term effects [44]. With the increasing numbers of adolescents and young adults who are taking cross-sex hormones, effects of pubertal suppression on BMD have not been systematically explored and need to be studied over the long term [45].

The research on fractures in transgender individuals is also sparse. In a systematic literature review by Weinand and Safer [46] on cross-sex hormones safety for adult transgenders, results indicated that a considerable amount of the existing data has been generated from case reports with very few large cohort studies addressing long-term effects of hormone therapy. A cross-sectional study conducted in Belgium by [44], a pioneer in transgender research, explored the side effects of cross-sex hormones use in 100 transgenders after sex assignment surgery who had on average a 10-year use of these hormones. Results indicated that transmen did not have osteoporosis as a side effect, but transwomen had significantly

more low bone density and osteoporosis at the lumbar spine and radius.

The evolution of bone density, geometry, and bone turnover in transwomen during the initial 2 years of monitored use of cross-sex hormones was investigated by Van Caenegem et al. [47] and is recognized as one of the first prospective studies in this area. Transwomen at the onset of the study before using cross-sex hormones had lower bone density and smaller bone size compared with age matched control men. With the monitored use of prescribed cross-sex hormones, bone turnover decreased, but there was a significant decrease in muscle mass and strength. Research recommendations include lengthening the time of follow-up for addressing the long-term effects of cross-sex hormones on bone and the effect in older individuals. In fact, the time is ripe for educating transgenders about the use of cross-sex hormones to increase knowledge about osteoporosis prevention and bone health awareness [48].

Furthermore, adaptation of recommendations for osteoporosis screening to transgender populations is complicated by existing recommendations that vary widely for non-transgender people, including lack of consensus about screening for non-transgender men, and lack of recommendations on the frequency of screening.

Screening for Osteoporosis in Transgender Individuals

The Endocrine Society recommends that both male-to-female and female-to-male transgendered persons on cross-hormone therapy be considered for BMD testing at baseline if clinical risk factors for osteoporotic fractures are present. In individuals at low risk, screening for osteoporosis should be conducted at 60 years of age and in those who are not compliant with hormone therapy [49]. Screening between ages 50 and 60 should be considered for those with established risk factors for osteoporosis. Transgender people (regardless of birth assigned sex) who have undergone gonadectomy and have a history of at least 5 years without hormone replacement should also be considered for bone density testing, regardless of age (Grading: X C W). There are three main reasons to perform central DXA: (1) diagnosing osteoporosis; (2) determining fracture risk (50 years of age or older); and (3) monitoring response to treatment [50]. Of these indications, only the monitoring of treatment response (i.e., determining change in BMD over time) is sex or gender neutral. The subject is being compared with him- or herself and any observed change in the BMD has the same statistical relevance as if the person's sex had been maintained between serial scans.

However, the scanner software determines the subject's standard scores (T-scores and Z-scores) based on the sex entered by the technologist. For any given BMD measurement, the corresponding standard score will be different for men and women because their reference population databases differ. There are as yet no specific reference databases for transgendered persons. The T-score is used to diagnose osteoporosis by determining diagnostic category as defined by the World Health Organization. It is also a key measurement used in the estimation of fracture risk in the widely used FRAX (Fracture Risk Assessment Tool, World Health Organization, Geneva, Switzerland) fracture risk prediction tool, as well as in other such tools as Canadian Association of Radiologists and Osteoporosis Canada (CAROC) system, Foundation for Osteoporosis Research and Education Fracture Risk Calculator (FORE FRC), and the Garvan Fracture Risk Prevention Tool, all of which require that either male or female sex be entered into the calculator [51]. It follows that both parameters (i.e., diagnostic category and estimated fracture risk) might not accurately reflect the bone health of individuals whose sex/ gender identity as recognized by the scanner differs from their actual biological sex. A similar dilemma exists in interpreting the laboratory results of transgendered persons on hormonal therapy [52].

It is probable that most technologists and physicians performing and interpreting DXA scans will not be fully aware of the treatment protocols of the transgendered patients referred to them for assessment. The densitometrist's report can confidently indicate serial changes in BMD irrespec-

tive of the recorded sex of the patient, but the assignment of a diagnostic category and estimation of 10-year fracture risk are problematic because our normative databases assume that the individual conforms to his or her natal sex.

A solution for the DXA technologist might be to process each transgendered patient twice, the first time based on the sex declared on the patient questionnaire and the second time based on the opposite sex. This will provide two sets of T-scores, 1 for each sex. The reporting physician can then decide how to best interpret and report on the data. For example, diagnostic category and fracture risk could be calculated twice using the standard male and female reference databases. Both reports could be issued to the referring clinician, who is likely the individual best positioned to determine if the transgendered person is biologically male or female, and to assess the clinical implications of the DXA results. It has been suggested that in some individuals, the clinician may wish to assign a fracture risk that is intermediate between the biological male and female values [53]. However, there are disadvantages of such an approach, in terms of added time, inaccuracy, inapplicability for monitoring, as well as the potential for creating confusion. Clearly, individual facilities will need to determine the most appropriate policy for each to adopt.

Advice should be given to modify risk factors for osteoporosis, including tobacco cessation, correct low vitamin D levels, maintain calcium intake in line with current guidelines for non-transgender people, weight bearing activity, and moderation of alcohol consumption [54].

Implications for Standard Clinical Practice

Currently, there is no published research on transgenders' bone health and osteoporosis prevention. This is an important area for future research, with the growing number of transgenders who are not only at risk for osteoporosis and possible fractures just as the general public is at risk, but who are at an additional risk because of long-term use of cross-sex hormones. Little is known about the long-term use of cross-sex hormones, particularly when initiated in young adulthood and continued into adulthood.

Determining transgenders' health belief perceptions of bone health and osteoporosis is important because of their unique healthcare issues. Improving osteoporosis-preventing behaviors, particularly dietary calcium intake and weight-bearing exercise, are issues that both men and women face during aging as bone density decreases [38]. However, the transgender population is faced with compounding issues of cross-sex hormone use, particularly when they self-manage use of hormones. Self-management can result in hormone imbalance, which can have a long-term effect on bone health. Earlier study revealed that transgenders lack knowledge about bone health and behaviors that promote bone health and prevent osteoporosis [55]. Therefore, it is important that healthcare providers consider the transgenders' knowledge deficits in relation to osteoporosis prevention and bone health promotion. Clinical implications include conducting appropriate assessments and providing education when caring for transgenders. Thorough assessments are needed to screen the transgenders for their use of cross-sex hormones (self-regulated or regulated by a health professional) and determining the transgender' knowledge and health beliefs regarding osteoporosis prevention and promotion of bone health [56].

It is vital to establish a respectful communicating approach with the transgenders so that conversations about risk behaviors and hormone use can easily occur. By identifying gaps in the transgenders' knowledge, healthcare providers can educate this at-risk minority population on how to be proactive in maintaining bone health through awareness of risk factors (such as hormone use) and prevention behaviors (diet, exercise) [57]. Healthcare providers can influence positive bone health behaviors by taking on critical roles as a caregiver, educator, and advocate. By identifying knowledge gaps for transgenders, devising better prevention and wellness

plans, not only for bone health but also for the overall health and well-being, would be achievable [48, 58].

In conclusion, many healthcare professionals have not received formal training in dealing with transgendered patients and may not be comfortable in interacting with and providing care for them. Having surgical therapies such as male orchiectomy or female oophorectomy, cross-hormone therapy, as well as the high prevalence of exposure to modifiable risk factors for osteoporosis would have a negative impact on the transgenders' bone health and make them prone to develop osteoporosis. Until expert guidelines are developed, facilities that deal regularly with transgendered patients may wish to consider the following policy: When assessing a declared transgendered person for a DXA scan, the densitometrist should follow current social convention and respect the patient's chosen gender identity by entering the sex declared by the patient. After the scan has been completed, the initial printout will reflect this declared identity. The densitometrist should then change the recorded sex, issuing a second printout. Both documents are made available to the physician reporting the scan, who may wish to consider issuing 2 reports for the patient, assigning diagnostic category and fracture risk for both a female and a male individual. This is a policy decision that will need to be made locally. However, interval change in BMD, if the scan is a follow-up, will be identical on the two documents. Future longitudinal studies to investigate the long-term impact of cross-sex hormones use on bone health. A larger sample would provide the opportunity to analyze daily calcium and vitamin D intake by participant age. Most importantly, intervention studies are needed to determine the best ways to access and educate this historically private population regarding bone health and osteoporosis preventing behaviors. Including ethnic and cultural considerations of transgenders in future research would provide a diverse perspective of the use of cross-sex hormones and bone health and prevention of osteoporosis. Healthcare providers can play a key role in helping promote transgender' awareness for bone health.

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Part II

Diagnosis: Clinician's Guide

7 Osteoporosis Risk Assessment Tools

Yasser El Miedany

Introduction

Numerous risk factors for osteoporosis and fractures have been identified, and several tools have been developed to integrate risk factors into a single estimate of fracture risk for individuals. Developed prediction tools, such as fracture risk assessment tool (FRAX) algorithm [1], Qfracture algorithm [2], and Garvan fracture risk calculator (Garvan) [3, 4], have been developed aimed at assisting clinicians in the management of their patients through the calculation of the patient's 5-year or 10-year risk of fracture based on a combination of known risk factors. In addition to these most popular algorithms, several other tools exist which vary according to the type and number of risk factors included. Common to all these tools is the ability to identify women at increased risk of osteoporotic fracture and to stratify them into risk categories for osteoporosis or fracture. Several studies [5–10] have compared various tools for their ability to identify women at highest risk of fracture. Most of these studies reached the conclusions that the simpler tools perform as well as the more complex tools.

Prior to the advent of these algorithms, self-risk assessment tools were available to identify women with low BMD and/or to estimate the risk of fracture. These include age, body size, no estrogen (ABONE) [11], the osteoporosis risk assessment instrument (ORAI) [12], the Osteoporosis Self-assessment Tool equation (OST) [13, 14], the simple calculated osteoporosis risk estimation (SCORE) tool [15], the study of osteoporotic fractures (SOF)-based screening tool [16], and the osteoporosis index of risk (OSIRIS) [17].

Targeting individuals with increased risk of osteoporotic fracture is an important challenge in the field of osteoporosis. Risk assessment tools may contribute to healthcare decision-making by identifying which patients would benefit most from DXA scanning or treatment. This chapter will review the evidence of osteoporosis screening, benefits, and harms of early detection of osteoporosis, as well as the most common osteoporosis risk assessment tools, including self-assessment tools. The chapter will expand to discuss thresholds for intervention and rooms for improvement.

The Evidence

Screening for osteoporosis, by measuring bone density, can be done with a number of technologies: dual-energy X-ray absorptiometry (DXA), which can measure bone density in the whole body; ultrasound, for measurement in the heel, finger, wrist, and knee; CTXA [a software

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application] for measurement on the hip; and quantitative computed tomography (QCT) for measurement of the vertebrae and wrist.

Very few studies have addressed the use of these technologies in a mass-screening scenario. Though there are studies of the relative detection rate and of the cost of different technologies, these studies do not mention whether population-based screening is effective or cost effective. One study, however, has calculated that the use of ultrasound examinations, in screening at the population level before an actual measurement is done by DXA, and it concluded that it is not a cost-effective strategy [18].

Validated questionnaires may also be used to identify high-risk patients who might benefit from treatment or to pre-screen those who may need to have their bone density measured. Questionnaires assessed in these studies include the osteoporosis self-assessment tool (OST), the osteoporosis index of risk (OSIRIS), the simple calculated osteoporosis risk estimation (SCORE), the osteoporosis risk assessment instrument (ORAI), and the age, body size, no estrogen (ABONE) decision rules [19–21].

Findings from studies of the use of different pre-screening tests demonstrate that these tests may be cost effective in mass-screening strategies. One study calculated that pre-screening at the population level would cost about €300 per patient. Again, this calculation does not provide any information on whether mass screening is effective or cost-effective [22].

A prospective study on the effect of bone mineral density measurements for screening was performed in the United Kingdom on a population of 6282 women 50–54 years of age, with a 5-year follow-up. Of the women screened, 36% were found to have a bone density that required intervention. These patients were sent to a general practitioner (GP) for treatment and follow-up. A total of 1462 women were followed up, and, of these, 12% were already being treated (with HRT, which was the treatment of choice at that time) at the start of screening, 57% were found to be suitable for HRT after consultation with the primary care physician, and 60% of these rejected treatment. The authors concluded that screening all postmenopausal women by measuring bone mineral density was not acceptable for several reasons, of which the potentially low adherence to treatment following screening was a prominent reason [23]. Also, the sensitivity and specificity of population-based screening for osteoporosis is rather low [24].

At the WHO level, screening for osteoporosis has been discussed in WHO technical reports, in which the arguments for general screening of all women were found to be weak [25]. Many other studies, reviews, and agencies have concluded that the evidence is insufficient to recommend general screening for osteoporosis, although they acknowledge the evidence that bone density measurements may be used to diagnose patients in need of treatment [26–31].

However, this conclusion, that the evidence is insufficient to recommend general screening for osteoporosis, is not shared universally. Based on a systematic review of the literature, the United States Preventive Services Task Force found good evidence that the risk of osteoporosis and fracture increases with age and other factors, that bone density measurements accurately predict the risk of fractures in the short term, and that treating asymptomatic women with osteoporosis reduces their risk of fracture. On the basis of this indirect evidence, the Task Force concluded that the benefits of screening and treatment are, at least, of moderate magnitude for women at increased risk by virtue of age or presence of other risk factors, and it recommended that routine screening begin at 65 years of age for women at increased risk for osteoporotic fractures [32, 33].

Benefits and Harms of Early Detection of Osteoporosis

There is convincing evidence that bone measurement tests are accurate for predicting osteoporotic fractures in women and men. A study [34] that evaluated the effect of screening for osteoporosis on fracture rates reported a reduction in hip fractures but did not find a reduction in other types of fractures [35, 36]. In concordance, mul-

tiple studies showed that drug therapies reduce fractures in postmenopausal women with osteoporosis. For women 65 years and older, there is convincing evidence that screening can detect osteoporosis and that treatment of women with osteoporosis can provide at least a moderate benefit in preventing fractures. For postmenopausal women younger than 65 years who are at increased risk of osteoporosis, there is also adequate evidence that screening can detect osteoporosis and that treatment provides a moderate benefit in preventing fractures.

For men, there has been inadequate evidence reported on the benefits and harms of treating screen-detected osteoporosis to reduce the risk of osteoporotic fractures.

On the other hand, a single study [35] has reported harms of screening for osteoporosis. It reported no increase in anxiety and no decrease in quality of life from screening. Based on the nature of screening with bone measurement tests and the low likelihood of serious harms, the United States Preventive Services Task Force (USPSTF) found adequate evidence to bound these harms as no greater than small. Harms associated with screening may include radiation exposure from DXA and opportunity costs (time and effort required by patients and the healthcare system).

Harms of drug therapies for osteoporosis depend on the specific medication used. The risk of serious adverse events, upper gastrointestinal events, or cardiovascular events associated with the most common class of osteoporosis medication (bisphosphonates) is no greater than small [33]. Therefore, overall, it can be concluded that the adequate evidence that the harms of osteoporosis medications are small.

Risk Assessment Tools

In deciding which women to screen with bone measurement testing, clinicians should first consider factors associated with increased risk of osteoporotic fractures. These include parental history of hip fracture, smoking, excessive alcohol consumption, low body weight, as well as high risk of falling. In addition, menopausal status in women is also an important consideration because studies demonstrating treatment benefit mainly enrolled postmenopausal women. For postmenopausal women younger than 65 years who have at least one risk factor, a reasonable approach to determine who should be screened with bone measurement testing is to use a clinical risk assessment tool.

Assessment of bone mineral density (BMD) provides a crucial determinant of fracture risk and many guidelines have used BMD thresholds to determine whether treatments should be recommended. However, the multifactorial nature of fracture risk means that BMD does not capture non-skeletal determinants of fracture risk such as liability to fall. A number of risk factors for fracture have been identified that contribute significantly to fracture risk over and above that provided by BMD [37]. A good example is age. The same BMD has a different significance at different ages, such that fracture risk is much higher in the elderly than in the young [38, 39]. This is because age contributes to risk independently of BMD. Several tools are available to assess osteoporosis risk, these include as follows.

FRAX

Over the past years, a series of meta-analyses has been undertaken to identify additional clinical risk factors that could be used in case finding strategies, with or without the use of BMD. This gave rise to the development of FRAX®, University of Sheffield, a tool that integrates the information derived from clinical risk factors and BMD and consequently assesses a person's 10-year risk of fracture probability [40].

FRAX (Fig. 7.1) calculates fracture probability in individuals from age body mass index and dichotomized risk factors comprising prior fragility fracture, parental history of hip fracture, current tobacco smoking, ever use of long-term oral glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis, and alcohol consumption (Table 7.1) [40]. Femoral neck

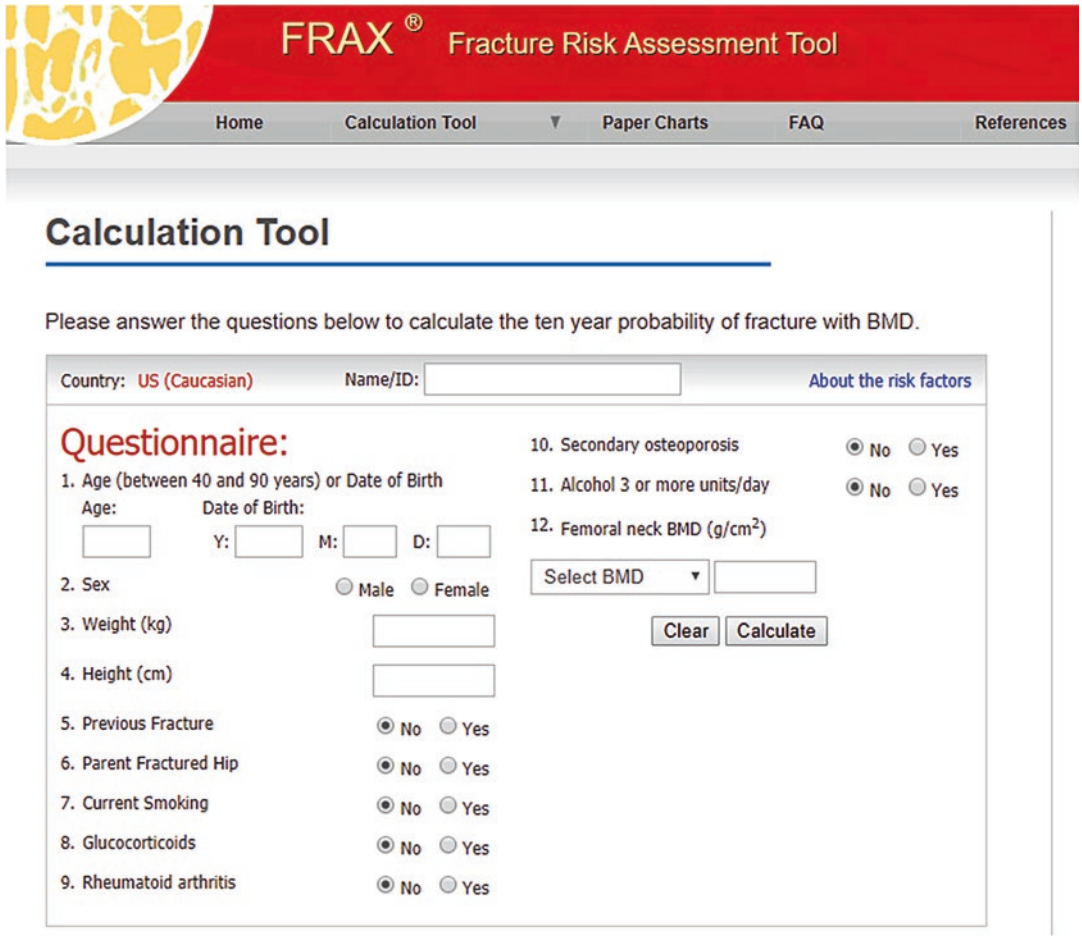

Fig. 7.1 Fracture risk assessment tool "FRAX"

Table 7.1 Definitions of the risk factors included in the fracture risk assessment tool*

Risk factor	Risk factor and response clarification
Age	The model accepts ages between 40 and 90 years. If ages below or above are entered, the program will compute probabilities at 40 and 90 year, respectively
Sex	Male or female. Enter as appropriate
Weight	This should be entered in kg
Height	This should be entered in cm
Previous fracture	A previous fracture denotes more accurately a previous fracture in adult life occurring spontaneously, or a fracture arising from trauma which, in a healthy individual, would not have resulted in a fracture. Enter yes or no (see also notes on risk factors)
Parent fractured hip	This enquires for a history of hip fracture in the patient's mother or father. Enter yes or no
Current smoking	Enter yes or no depending on whether the patient currently smokes tobacco (see also notes on risk factors)
Glucocorticoids	Enter yes if the patient is currently exposed to oral glucocorticoids or has been exposed to oral glucocorticoids for more than 3 months at a dose of prednisolone of 5 mg daily or more (or equivalent doses of other glucocorticoids) (see also notes on risk factors)
Rheumatoid arthritis	Enter yes where the patient has a confirmed diagnosis of rheumatoid arthritis. Otherwise enter no (see also notes on risk factors)

Table 7.1 (continued)

Risk factor	Risk factor and response clarification
Secondary osteoporosis	Enter yes if the patient has a disorder strongly associated with osteoporosis. These include type I (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease
Alcohol 3 or more units/day	Enter yes if the patient takes three or more units of alcohol daily. A unit of alcohol varies slightly in different countries from 8–10 g of alcohol. This is equivalent to a standard glass of beer (285 ml), a single measure of spirits (30 ml), a medium-sized glass of wine (120 ml), or 1 measure of an aperitif (60 ml) (see also notes on risk factors)
Bone mineral density (BMD)	(BMD) Please select the make of DXA scanning equipment used and then enter the actual femoral neck BMD (in g/cm^2). Alternatively, enter the T-score based on the NHANES III female reference data. In patients without a BMD test, the field should be left blank (see also notes on risk factors) (provided by Oregon Osteoporosis Center)
Notes on risk factors	
Previous fracture	A special situation pertains to a prior history of vertebral fracture. A fracture detected as a radiographic observation alone (a morphometric vertebral fracture) counts as a previous fracture. A prior clinical vertebral fracture or a hip fracture is an especially strong risk factor. The probability of fracture computed may therefore be underestimated. Fracture probability is also underestimated with multiple fractures
Smoking, alcohol, glucocorticoids	These risk factors appear to have a dose-dependent effect, i.e., the higher the exposure, the greater the risk. This is not taken into account and the computations assume average exposure. Clinical judgment should be used for low or high exposures
Rheumatoid arthritis	RA is a risk factor for fracture. However, osteoarthritis is, if anything, protective. For this reason reliance should not be placed on a patient's report of "arthritis" unless there is clinical or laboratory evidence to support the diagnosis
Bone mineral density	The site and reference technology is DXA at the femoral neck. T-scores are based on the NHANES reference values for women aged 20–29 years. The same absolute values are used in men

*https://www.sheffield.ac.uk/FRAX/tool.aspx?country=58

BMD can be optionally input to enhance fracture risk prediction. Fracture probability is computed taking both the risk of fracture and the risk of death into account. The use of clinical risk factors in conjunction with BMD and age improves sensitivity of fracture prediction without adverse effects on specificity [41]. Even if the performance of FRAX is enhanced by the use of BMD tests, it should be recognized that FRAX without BMD has a predictive value for fractures that is comparable to the use of BMD alone [42–44]. The availability and access to densitometry in many countries is low [43], so that a major advantage of FRAX is the ability to assess fracture risk where BMD is unavailable.

Fracture probability varies markedly in different regions of the world [44]. Thus, the FRAX® models need to be calibrated to those countries where the epidemiology of fracture and death is known. Models are currently available for 58 countries across the world: for Argentina, Armenia (surrogate), Austria, Australia, Belgium, Brazil, Canada, Chile, Czech, China (revised 2013), Colombia, Croatia, Denmark, Ecuador, Estonia, France, Finland, Germany, Greece, Hong Kong, Hungary, Iceland, India (surrogate), Indonesia, Ireland, Israel, Italy, Japan, Jordan (updated), South Korea, Kuwait, Lebanon, Lithuania, Malta, Mexico, Morocco, Netherlands, New Zealand, Norway, Palestine (surrogate), the Philippines, Poland, Portugal, Romania, Russia, Singapore, Slovakia, Sri Lanka (surrogate), Spain, Sweden, Switzerland, Taiwan, Thailand, Tunisia, Turkey, the UK, the USA, and Venezuela. The model is available in 27 languages: Arabic, Bengali, Chinese (traditional and simplified), Czech, Danish, Dutch, English, Finnish, French, German, Greek, Icelandic, Indonesian, Italian Japanese, Korean, Lithuanian, Norwegian, Polish, Portuguese, Romanian, Russian, Slovak, Spanish, Swedish, Thai, and Turkish [45].

FRAX has been widely used for the assessment of fracture risk since the launch of the website in 2008 and currently processes approximately 225,000 calculations per month. Following regulatory review by the US Food and Drug Administration (FDA), FRAX was incorporated into DXA scanners to provide FRAX probabilities at the time of DXA scanning. For those without internet access, handheld calculators and an application for Apple and Android smartphones have been developed by the IOF (http://itunes.apple.com/us/app/frax/id370146412?mt=8) and (https://play.google.com/store/apps/details?id=com.inkrypt.clients.iof.drfrax). A paper-based FRAX pad allows patients to document risk variables prior to medical consultation and is available from the IOF (www.iofbonehealth.org) in several languages.

The limitations of FRAX (Table 7.2) have been reviewed recently [46, 47]. Though the FRAX tool has been appreciated for its simplicity for use in primary care, yet it has been criticized as it does not take account of exposure response. For example, the risk of fracture increases with exposure to glucocorticoids (both dose and duration), but FRAX only accommodates a yes/no response to the relevant question. Other well-researched examples of "dose–response" include the number of prior fractures and the consumption of alcohol. Other concerns are the lack of provision for lumbar spine BMD which is commonly recommended in treatment guidelines, and the absence of measurements of the material or structural properties of bone. A concern that treatment might invalidate the interpretation of FRAX is misplaced [48].

Table 7.2 Limitations of FRAX

FRAX in fracture risk assessment
Inability to identify the imminent fracture risk (Enable to differentiate between recent and old fractures)
High, moderate, and low exposure to glucocorticoids
Concurrent data on lumbar spine BMD
Information on trabecular bone score (TBS)
Hip axis length
Fall history/fall risk
Underestimates the risk of fracture in diabetic patients
FRAX in guideline development
No controlled trials
Age-dependent thresholds are ageist
Inequity across countries
Sensitivity of NOGG in subgroups
FRAX (general considerations)
Reliance on computer access
Not all countries have FRAX models
Efficacy in patients selected without BMD

If FRAX is to be made more accurate by the inclusion of different degrees of exposure, then information is required not only on the risk of fracture associated with these exposures but also on their dependence on the other risk variables in FRAX and their independent effect on the death hazard. This demands the collection of new population cohorts that include such information as well as the other FRAX variables in sufficient numbers and with wide geographical representation.

In order to overcome some of these, relatively simple arithmetic procedures have been proposed which can be applied to conventional FRAX estimates of probabilities of hip fracture and a major fracture to adjust the probability assessment with knowledge of steroid dose and duration [20], BMD at the lumbar spine BMD [49, 50], trabecular bone score (TBS) [51–53], hip axis length [54], as well as moderate or high risk of falling-over/ history of recurrent falls.

Such analyses can inform the clinician how to temper clinical judgment on the existing output of the FRAX models. The most frequent concern, however, is the omission of falls as a risk variable in the FRAX model, particularly as this is included in other risk assessment tools. Indeed, a Task Force of the ISCD recommended that falls should be incorporated into FRAX [55]. While, from the literature on falls risk, this view is a sound academic conclusion, the incorporation into FRAX is problematic for several reasons. First, at the time of the release of FRAX, existing falls data were not of adequate quality, including the heterogeneous construct of questions on falls. Second, falls risk can be considered, as inherently taken into account in the algorithm, though not as an input variable. Thus, the fracture probability given for any combination of risk factors assumes that the falls risk is that observed (but not documented) in the cohorts used to construct FRAX. Third, the interrelationship of falls risk

with the other FRAX variables has been inadequately explored on an international basis. Fourth, the relationship between the risk variable and mortality needs to be accounted for, but there are no data available.

FRAX in Patients' Management

The use of FRAX in clinical practice demands consideration of the fracture probability at which to recommend treatment—termed the intervention threshold. Many different approaches have been used to set intervention thresholds with FRAX. However, the thresholds used have varied since they depend critically on local factors such as reimbursement issues, health economic assessment, willingness to pay for health care in osteoporosis, and access to DXA. FDA-approved medical therapies in postmenopausal women and men aged 50 years and older, based on the following:

1. A hip or vertebral (clinical or morphometric) fracture.
2. T-score ≤ -2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes.
3. Low bone mass (T-score between -1.0 and -2.5 at the femoral neck or spine) and a 10-year probability of a hip fracture $\geq 3\%$ or a 10-year probability of a major osteoporosis-related fracture $\geq 20\%$ based on the US-adapted WHO algorithm.
4. Clinicians' judgment and/or patient preferences may indicate treatment for people with 10-year fracture probabilities above or below these levels.

QFracture

In 2009, Hippisley-Cox and Coupland published a paper describing the development and validation of QFracture (www.qfracture.org)—a set of risk prediction algorithms to predict 10-year risk of hip fracture and osteoporotic fracture (hip, vertebral, or distal radius fracture) in primary care. The algorithms were developed using data from a sample of two thirds of practices in the QResearch database and validated using the remaining third so that the validation sample is physically separate from the derivation sample. QResearch is a database derived from general practices using the EMIS clinical system (EMIS is the clinical system used by more than 55% of GP practices nationally in the UK). The resulting publicly available web calculator and open source software can be found at www.qfracture.org.

Like the FRAX tool it takes into account history of smoking, alcohol, corticosteroid use, parental history (of hip fracture or osteoporosis), and several secondary causes of osteoporosis (Fig. 7.2). Unlike FRAX it also includes a history of falls (yes/no only over an unspecified time

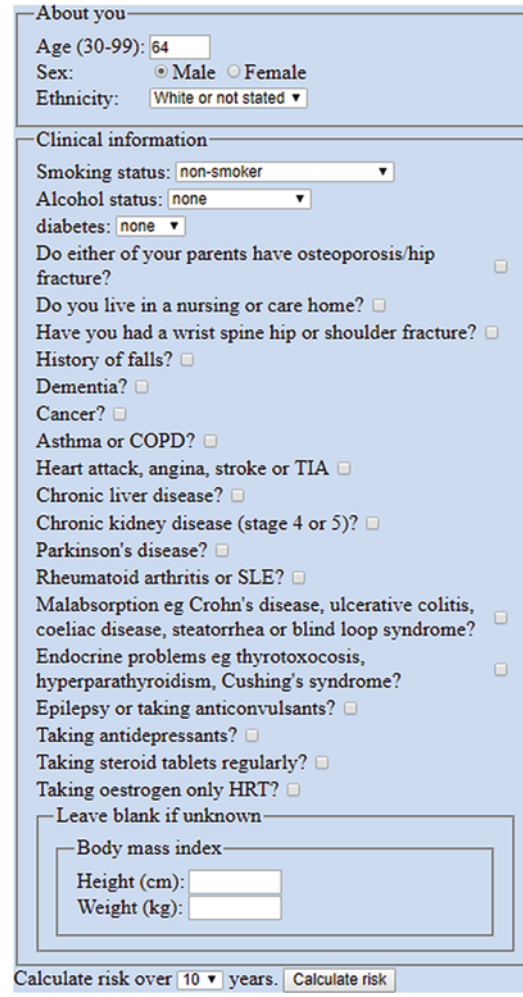

Fig. 7.2 QFracture®-2016 risk calculator: http://qfracture.org

frame), utilizes a large number of clinical risk factors and no provision is made for BMD. It has been internally validated (i.e., from a stratum of the same population), and externally validated in a similar population (routinely collected data in general practitioner records). The performance characteristics and calibration in the UK have been compared with FRAX with comparable results for hip fracture [56]. The tool has not been calibrated to the epidemiology of other countries. A feature of QFracture is that it is more cumbersome (more questions) and does not accommodate the inclusion of BMD. BMD measurements are dismissed as "expensive and inconvenient tests" and so the model ignores a wealth of data demonstrating the utility of BMD testing in fracture risk assessment [57].

Garvan

The Garvan fracture risk calculator or Garvan scale (www.garvan.org.au) was devised by Australian researchers at the Garvan Institute of Medical Research to predict in a given patient the absolute risk of having any osteoporotic fracture within 5 and 10 years [58]. The Garvan tool is based on many fewer men and women from a single study, the Australian Dubbo Osteoporosis Epidemiology Study (DOES) of approximately 2500 men and women age 60 years or more. It differs from FRAX by including a history of falls (categorized as 0, 1, 2, >2 in the previous year), and the number of previous fragility fractures (categorized as 0, 1, 2, >2), but does not include other FRAX variables such as parental history of hip fracture, secondary osteoporosis, rheumatoid arthritis, glucocorticoid use, smoking, and intake of alcohol (Fig. 7.3). The output of the tool differs from FRAX in that it reports the risk of a larger number of fracture sites (additionally includes fractures of the distal femur, proximal tibia/fibula, distal tibia/fibula, patella, pelvis, ribs sternum, hands, and feet excluding digits) [59].

The Garvan scale, although apparently very practical and easy to use, is hampered by the limited relevant bibliography. In comparison to the FRAX®, the Garvan tool has been less widely used, showing often divergent results in some studies which compared both scales [60].

Comparative Features

There are important differences in the input variables, output, and model features that make comparison of the models problematic (Table 7.3).

Comparison of Input

With regard to *input variables*, both Garvan and QFracture include a history of falls, whereas this is not an input variable in FRAX. In particular, the Garvan tool weights the number of falls in the past year. Whereas falls are a strong risk factor for fracture, the incorporation of falls into FRAX is problematic for several reasons as mentioned earlier [61, 62]. Putting these technical problems aside, risk assessment tools are intended to identify a risk that is amenable to a therapeutic intervention. However, falls as a risk variable does not consistently pass the test of reversibility of risk [63, 64], a necessary feature of any risk variable used in tools to direct interventions [42]. Recently, an analysis in elderly men, available as a meeting abstract, indicated that the predictive value of falls for fracture waned significantly with time [65, 66]. If the phenomenon is replicated more generally, then this would further question the utility of falls history in the long-term (e.g., 10-year) assessment of fracture risk. In their review, Kanis and his colleagues [57] suggested that a useful role of fall history in fracture risk assessment remains sub judice. However, on the other hand, a recent study [61] revealed that self-report number of falls in the previous year is strongly associated with incident fracture risk in the routine clinical practice setting, and this risk is independent of age, sex, BMD, and baseline fracture probability. Moreover, there is dose-response with multiple falls (up to a maximum of 3) conferring greater risk than a single fall.

In addition to falls, there are also few data that many of the QFracture risk factors (cardiovascular disease, type 2 diabetes, asthma, tricyclic antidepressants usage, history of falls or liver disease) which characterizes a risk that is amenable to bone-targeted interventions. Other important dif-

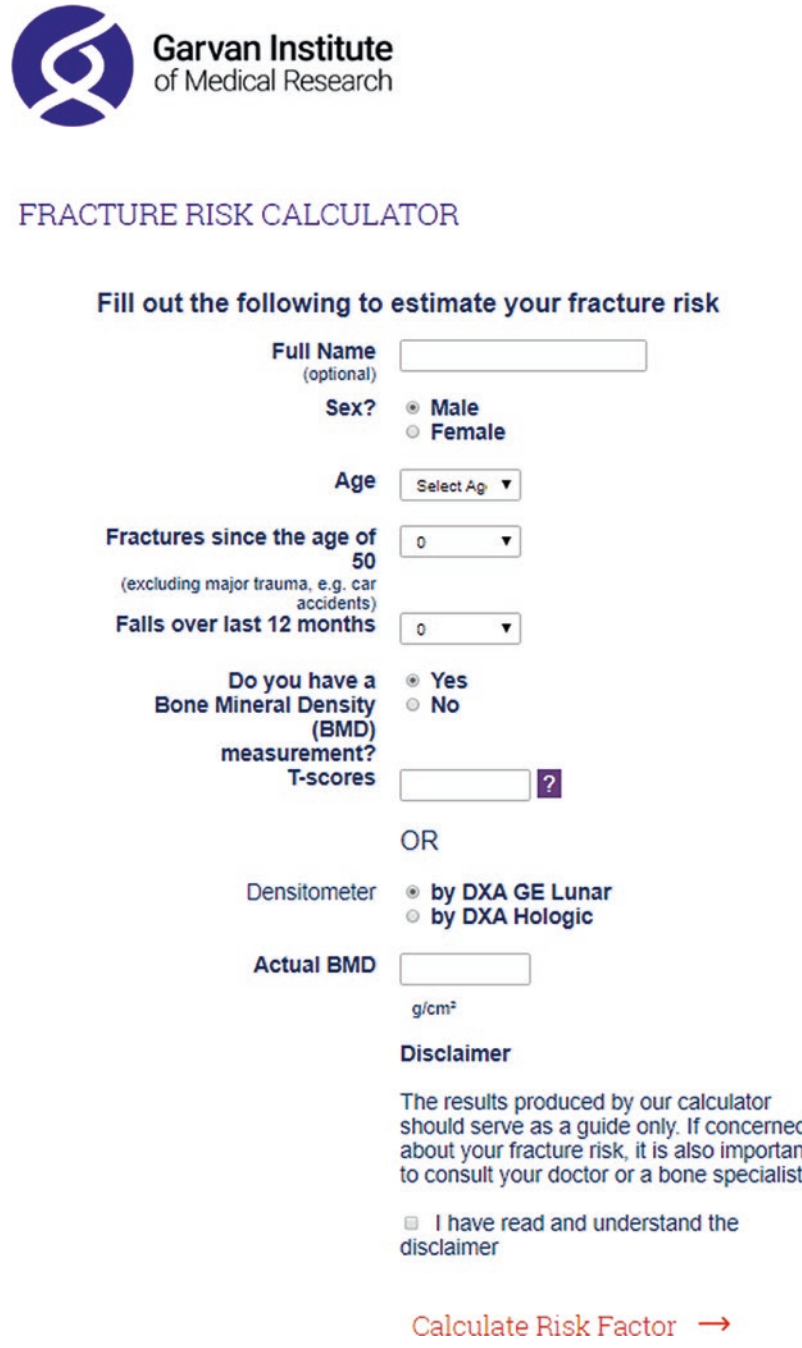

Fig. 7.3 Garvan risk assessment tool

ferences between models include the question construct for fracture history given as past fragility fracture (for FRAX), fractures since the age of 50 years (Garvan) or past wrist, spine, hip or shoulder fracture (QFracture). For BMD, the femoral neck is the reference site for FRAX and for Garvan but is not an input variable for QFracture.

Comparison of Output

Considering the output and model features, the Garvan instrument includes many more fracture

Table 7.3 Comparative features of FRAX, Qfracture, and Garvan

	FRAX	Qfracture	Garvan
Imminent fracture risk	No	No	No
Externally validated	Yes, internationally	Yes, UK only	Yes (Canada)
Calibrated	Yes	Yes (Hip only)	No
Applicability	International	UK	Uncertain
Adjustment for competing risk of mortality	Yes	No	No
Input variables			
Falls	No	Yes	Yes
BMD	Yes	No	Yes
Prior fracture	Yes	Yes	Yes
Family history	Yes	Yes	No
Output			
Fracture site	Hip, forearm, spine humerus	Hip, forearm, spine, shoulder	All fractures excluding digits
Metric	Probability	Incidence	Incidence
Outcome	10-year risk of major fracture 10-year risk of hip fracture	Risk of hip fracture or osteoporotic fracture (hip, spine, wrist, or shoulder) over the next 1–10-years	5- and 10-year risk of total fracture 5- and 10-year risk of hip fracture
Cutoff points	10-year probability of a hip fracture ≥3% or a 10-year probability of a major osteoporosis-related fracture ≥20% (based on the US-adapted WHO algorithm)	For women, the cut off for the top 10% at highest risk is a 10-year risk of 11.1% For men, the cut off for the top 10% at highest risk is 2.6%	Value lower than 18.5% indicate low fracture risk [a]
AUC for hip fracture[b]	0.78 (0.70–0.88)	0.69 (0.64, 0.74)	0.78 (0.74, 0.82)
Time to complete the questionnaire	Shorter	Longer	Shorter
Website	shef.ac.uk/FRAX	qfracture.org	Garvan.org.org/bone-fracture-ris

[a]Reyes Domínguez et al. [60]
[b]Gourlay et al. [102]

outcomes than QFracture or FRAX. Compared with FRAX, the inclusion of these additional fractures is expected to inflate fracture risks in women by 34–45% depending on age [67]. The outcome variable differs between models, not only in the fracture sites but also in the metric. In the case of FRAX, the algorithm computes a fracture probability (i.e., a metric that incorporates the death hazard) which is not synonymous with simple fracture incidence [68].

A comparison of the performance characteristics of the three prediction models appear to be comparable mainly for hip fracture risk [69–75] taking into account the methodological flaws in most of the comparative studies [68–75]. When QFracture and FRAX are applied to the UK population, there is reasonable concordance for hip fracture risk since both are calibrated to the UK, though in different ways. The Garvan instrument is calibrated only to Dubbo and is the outlier. The concordance of the Garvan and FRAX tools is reported in Canada [69]. This was considered by Kanis et al. [70] as a fortuitous accident occasioned by the similar epidemiology between Canada and Dubbo. The claim of good calibration in Norway is not supported by the evidence [71–74].

Whereas QFracture and FRAX are comparably calibrated for hip fracture risk [69, 71, 75], a quite different pattern is evident for major osteoporotic fractures where the probabilities derived

from FRAX are markedly higher than the incidences from QFracture. The Garvan instrument gives even higher values for the same clinical scenarios. The Garvan tool provides the highest risks, in part because the output is the 10-year incidence of all fractures (minus those at the digits), whereas QFracture gives the lowest estimates [76–78].

The reason for the discrepancy is that QFracture is derived from General Practitioner records that are often incomplete for some important variables [78]. For example, GP records are reasonably accurate for the documentation of hip fracture but notoriously unreliable for other major fractures, particularly vertebral fractures [79]. Thus, the prevalence of a prior major fracture in the QFracture data base is 1.9% [72], whereas prior fracture is estimated at 21–45% in women from the UK, depending on age [80–83]. Of these, approximately half will be major fractures. For a parental history of osteoporosis or hip fracture, the prevalence is given at 0.3% in the QFracture database, whereas meta-analysis of prospective studies gives a prevalence of parental hip fracture at 13% [81]. The impact of the inaccuracies is difficult to quantify but is likely to decrease the median of the distribution of 10-year risk in the population. Empirical observation supports this view in that at each tenth of risk category, QFracture risk is lower than FRAX-based probabilities.

In concordance, the poor and inaccurate capture of clinical risk factors is likely to bias the weights for both hip fracture risk and major fracture risk. In the case of FRAX and Garvan, the probability of fracture is approximately doubled with a prior history of fracture consistent with worldwide observation [73, 82]. In the case of major fracture incidence, QFracture determines an increase in risk ratio of approximately only 8%, rather than the expected doubling of risk [78]. As expected from meta-analysis, the impact of a prior fracture is somewhat greater at younger ages [73] and is accommodated in FRAX. In contrast, the weighting given for a prior fracture as a risk fracture is unrealistic for QFracture and does not vary with age (the latter, also the case for Garvan).

A further problem arises in considering the pattern of fractures with age. As expected, FRAX probabilities of a major fracture exceed that of hip fracture at all ages. In the case of QFracture, the incidence of hip fracture and the incidence of major fracture are identical from the age of 85 years. This implies that no fractures of the spine, humerus, or distal forearm arise in women from the age of 85 years. Again, this contrasts with empirical observations [83, 84]. Indeed, fragility fractures other than hip fracture account for 64–67% of fractures in women and men (respectively) aged 85–89 years [67].

Osteoporosis Self-Assessment Tool

Prior to the advent of FRAX, other risk assessment tools were available to identify women with low BMD and/or to estimate the risk of fracture. Most of the tools were based on fewer clinical risk factors and aimed at predicting low BMD. These include age, body size, no estrogen (ABONE), the osteoporosis risk assessment instrument (ORAI), the osteoporosis self-assessment tool (OST) equation, the simple calculated osteoporosis risk estimation tool (SCORE), and the study of osteoporotic fractures (SOF)-based screening tool. The ABONE and ORAI risk assessment tools use information regarding age, weight, and estrogen use [11, 12]. The OST risk assessment tool uses information regarding weight and age [14]. The simple calculated osteoporosis risk estimation (SCORE) uses information about race, rheumatoid arthritis, history of minimal trauma fracture after age 45 years, age, estrogen therapy use, and weight [15], whereas the osteoporosis index of risk (OSIRIS) include data from age, body weight, current hormone replacement therapy use, and history of previous low impact fracture [17]. The SOF-based risk assessment tool uses information regarding first-degree relatives with hip fracture, weight, presence of dementia, corticosteroid use, seizure medication use, benzodiazepine use, previous fracture at/after age 50, use of menopausal hormone therapy, heart rate, height at age 25, age, race, walking for exercise, ability to rise from a chair

without arms, and amount of time per day spent "on feet" [16].The justification for such tools is primarily to identify women who are more likely to have low BMD and then could undergo BMD measurement for a definitive assessment. All these tools have been developed in women, validated in independent cohorts, and the performance of the tools was similar to that seen in the development cohorts [14, 15, 67, 85, 86]. Table 7.4 shows a comparison of the clinical risk factors used to calculate the most common osteoporosis self-assessment fracture risk assessment tools. This is presented in comparison to the most common fracture prevention tool, FRAX. No studies determined the effectiveness of the individual tools in selecting patients for therapy and thus improving fracture outcomes [87, 88].

Osteoporosis Self-Assessment Tool (OST)

The osteoporosis self-assessment tool (OST) is a predictive algorithm currently in use to predict the risk for osteoporosis [13]. It was first established by Koh et al. [13] using data of postmenopausal women from eight Asian countries. The screening algorithm was only based on age (years) and body weight (kg): OSTA score = (body weight − age) × 0.2, with three osteoporosis risk categories, low risk (>−1), moderate risk (−1 to −4), and high risk (<−4). It performed well to determine women at risk of osteoporosis [14]. The performance of OST among Asian men was first assessed by Kung et al. [89] and it demonstrated a moderate performance in predicting osteoporosis [89]. OST has been known as OSTA (OST for Asians) when it is applied to Asian women. The establishment of OSTA only involved postmenopausal women and men from East and Southeast Asia. The OST was later validated in several studies in Asian and White populations and was compared to other risk indices in large samples of postmenopausal women [88, 90]. Results revealed that The OST is effective and efficient tools to help target high-risk women for DXA testing [14].

Table 7.4 The clinical risk factors used to calculate the most common osteoporosis self-assessment risk in comparison to FRAX

	FRAX	SCORE	OST	ORAI	ABONE	OSIRIS
Clinical risk factors by tool	Age Sex Body mass index History of fracture History of parental hip fracture Current smoking Steroid use Rheumatoid arthritis Alcohol use Disease history associated with secondary osteoporosis	Age Weight Race Fracture history Rheumatoid arthritis Estrogen use	Age Weight	Age Weight Current estrogen use	Age, weight, estrogen use	Age, weight, previous fracture, current estrogen use
AUC	Total fracture*: 0.69 (0.54e0.83) Hip fracture: 0.78 (0.70–0.88)	0.65–0.87	0.32–0.82	0.32–0.84	0.67–0.72	0.63–0.80
Suggested threshold for bone density screening	≥9.3%	≥6	<2	≥9	>2	<−3

FRAX fracture risk assessment tool, *SCORE* simple calculated osteoporosis risk estimation, *OST* osteoporosis self-assessment tool, *ORAI* osteoporosis risk assessment instrument, *AUC* area under the curve in receiver operating characteristics curve, *ABONE* age, body size, no estrogen, *OSIRIS* osteoporosis index of risk
*10-year major osteoporotic fracture risk

Index of Risk (OSIRIS)

OSIRIS is a simple index based on four easy-to-collect variables from postmenopausal women, which showed a high degree of accuracy and performed well for classifying the degree of risk of osteoporosis in western European women of Caucasian lineage. Three categories were arbitrarily created using OSIRIS, with cutoff range of: +1 and −3. The low risk category (OSIRIS > +1) represented 41% of all women; only 7% of the women in this category had osteoporosis. The prevalence of osteoporosis was very high (66%) among the group at high risk (OSIRIS < −3 representing 15% of all women). The prevalence of osteoporosis was 39% in the intermediate risk group (−3 < OSIRIS < +1, 44% of all women). Based on this instrument, a strategy was proposed that would initiate treatment in women with very high risk, postpone BMD measurement in women with low risk and limit BMD measurement to women with intermediate risk of osteoporosis, this would spare more than 55% of the densitometry bill compared with a mass screening scenario [17].

Performance of Fracture Risk Model

The performance of a predictive model is commonly assessed by 2 metrics: discrimination and calibration. Discrimination is the capability of a model to separate individuals who will sustain a fracture along a continuum from those who will not. The primary metric of discrimination is the area under the receiver operating characteristic curve (AUC) which evaluates the compromise between sensitivity and specificity and is thus a global estimate of prognostic accuracy. Calibration assesses the agreement between observed and predicted risk of fracture over the range of predicted probabilities.

Over the past 10 years, there have been several independent studies examining the prognostic performance of the Garvan model [9, 91–93], FRAX [94–99], or both Garvan and FRAX [9, 100]. In general, the discrimination for hip fracture was better than for total fractures. In predicting hip fracture risk, the median AUC value for Garvan was 0.80, which was equivalent to that of FRAX (AUC, 0.78). In predicting major fracture risk, the median AUC value for Garvan and FRAX was 0.76 and 0.69, respectively [104]. However, it should be noted that as a norm, AUC value for outcome with low frequency (e.g., less than 100 events) such as hip fracture is often overoptimistic [105]. It appears that the discrimination of fracture in men was lower than women [106]. In certain populations [91, 93, 100], it appears that the Garvan model performed well in the discrimination of fracture, particularly in men [103]. For instance, in the Canadian Multicenter Osteoporosis Study, the Garvan model yielded good discrimination, particularly for hip fracture (AUC 0.80 for women and 0.85 for men) [91]. In a recent systematic review, the average AUC for total fracture by FRAX and Garvan was 0.67 (95% confidence interval, 0.64–0.71) and 0.70 (95% CI, 0.64–0.75) [107].

While the discriminatory ability of FRAX and Garvan was comparable, their calibration was very different. Most studies have consistently shown that FRAX tended to underestimate the risk of fracture [100, 101, 103, 108], particularly in diabetic patients [109]. Several studies have indicated that the Garvan model had very good calibration. A validation study on 1422 postmenopausal women living in New Zealand found that the Garvan predicted fracture risk was 99% in agreement with the observed number of fractures; however the Garvan model tended to overestimate the risk of fracture among individuals in the top quartile of fracture risk which was also noted in the initial development study [100]. In the CaMoS cohort, the Garvan model also shows a remarkable agreement between predicted 10-year probability of fracture and observed 10-year risk of fracture [91].

The concordance in the predicted probabilities of fracture between Garvan and FRAX was modest, with the coefficient of correlation being 0.67 [110]. A reason for the discordance is that the Garvan model takes into account the prevalence of falls in the risk estimation, but the FRAX model did not [49]. A validation study in 2012 postmenopausal women of Polish background found that there was a considerable discrepancy in risk estimates between Garvan and FRAX

models with the Garvan model predicting fracture more accurately than FRAX [45]. Despite the fact that there are differences in predicted risk of fracture between Garvan and FRAX, the majority of the differences do not seem to impact on treatment recommendation [111].

The discordance between Garvan and FRAX is expected, because the two models use different profiles of risk factors. In essence, the estimated risk is a conditional probability that is dependent on the risk factors and their statistical weights. The estimated weight associated with each risk factor is dependent on the statistical method that is used to model the relationship between the risk factor and fracture. The weights associated with 5 risk factors in the Garvan model were derived from the multivariable Cox proportional hazards analysis [29], whereas the method of derivation of the FRAX model is not known [112]. Thus, an individual can have different predicted risks of fracture dependent on which factors are considered in the prediction [113]. It is also important to appreciate that the predicted risk is actually an average kind of "wisdom of the crowd" [114], with "true" values fluctuating below or above the typical value. Therefore, an individual does not necessarily have a unique risk value. This subtle fact also explains why different valid predictive models can yield substantially different results for an individual.

Is the predicted fracture risk concordant with clinical guidelines? In a validation on 801 men who have been followed up for 10-years, Pluskiewicz et al. [103] found that the Garvan-predicted risk of fracture was more concordant with treatment indication than FRAX-predicted risk. For instance, among 218 men with a prior fracture (i.e., indicated for treatment), 82% of them had Garvan predicted risk ≥20% compared with only 8% had FRAX-predicted risk ≥20%. Similarly, among men with osteoporosis (i.e., indicated for treatment), the proportion of men with ≥20% predicted risk by Garvan and FRAX was 72% and 10%, respectively [103]. Thus, it appears that the threshold of 20% predicted risk for defining "high risk" is reasonably consistent with current clinical guidelines.

However, it remains unknown whether treating patients with high risk as defined by the current predictive models will reduce their risk of future fracture. Virtually all RCTs evaluating antifracture efficacy selected patients based on low BMD (i.e., osteoporosis) and/or the presence of a preexisting fracture, and among these patients, pharmacological interventions have shown good efficacy [10]. As no clinical trials have been performed on individuals with high risk of fracture based on either FRAX or Garvan, it is not known whether these patients can be benefited from pharmacological treatments. Nevertheless, post hoc analyses of RCTs appear to suggest that those with high risk of fracture at baseline (as assessed by FRAX) had a slightly greater relative risk reduction of fracture associated with denosumab [115] and bazedoxifene [116], but not with strontium ranelate [117] and raloxifene [118]. In another post hoc analysis [67], it was found that among women in the top 25th percentile of fracture probability (average probability of 24%), clodronate treatment reduced the risk of fracture by 23% over 3 years; among those in the top 10% percentile (average fracture probability of 30%), treatment reduced the fracture risk by 31% [119]. Taken together, these results seem to be consistent with the hypothesis that treatment of individuals at high risk or moderate risk identified by predictive models could reasonably be expected to reduce fractures.

The Concept of Very High Fracture Risk

In 2020, the dichotomisation of high risk into high- and very-high-risk categories was published by the IOF and the ESCEO [120]. Basically, this was based on the assessment of the 10-year probability of a major osteoporotic fracture (clinical spine, hip, forearm, or humerus). Women with fracture probabilities below the lower assessment threshold can be considered at low risk. Women with probabilities above the upper assessment threshold can be considered for treatment. Women with probabilities between the upper and lower assessment threshold should be referred for BMD measurements and their fracture probability reassessed. The subgroup eligi-

ble for treatment were then stratified into high and very high fracture risk categories.

This new concept of high fracture risk was driven by the data emerging from drug trials of the recently approved romosozumab, abaloparatide, as well as the established medications such as teriparatide. In contrast to antiresorptive therapies, anabolic agents demonstrated a more rapid and greater fracture risk reductions [121–123]. Such strategy of tailoring the medical management to the patient's needs represents a revolution in the management of osteoporosis, particularly for those subjects at very high fracture risk. So, while the current guidelines for management of postmenopausal women at high fracture risk advise to start with antiresorptive therapy (mostly oral bisphosphonates) [124–126], according to the recent recommendations, it would be more suitable for postmenopausal women at very high fracture risk to start treatment with anabolic therapy followed by an antiresorptive agent [123, 127–129].

Thresholds for Intervention

Critically, none of the fracture risk assessment tools currently available directly yield an indication for treatment. Thus, the probability or risk generated needs to be interpreted, and thresholds set, above which pharmaceutical intervention is judged to be warranted. The cost-effectiveness of a therapeutic approach is often a key consideration in threshold setting.

There are two major approaches to the health economic assessment in a particular condition [130, 131]. First, one can assess the cost-effectiveness of the intervention, and set the threshold for intervention, for example FRAX probability, accordingly. Alternatively, one can derive a clinically informed and appropriate intervention threshold and use cost-effectiveness analysis to validate a threshold. The 2017 National Institute for Health and Care Excellence (NICE) updated Multiple Technology Appraisal (MTA) on bisphosphonate use in osteoporosis [132] serves as an example of how, for a common disorder, the strict application of cost-effectiveness thresholds for relatively inexpensive drugs may lead to counterintuitive and potentially harmful guidance (Fig. 7.4) [130, 133]. The widespread availability of low-cost generic forms of the main oral and intravenous bisphosphonates resulted in oral treatments being deemed cost-effective above a 1% risk of major osteoporotic fracture. Unfortunately, these were initially interpreted by some payers as clinical intervention thresholds, but, in fact, NICE directs practitioners to the UK National

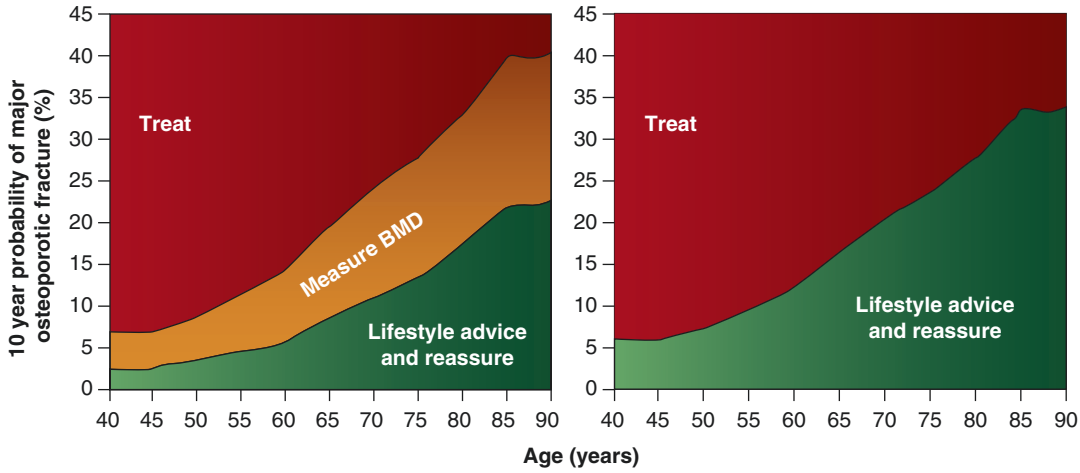

Fig. 7.4 Assessment and treatment thresholds without (left) or with (right) BMD test to compute fracture probability for men and women. (Adapted from: Kanis et al. [134]. © The International Osteoporosis Foundation and National Osteoporosis Foundation, reprinted with permission)

Osteoporosis Guideline Group (NOGG) guidance, which provides an illustration of the alternative approach to threshold setting. NOGG developed its guidance on the basis of clinical appropriateness, setting the threshold at the age-specific 10-year FRAX probability of fracture equivalent to women having already sustained a fracture. This approach, which avoids inappropriate overtreatment of older individuals and undertreatment of younger individuals, has been shown to be cost-effective [134] and has been adopted in many countries [135].

The approach to threshold setting varies substantially across the world, with guidelines using either fixed or variable age-dependent threshold, and, sometimes, combining a probability threshold with the requirement for BMD in the osteoporotic range [136]. Even between the USA and UK guidance, there is marked heterogeneity. The National Osteoporosis Foundation in the USA suggests BMD assessment in women and men aged ≥65 years or 70 years, respectively, or at younger ages if they have had a prior fracture, and treatment for those with either a history of vertebral or hip fracture, osteoporosis on BMD assessment, or osteopenia and a 10-year FRAX-calculated probability of a hip fracture ≥3% or major osteoporotic fracture ≥20% [137]. Conversely, as mentioned above, the UK National Osteoporosis Guideline Group (NOGG) recommends the use of FRAX with or without BMD as the first step in risk assessment, with prior fragility fractures at older ages usually a sufficient basis for treatment regardless of other risk factors (Fig. 7.5). Where a 10-year probability has been generated by FRAX, threshold graphs are subsequently used to guide appropriate intervention. The possible outcomes include patient reassurance with further risk calculation at a later date (low risk), BMD assessment (intermediate risk), or immediate treatment without the need for BMD assessment (high risk) [138]. Once BMD has been performed, the 10-year probability of fracture is plotted by age, either above or below a single treatment threshold, which is set at the 10-year fracture probability conferred by having had a previous fragility fracture, corresponding to older UK national guidance. The treatment threshold, thus, increases with age, but even so, the proportion of women potentially eligible for treatment rises from 20 to 40% across the age range assessed (Fig. 7.6). A key message is that it should not be assumed that one size will fit all countries. For example, intervention in China at a threshold of 20% for FRAX major osteoporotic fracture, a threshold used in the USA, would lead to only a very tiny proportion of the population treated [136]. Accordingly, the International Osteoporosis Foundation has published guidance relating to osteoporosis and corticosteroid-induced osteoporosis, which can be readily modified to reflect national priorities and subsequent treatment thresholds [139–143].

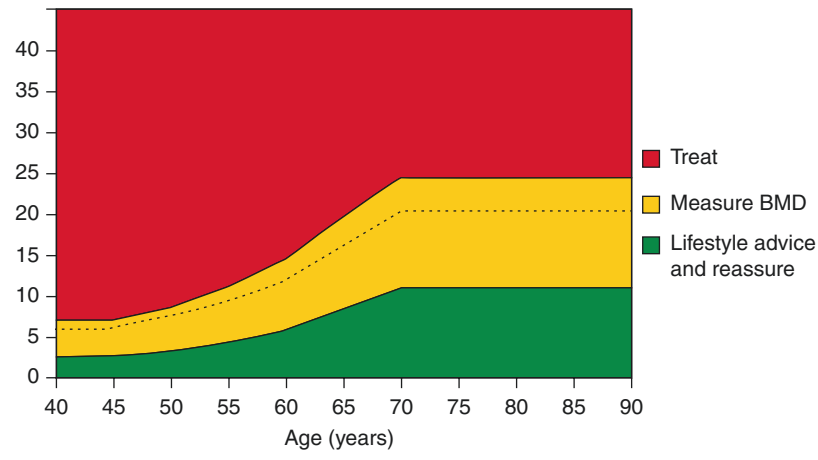

Fig. 7.5 NOGG osteoporosis recommendation for management

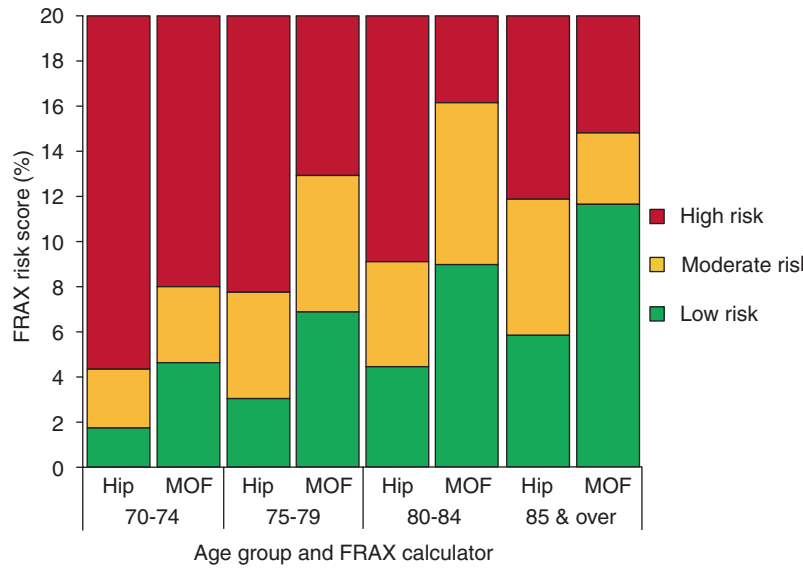

Fig. 7.6 Graphical representation of our proposed age-stratified FRAX hip and major osteoporotic fracture risk score thresholds. (Quoted under open access scheme from: Inderjeeth and Raymond [182])

Closing the Gap: Intervention Thresholds of Very High vs High Fracture Risk

Two approaches have been published describing how to identify the high and very high fracture risk categories; these are as follows.

National Osteoporosis Guideline Group (NOGG)

NOGG developed age-dependent assessment thresholds for the UK. The intervention threshold is set at a risk equivalent to that associated with a prior fracture. Two bounds around the intervention threshold have been identified where the assessment of BMD will help to determine whether the individual close to the threshold either exceed that bound or lie below the intervention threshold. These are called assessment threshold for bones. The lower assessment threshold was set to rule out the requirement for BMD testing among women without any clinical risk factors [144, 145]. The upper assessment threshold was set at 1.2 times the intervention threshold [146]. Very high risk is identified as the risk lying above the upper assessment threshold, whereas high risk lies between the intervention threshold and the upper assessment threshold. On the other hand, low risk is reported when the risk lies below the intervention threshold. The assessment thresholds are illustrated in Fig. 7.7 [147].

European Society of Endocrinology

In 2019, the European Society of Endocrinology published its algorithm for the management of postmenopausal osteoporosis [148]. The algorithm was based on the proposal that a determination of fracture risk would include measurement of lumbar spine and hip BMD and inserting the total hip or femoral neck BMD value into the FRAX tool. Using that FRAX algorithm, four risk categories were identified: "*low risk*" includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above −1.0, and 10-year hip fracture risk <3% and 10-year risk of major osteoporotic fractures <20%; "*moderate risk*" includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above −2.5, or 10-year hip fracture risk <3% or risk of major osteoporotic fractures <20%; "*high risk*" includes a prior spine or hip fracture, or a BMD T-score at the hip or spine of −2.5 or below, or 10-year hip fracture risk ≥3%, or risk of major osteoporotic fracture risk ≥20%; and "*very high risk*" includes multiple spine fractures and a BMD T-score at the hip or spine of −2.5 or below (Table 7.5).

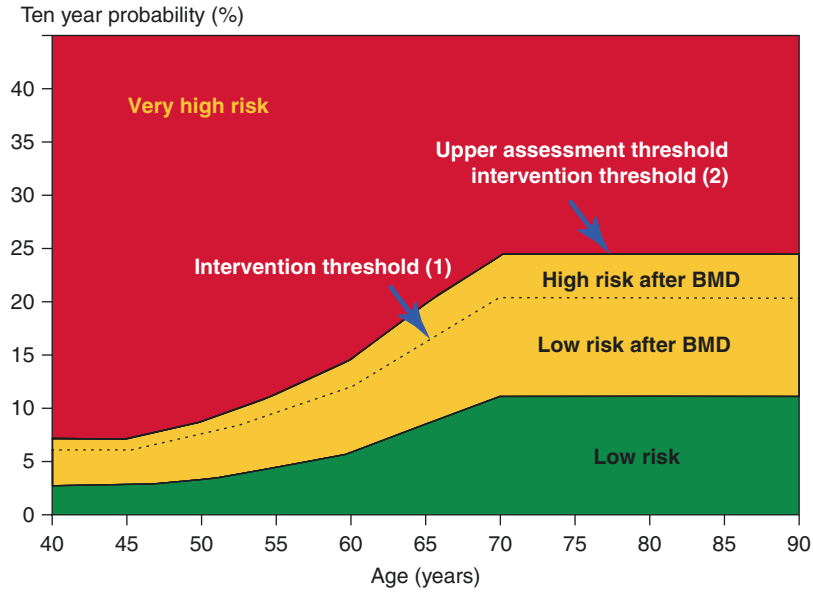

Fig. 7.7 Infographic outlining the four osteoporosis risk categories. Initial risk assessment relies on using FRAX with clinical risk factors alone. Two intervention thresholds are identified. FRAX probability in the red zone, above intervention threshold (2) indicates very high risk. For this group of people an initial course of anabolic therapy followed by antiresorptive treatment may be appropriate. FRAX probability in the green zone suggests low risk, with advice to be given regarding lifestyle, calcium, and vitamin D supplementation. FRAX probability in the intermediate (yellow) zone should be followed by BMD assessment and recalculation of FRAX probability including femoral neck BMD. After recalculation, if the risk got in the red zone above intervention threshold 2 this indicates very high fracture risk, whereas if the risk got in between intervention threshold 1 and below intervention threshold 2 this would indicate high risk, which suggests initial antiresorptive therapy. If the risk lie below the intervention threshold 1, this would indicate low risk (management would be similar to green zone. Patients with a prior fragility fracture are designated either at high risk or possibly at very high risk dependent on the FRAX probability. (Amended from figure 7.1 published in: Kanis et al. [120] (quoted under open access scheme)

Table 7.5 Characteristics of the four osteoporosis risk categories identified according to the European Society of Endocrinology

	Low risk	Moderate risk	High risk	Very high risk
FRAX	Hip: <3%	Hip: <3%	Hip: ≥3%	Hip: ≥4.6%
	Spine: <20%	Spine: <20%	Spine: ≥20%	Spine: ≥30%
BMD	Above −1.0	−1.0 to −2.5	≤ −2.5	≤ −2.5
Fracture	No prior hip or spine fractures	No prior hip or spine fractures	A prior hip or spine fractures	Multiple spine fractures, multiple spine fractures, fracture while on anti-osteoporosis medication, fractures while taking drugs that affect bone adversely (e.g., long-term glucocorticoid therapy), high risk of falls or previous history of injurious falls [149]

BMD bone mineral density

Fracture Risk Assessment Tools: Room for Improvement

From the point of view of predictive accuracy, all current models for fracture risk assessment are suboptimal. Indeed, the average AUC value for total fracture prediction by FRAX and Garvan was only ~0.7 [150] which may be considered "adequate." The challenge is to find ways to improve the accuracy of fracture prediction. Table 7.6 shows a summary of the potential options to improve predictive accuracy of fracture

Table 7.6 Towards a new concept of fracture prediction—potential options to improve predictive accuracy of fracture risk assessment

New modelling approaches	New markers
Fracture type specific prediction	Trabecular bone score
Time-variant predictions	Bone turnover markers
Ethnic-specific models	Genetic profiling
Artificial intelligence and fracture risk prediction	

risk assessment. In their article, Liu et al. [143] postulated that the accuracy can be improved by incorporating new markers for fracture risk and by adopting new modelling strategies.

Genetic Profiling

It is well known that the risk of fragility fracture is partly influenced by genetic factors. Almost half of the variance in fracture susceptibility among individuals is due to hereditary factors [151]. Over the past 20 years or so, several large-scale collaborative studies [69] have revealed that there are 62 loci that are associated with BMD; among the 62 single nucleotide polymorphisms (SNPs) identified, 8 SNPs were associated with fracture risk at the genome-wide significance level [152]. A common characteristic of these SNPs is that their effect sizes were modest, with odds ratios ranging between 1.1 and 1.4, suggesting that individually they have limited utility for fracture prediction. Nevertheless, a genetic profiling may help improve the accuracy of fracture prediction. A simulation study showed that a genetic profile of up to 50 genetic variants, with each having a modest effect size (odds ratio, 1.01–1.35) could improve the accuracy of fracture prediction by 10% points of AUC [153–155]. Recent study revealed that the incorporation of an "osteogenomic profile" of 62 BMD-associated SNPs into existing Garvan fracture risk calculator could modestly improve the predictive accuracy of fracture [156], and this finding was consistent with a previous observation from MrOS study [157]. Taken together, these latest results studies suggest that genetic profiling could help improve the accuracy of fracture prediction over and above that of clinical risk factors.

Trabecular Bone Score

Trabecular bone score (TBS) is a measure of the distributional trabecular architecture [158]. TBS is derived as a texture parameter that reflects pixel grey level variation in dual-energy X-ray absorptiometry images. Previous studies have reported that TBS is significantly correlated with trabecular number, trabecular separation, and structure model index [159]. Moreover, TBS was found to be associated with fracture risk in elderly women and diabetic patients [160] independently of BMD and classical clinical risk factors [161]. A recent meta-analysis found that TBS was a FRAX-independent predictor of fracture risk [162], suggesting that TBS could improve the discriminatory power of fracture risk assessment for an individual.

Bone Turnover Markers

Several cross-sectional and longitudinal studies have observed that fragility fractures occur not only because of low BMD but also as a result of rapid bone turnover that leads to adverse architectural changes. There is accumulating evidence that accelerated bone resorption is a risk factor for fracture, independent of BMD, and other clinical risk factors [163]. For instance, increased urinary levels of the pyridinium crosslink, deoxypyridinoline (DPD), was associated with a two- to threefold increase in the risk of hip fracture [164]. Increased urinary type I collagen C-telopeptide (CTX) and free deoxypyridinoline (DPD) levels were associated with a twofold increase in hip fracture risk after adjusting for BMD and physical mobility [165]. In men, increased bone resorption was also associated with increased fracture risk [166]. A meta-analysis of longitudinal studies found that increased serum levels of serum aminoterminal propeptide of type I collagen and C-telopeptide (CTX) were modestly associated with an increase in fracture risk in men and women [167]. These results strongly suggest that the incorporation of bone turnover markers into the existing prognostic models could improve the prediction of abso-

lute fracture risk. However, the use of bone turnover markers for fracture risk assessment is faced with challenges in the standardization of measurements and treatment of intrasubject variability.

Fracture Type-Specific Prediction

Existing individualized risk assessment models were developed for predicting the risk of total (or major) fractures and hip fracture. The implicit assumption behind the development of these models is that all fracture types share common risk factors. However, this assumption is unlikely true, as a risk factor for one fracture type may not be associated with another fracture type. For instance, fall is a major risk factor for hip fracture, but it is not a risk factor for vertebral fracture. Therefore, future models should move away from the "one size-fits-all" approach by focusing on specific fracture sites.

Artificial Intelligence

Most, if not all, existing models were developed under the assumption that there are no interactions between risk factors. However, this assumption may not be true, because complex interactions between risk factors are likely present but not detected by traditional statistical methods. In the presence of interactions or potential interactions, implementing artificial intelligence such as artificial neural network (ANN) can be useful in the prediction of fracture. By imitating human brain functions, ANN can model complex real-world relationships, including interacting variables. Recent studies have demonstrated that ANN performed better than traditional statistical models in terms of predicting vertebral fracture among postmenopausal women [168] and mortality following a hip fracture [169]. Earlier study [170] has shown that for hip fracture prediction, artificial neural network (ANN) yielded a more accurate prediction than traditional statistical methods such as the logistic regression model. From a conceptual viewpoint, it is important to distinguish between prediction and association [171, 172]. Traditional statistical methods focus on association which is mainly concerned with the identification of statistically significant predictors to explain the relationship between the predictors and an outcome for a group of individuals. On the other hand, prediction is concerned with the derivation of rules based on observed data for forecasting specific outcomes for an individual. Although a strong association can translate into a good prediction, they are not synonymous. Indeed, a statistically significant association in a group of individuals does not necessarily translate into good prediction for an individual [173]. A risk factor may achieve statistical significance (i.e., $p < 0.05$) with large sample size even if it is a poor predictor of future outcome. A risk factor or a set of risk factors may be statistically significantly associated with an outcome due to larger effect on a small number of events in the population; yet provide poor prediction for individuals in the population [174]. Therefore, it has been proposed that future fracture risk assessment models should move beyond association analysis and adopt more prediction analyses [170]. Instead of finding factors that are associated with fracture, we should focus on the factors that have high predictive value of fracture risk. The factors that influence fracture risk are likely to be related, and their effects on fracture risk are likely interactional. Prediction analysis using machine learning approach(e.g., ANN and deep learning) may be statistically less elegant, but it could help identify potential highly predictive factors that are ignored by traditional association analysis [170, 171].

Time-Variant Predictions

All risk factors change with time, and the rates of change are highly variable between individuals. For example, BMD in the elderly declines with advancing age, and the rates of decline vary substantially among individuals [175]. However, all existing predictive models assume that risk factors are constant with time. Of course, this assumption is not realistic, but it is a convenient

starting point for building a predictive model. Therefore, one important aspect of future model development should take the time-varying nature of risk factors into account to achieve a better estimate of risk for an individual.

Ethnic-Specific Models

It is important to keep in mind that all existing predictive models (e.g., FRAX, Garvan, and Qfracture) were developed from data pertaining to North American and European populations, not Asian or African populations. These models have also been largely validated in Caucasian populations, and their performance in Asian populations is not well documented. Nevertheless, few studies have attempted to assess the utility of FRAX in the prediction of fracture in Asian individuals. In a validation analysis based on the Hong Kong Osteoporosis Study (266 postmenopausal women), the AUC of the FRAX model for predicting total fracture was ~0.73, which is not substantially different from the model with BMD alone (AUC, 0.71) [176]. In a study carried out by Chen et al. [177] on 198 Chinese individuals with very recent fracture, it was observed that the average FRAX-predicted fracture risk was 6.6%, with only 2 individuals (1%) who had 10-year risk ≥20%, suggesting a poor calibration. In a Japanese population, FRAX model had a moderate discrimination for self-reported total fracture (AUC, 0.69), which is similar to the model with age and femoral neck BMD (AUC, 0.69) [141]. In an analysis of 405 postmenopausal women and139 men with fractures, Min et al. [178] observed a ~twofold difference in FRAX-predicted risk of fracture between the Korean FRAX model and Japanese FRAX model, despite the fact that the two populations have similar background risk. Taken together, these results suggest that the FRAX model has modest prognostic performance in Asian populations. Thus, there is a strong need for the development of individualized fracture risk assessment models for Asian populations. This is true, because at the population level, the incidence of fracture in Asians is generally lower than that in Caucasian populations [179], and the distribution of behavioral risk factors for fracture is expected to be different between Asian and Caucasian populations.

On another front, the prevalence of cigarette smoking in Asian women is lower than that in Caucasian women, but Asian men are more like to smoke than Caucasian men [180], and these ethnic-related differences need to be methodologically weighed in the estimation of fracture risk for an individual. It would be unrealistic to assume that Asian men and women share exactly the same risk factor profile as Caucasian populations; it is even more unrealistic to assume that the magnitude of association between smoking and fracture in Caucasian women is the same as in Asian women. Experience in the field of cardiovascular disease shows that the Caucasian based models (e.g., Framingham risk score and QRISK2) did not perform well in Asian populations [181]. International prospective population-based studies are urgently needed for the development and validation of new fracture risk assessment models for Asian populations.

Any statistical model is an imperfect representation of reality. Model development is a struggle between complexity and simplicity. Overly complex models with too many factors may yield better accuracy but they are of little practical use because it is hard to implement such models in practice. On the other hand, too simple models can miss high-risk individuals. Nevertheless, given the current modest calibration and discrimination of simple models, the addition of highly predictive factors to the existing models is likely to help improve the accuracy of prediction without increasing the burden complexity.

In conclusion, over the past 10 years, a number of individualized risk assessment models have been developed and implemented in clinical setting. The advance of these models represents a significant achievement of translational osteoporosis research. The FRAX tool is the most commonly established tool that is used worldwide, to calculate 10-year fracture risk probability. This can aid discussion with patients and help in decisions regarding treatment for osteoporosis and in fracture prevention. The ultimate goal of risk

assessment model is to provide clinicians and patients with accurate and reproducible risk estimate that helps guide clinical decisions. Current fracture risk assessment models have contributed substantially to the management of osteoporotic patients over the past decade. Still, much remains to be done to enhance the discrimination and calibration of existing models, as well as to develop new models which can help maximize benefits and preclude potential problems of overmedicalization and false assurance.

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Current Imaging Techniques

8

Yasser El Miedany

Introduction

Osteoporosis is derived from Greek, which literally means a bone with too many holes. The clinical diagnosis of the disease is based on a spectrum of illness characterized by "progressive loss of the bone mass associated with deterioration of the bone microarchitectural" [1, 2]. Bone ultrastructure studies revealed that the bone is a mineralized connective tissue and is comprised of 80% cortical (compact) and 20% trabecular (cancellous) bone. The load-bearing capacity of bone depends on the amount of bone (i.e., mass), the size, the spatial distribution of the bone mass (i.e., geometry and microarchitecture), and the intrinsic properties of the materials that form the bone [3, 4]. Bone wise, osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture [5].

Low bone mass is part of the definition of osteoporosis, and assessment of bone mineral density (BMD) reflecting bone mass is the cornerstone in the diagnosis, risk prediction, and monitoring of treatment with antiosteoporotic drugs [6]. BMD has been shown to account for up to 60–90% of the variation in bone strength [7, 8]. In 1994, the World Health Organization (WHO) defined osteoporosis based on bone mineral density (BMD) measurement. Before this definition was applied, making a diagnosis of osteoporosis required the occurrence of a fragility fracture [9]. The redefinition allows for the prospective diagnosis of osteoporosis in asymptomatic patients before fragility fracture occurs [10].

Associated with the growing awareness of the significance of osteoporosis for public health and the development of new treatments for its prevention, in the past decade there has been a rapid evolution of new radiologic techniques for the noninvasive assessment of skeletal integrity (Table 8.1) [11, 12]. The technique most associated with the recent growth in bone densitometry is dual-energy X-ray absorptiometry (DXA) [13]. DXA was developed in the mid-1980s from the earlier technique of dual photon absorptiometry (DPA) by replacing the 153Gd radionuclide source with an X-ray tube. Because of the advantages of high precision, short scan times, low radiation dose, and stable calibration, DXA has proven to be appropriate in meeting the need for scanning equipment to assist in the diagnosis of osteoporosis and aid decisions about treatment. Table 8.2 presents a comparison between different tools available to assess for the BMD, its advantages and disadvantages. This chapter will discuss the importance of osteoporosis imaging both in diagnosis and management. It will also review quantitative imaging methods in osteopo-

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Table 8.1 Methods of measuring bone mineral density

Modality	Characteristics
Ionizing	
Ionizing: Gamma radiation	
Single-energy photon absorptiometry	Peripheral skeleton
Dual-energy photon absorptiometry	Central skeleton
Neutron activation analysis	Research method
Compton scattering	Research method
Ionizing: Radiographs	
Single-energy X-ray absorptiometry	Peripheral skeleton
Dual-energy X-ray absorptiometry	Peripheral and central skeleton
Quantitative computed tomography	Peripheral and central skeleton
Radiogrammetry	Peripheral and central skeleton
Nonionizing	
Magnetic resonance imaging	Research method
Spectroscopy	
Quantitative magnetic resonance	
Imaging	
Ultrasonography	Peripheral skeleton

Information from references [17–24]

rosis, including DXA, quantitative CT (QCT), ultrasound, as well as other recent developments in this aspect. It will also provide a comparison between these tools in terms of technique, radiation, measurement, precision, and ability to monitor therapy as well as the pros and cons of each tool.

Importance of Osteoporosis Imaging

In 2000, the National Institutes of Health assembled an expert panel focusing on the prevention, diagnosis, and treatment of osteoporosis [1]. The consensus definition provided by this panel is still used and has had an impact on osteoporosis imaging and related research for the past decade. According to the consensus, osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength primarily reflects the integration of bone mineral density (BMD) and bone quality. BMD is expressed as grams of mineral per area or volume, and in any given individual is determined by peak bone mass and amount of bone loss. Bone quality refers to architecture, turnover, damage accumulation (e.g., microfractures), and mineralization [7].

On another front, with use of pharmacotherapy, osteoporotic fractures can be prevented. However, clear guidelines are required to initiate these therapies, as they are expensive and side effects have been associated with these therapies, such as atypical subtrochanteric fractures with alendronate [14, 15]. Ideally biomarkers should be available that assess fragility fracture risk with high accuracy. However, so far, diagnostic techniques assessing the BMD remain to be the standard tool used to monitor the protective effect of pharmacotherapies, including assessing response and nonresponse to these therapies.

In addition to these quantitative techniques dedicated to bone mass and quality assessment, standard imaging techniques need to be applied to diagnose prevalent osteoporotic fractures, as this will affect therapy recommendations and may prevent future fractures. Correctly diagnosing and interpreting fragility fractures with all available imaging modalities is one of the major responsibilities we have as radiologists [16].

Dual X-ray Absorptiometry (DXA) Scan

Bone mineral density (BMD) testing is a widely available clinical tool to diagnose osteoporosis, predict fracture risk, and monitor response to therapy. While assessing the BMD at any skeletal site with a variety of technologies can predict fracture risk [25–27], DXA of the spine, hip, and forearm is the only method for diagnosis of osteoporosis in the absence of a fragility fracture and the best method for monitoring changes in BMD over time. This has been attributed to several reasons [26]:

- Biomechanical studies which revealed a strong correlation between mechanical strength and BMD measured by DXA [27].

Table 8.2 A comparison of different tools used to assess for the bone mineral density including the pros and cons of each tool

Techniques	Site	Measurement	Radiation	Precision	Monitoring of therapy	Pros	Cons
Dual-energy X-ray absorptiometry DXA	Spine, hip, forearm	aBMD/HAS/ VFA/TBS	Low	Excellent	Excellent	Many validation studies, diagnostics used in WHO definition (aBMD) Can measure several sites and several applications	Areal measurements and not volumetric Do not distinguish cortical and trabecular bone
Radiographic absorptiometry	Phalanx, metacarpals	BMD	High	Fair		Portable devices	No central measure possible
Quantitative computed tomography/high resolution QCT	Spine, hip, forearm	vBMD/ micro-architecture	High	Good	Good	Separate cortical and trabecular bone Structure analysis Volume BMD can be more correct for very small or very large or obese	Higher radiation than DXA Less validated
Digital X-ray radiogrammetry	Metacarpals	DXRBMD/ porosity	High	Fair		Use standard X-ray Low radiation High precision Can be used for historical X-rays	No central measure possible
Quantitative ultrasound	Calcaneus	BUA, SOS	None	Low	Low	Portable devices No radiation	Low precision
MRI	Spine, hip, forearm	Micro-architecture	None	Good	Good (still under research)	Microarchitecture Volume and structure No radiation	Higher costs and low availability Poor precision
Positron emission tomography	Spine, hip	Bone turnover	High	No data available	No data available	Bone turnover	Higher radiation Higher costs and low availability
Microindentation	Tibia	Hardness/ strength	None	Poor	No data available	Direct measure of a bone property	Invasive Less validated Poor precision

- Prospective cohort studies revealed a strong relationship between BMD measured by DXA and fracture risk [25].
- The World Health Organization (WHO) criteria for the diagnosis of osteoporosis are based on reference data obtained by DXA [28].
- The fracture risk algorithm (Fracture Risk Assessment Tool [FRAX]) uses femoral neck BMD measured by DXA.
- Randomized, clinical trials showing a reduction in fracture risk with drug therapy based on subjects who had their BMD measured by DXA [29].
- Earlier studies depicted a significant relationship between decreased fracture risk with drug therapy and increases in BMD measured by DXA [30]. However, the magnitude of fracture risk reduction that is attributable to increases in BMD is variable.
- Several technical advantages, including excellent DXA accuracy and precision [31] as well as very low radiation exposure [32].

DXA Technology

The standard dual-energy X-ray absorptiometry (DXA) instrument consists of a padded table on which the patient lies and a movable C-arm with a radiograph tube below the patient and a detector above the patient (Fig. 8.1). The radiograph tube generates photon beams of two different energy levels, thus the term "dual-energy." A collimator below the table limits the scatter of the photons and directs them toward the area of interest. The difference in attenuation (reduction in intensity) of the two photon beams as they pass through body tissue of variable composition distinguishes bone from soft tissue and allows quantification of bone mineral density (BMD). Denser and thicker tissue contains more electrons and allows fewer photons to pass through to the detector. A computer with specially designed proprietary software designed by each manufacturer completes the DXA "system" [33, 34].

Fig. 8.1 The standard DXA machine consists of a padded table on which the patient lies and a movable C-arm with a radiograph tube below the patient and a detector above the patient. Computer with specially designed proprietary software designed by each manufacturer completes the DXA system and analyze the measures

Radiation exposure to the patient is very small, less than one-tenth the dose of a standard chest X-ray and usually of a similar magnitude to daily background radiation. Radiation scatter beyond the edge of the DXA table is negligible. No shielding of the technologist or the room is necessary. As a safety precaution, the technologist should typically not sit within 3 feet of the table edge while the patient is being scanned. DXA measures bone mineral content (BMC, in grams) and bone area (BA, in square centimeters) and then calculates "areal" BMD in g/cm^2 by dividing BMC by BA [34].

There are significant differences in the technologies used by different manufacturers and sometimes different models of DXA made by the same manufacturer. Manufacturers use different methods for creating dual photon beams (e.g., K-edge filtering and voltage switching), different bone edge detection algorithms, different assumptions on body size and tissue composition, different calibration, and different types of photon detectors. Photon beams have different configurations, e.g., pencil beam and fan beam. The bone regions of interest (ROI) measured may be different, especially so with the femoral neck. In the 1990s, most people were using DXA machines, which report units in g/cm^2. But when the bone density machines became commercial, the different companies would not agree on a standard measurement. A person would be about 6% higher on a Lunar machine than on a Hologic machine, even though both said they were reporting g/cm^2. If the companies would have used the same standards, then we could always just look at the plain bone density in g/cm^2, just like we look at cholesterol in mg/dl or weight in kg. Unfortunately, that did not happen. Some investigators have tried, unsuccessfully, to establish a "standardized" unit of mg/cm^2. Equations have been published to convert Hologic, Lunar, or Norland measurements to standardized units. Therefore, the T-score was invented [35].

T-score, the value used for diagnosis of osteoporosis, is calculated by subtracting the mean BMD of a young adult reference population from the patient's BMD and dividing by the standard deviation (SD) of young adult population. Z-score, used to compare the patient's BMD to a population of peers, is calculated by subtracting the mean BMD of an age, ethnicity, and sex-matched reference population from the patient's BMD and dividing by the SD of the reference population. The mean BMD and SD of the reference populations used for these calculations is a critical variable in the determination of T-scores and Z-scores. However, due to the significant differences in the technologies used by different manufacturers, the reference databases used to calculate T-scores and Z-scores may be different. Therefore, it is not possible to make quantitative comparisons of BMD measured on different instruments, especially those made by different manufacturers, unless a cross-calibration study has been done [36].

Nomenclature

DXA, not DEXA, is the preferred acronym for dual-energy X-ray absorptiometry. T-score should be used with no italics, not T score, t-score, or t score. Similarly, Z-score with no italics, not Z score, z-score, or z score, should be used. These should be expressed to one decimal digit, e.g., −2.3, not −2 or −2.31. Bone mineral density (BMD) should be expressed to three decimal digits, e.g., 0.946 g/cm^2 [37].

Clinical Applications of DXA

Dual-energy X-ray absorptiometry (DXA) is used to diagnose osteoporosis or low bone mineral density (BMD), estimate the future risk of fracture, and monitor changes in BMD over time. In addition to evaluating the BMD, the whole-body DXA scan can also be used to measure total body composition and fat content with a high degree of accuracy. In other words, DXA gives a detailed snapshot of the body composition, breaking the body weight down into fat, bone, and lean tissue. New research shows that the scan is highly accurate compared with most other methods for determining body composition and highly useful for tracking change in muscle and fat over time.

Contraindications: DXA should not be done in women who are pregnant or may be pregnant because ionizing radiation, albeit it in very small doses is used. DXA should be postponed until pregnancy is completed. As with any medical test, DXA should not be done unless the results are likely to play a role in the management of the patient. It may not be possible to do a DXA of the hip and spine in some patients due to inability to get on the table. BMD measurement may not be valid in some situations due to skeletal structural abnormalities, such as severe osteoarthritis, surgical hardware, or scoliosis [37–39].

Skeletal site selection The World Health Organization (WHO) recommends that the international standard for diagnosis of osteoporosis be made using the T-score measured by DXA at the femoral neck [19]. However, the NOF and the International Society for Clinical Densitometry (ISCD) suggest that the diagnosis of osteoporosis in clinical practice be made by DXA using the lowest T-score of the lumbar spine (L1-L4), total proximal femur, or femoral neck. In the hip, Ward's area, trochanter, and other regions of interest (ROIs) should not be used for diagnosis (Fig. 8.2). If the forearm is measured, then the 33% radius (one-third radius) may be used for diagnostic purposes if it is the lowest of the skeletal sites measured [26].

The rationale for using the lowest T-score of these skeletal sites is that all are good predictors of fracture risk, and the use of the lumbar spine, hip, and forearm BMD is consistent with the original WHO diagnostic classification of 1994 [28].

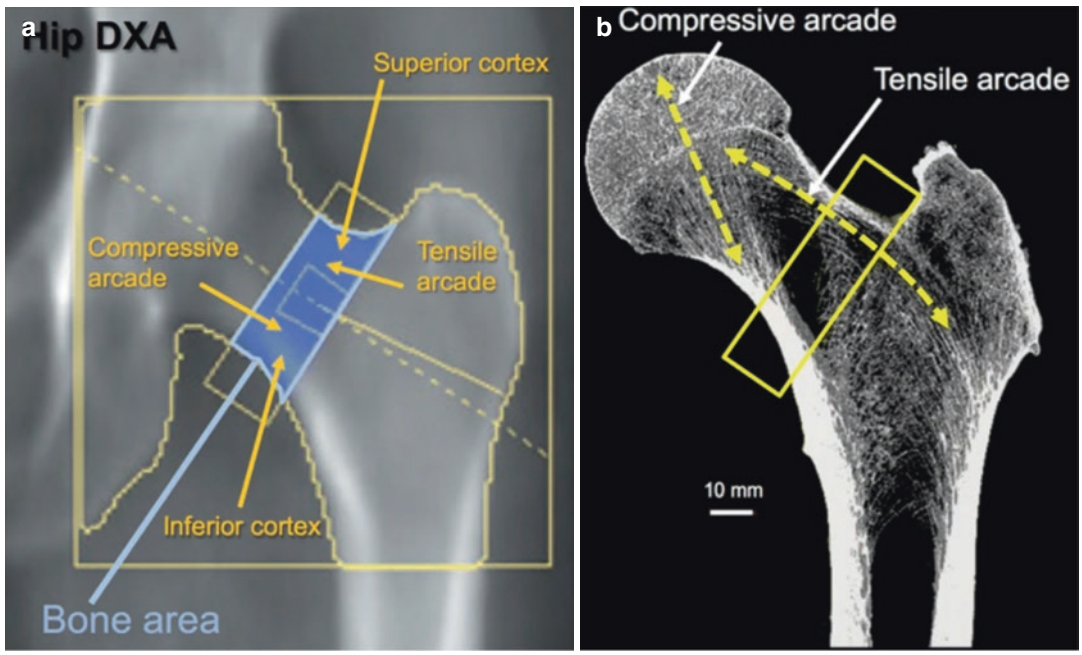

Fig. 8.2 Strategic arrangement of cortical and trabecular bone. The proximal femur experiences forces in different directions. (**a**) The critical aspects of femoral neck strength superimposed onto a hip DXA scan image. (**b**) With standing, the femoral neck experiences compress forces on the inferior surface and tensile forces on the superior surface. Compressive loads are reinforced with a compressive arcade composed of a thickened inferior cortex and an additional trabecular network. The tensile arcade is reinforced with a network of trabecular bone. These reinforcements are combined with lateral and medial cortices that provide additional reinforcements against side-to-side forces. NanoCT images were taken at 27 μm resolution using a phoenix nanotom-s (GE Sensing and Inspection Technologies, GmbH, Wunstorf, Germany). (Quoted under open access scheme from Choksi et al. [224]. under the terms of the Creative Commons Attribution)

Skeletal site selection is influenced by the risk factors. The standard is to scan the spine and the hip. However, in patients prone to have medication induced osteoporosis, such as long courses of steroids, patients with cancer prostate who are taking androgen depletion therapy or those with cancer breast who are taking hormone antagonist therapy are more likely to develop osteoporosis first in the distal forearm. Therefore, scanning the distal forearm in these people is advised [40, 41].

Reference databases The WHO recommends calculation of T-score with a uniform, standardized reference database in men and women of all ethnic groups, using the National Health and Nutrition Examination Survey (NHANES) III database for femoral neck measurements in young adult, Caucasian women [19]. In 2013, the ISCD Official Position on this issue was changed to be concordant with the WHO, with the recommendation of both organizations now being that a uniform Caucasian (non-race adjusted) female normative database for women and men of all ethnic groups [20]. It should be noted, however, that application of ISCD recommendation may vary according to local requirements and that most DXA systems currently in clinical use continue to report T-scores in males using a male reference database. Some DXA facilities may choose to continue to report T-scores in this manner despite the ISCD recommendation. DXA manufacturers should use NHANES III Caucasian data as the reference standard for femoral neck and total hip T-scores while continuing to use their own databases for the lumbar spine as the reference standard for T-scores. If local reference data are available, they should be used to calculate only Z-scores but not T-scores. The reference database for calculation of Z-score is matched for age, ethnicity, and sex (Fig. 8.3a, b).

Serial BMD testing Repeat BMD testing is recommended for patients being treated for osteoporosis, with the goal of stabilizing or increasing BMD, and for patients not being treated, in whom evidence of bone loss would lead to treatment. Serial BMD tests showing a change or stability of BMD may provide helpful clinical information, assuming the comparisons are technically valid and the clinician is knowledgeable regarding clinical implications.

Whenever possible, the same instrument should be used for serial DXA studies. Comparison of BMD measured with different instruments made by the same manufacturer or by a different manufacturer is discouraged for the reasons noted earlier. It is not possible to quantify BMD changes on measurements made on different instruments unless a cross-calibration study has been done. Comparison should be done using BMD in g/cm^2, not T-score, since changes in reference databases with software upgrades may cause spurious T-score changes.

Precision assessment The least significant change (LSC) with a 95% level of confidence should be established at each bone densitometry center for each technologist by in vivo precision assessment according to well-established guidelines [34]. LSC is defined as a change that is 2.77 times the precision error for each measured skeletal site, for each technologist, and it is best expressed as an absolute value (g/cm^2). Values for precision error supplied by the manufacturer of the DXA instrument are generally better than what is achievable in bone densitometry centers and should not be used for the calculation of least significant change (LSC).

Time interval for repeating DXA Repeat BMD testing may be considered when the results are likely to influence clinical management, such as when the expected amount of change in bone density equals or exceeds the LSC [34–36]. Consider repeat BMD testing one or 2 years after starting pharmacologic therapy, as soon as 6 months after starting glucocorticoid therapy, or perhaps never if very little change is expected or the results of testing are unlikely to influence patient management decisions.

Skeletal site to monitor The best skeletal site to monitor is one that responds quickly to therapy or lack of therapy and has a low LSC. Usually this is the lumbar spine. If the lumbar spine is not evalu-

able, as may occur with degenerative arthritis in older patients, then the total proximal femur should be considered.

Validity of comparisons Quantitative comparison of BMD measured with different instruments made by the same manufacturer or by a different manufacturer is discouraged as noted earlier. Comparison should be done using BMD in g/cm^2, not T-score, since changes in reference databases may cause spurious T-score changes [42]. Images of the skeletal site being compared should be carefully examined to assure correct positioning, labelling, and identification of bone edges. If

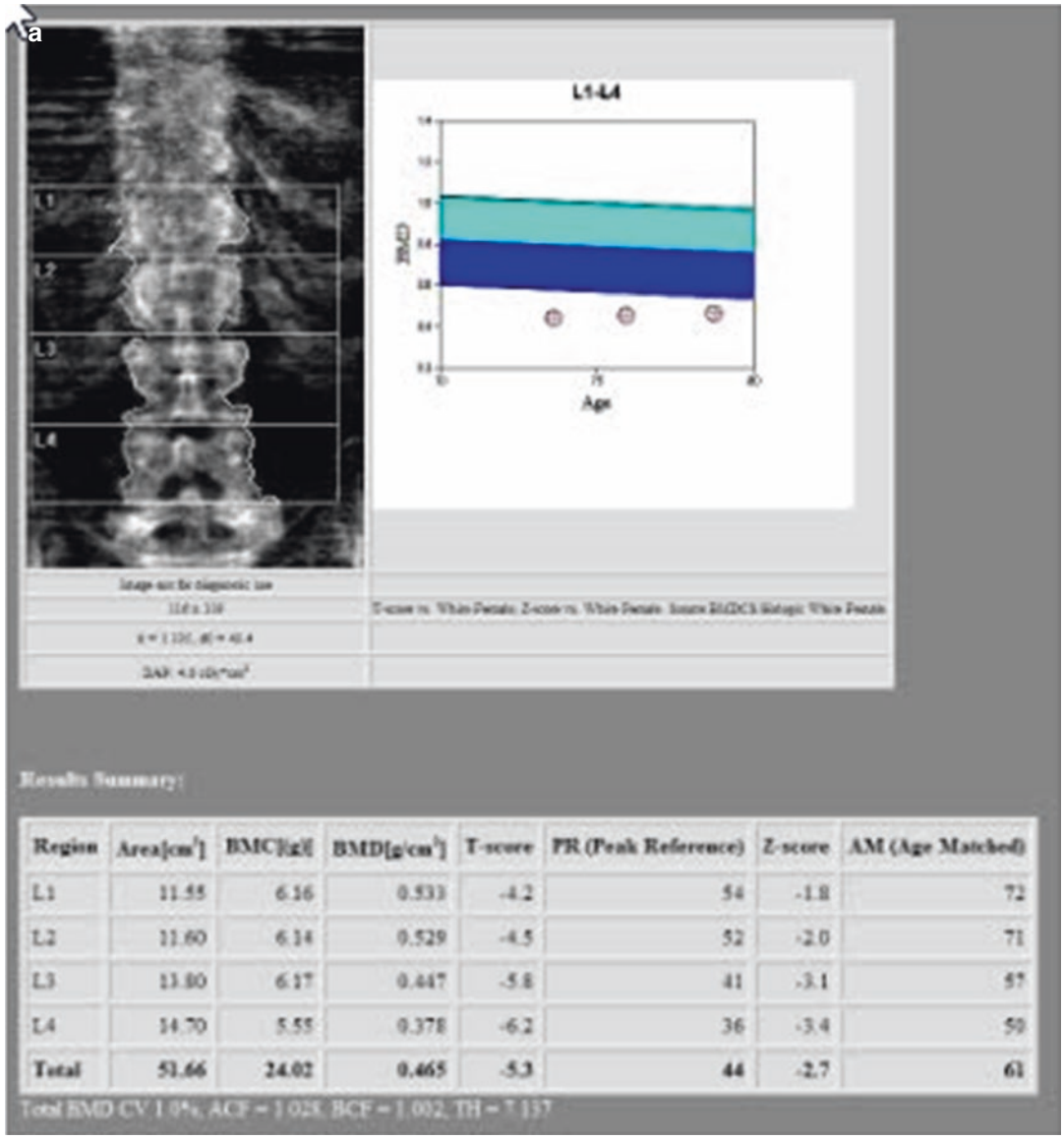

Fig. 8.3 DXA studies of the (**a**) proximal femur, (**b**): lumbar spine and (**c**) vertebral morphometry. L1-L4 in the lumbar spine of a 58-year-old woman are analyzed. If there is any deformed or degenerated vertebral bodies, it should be excluded. A T-score of −5.3 is in the osteoporosis range. (**b**) In the proximal femur of a 66-year old woman, the lowest T-score of total hip and femoral neck regions of interest is used to classify the bone as normal, osteopenic, or osteoporotic. In this postmenopausal woman the T-score was −3.1, which is in the osteoporosis range

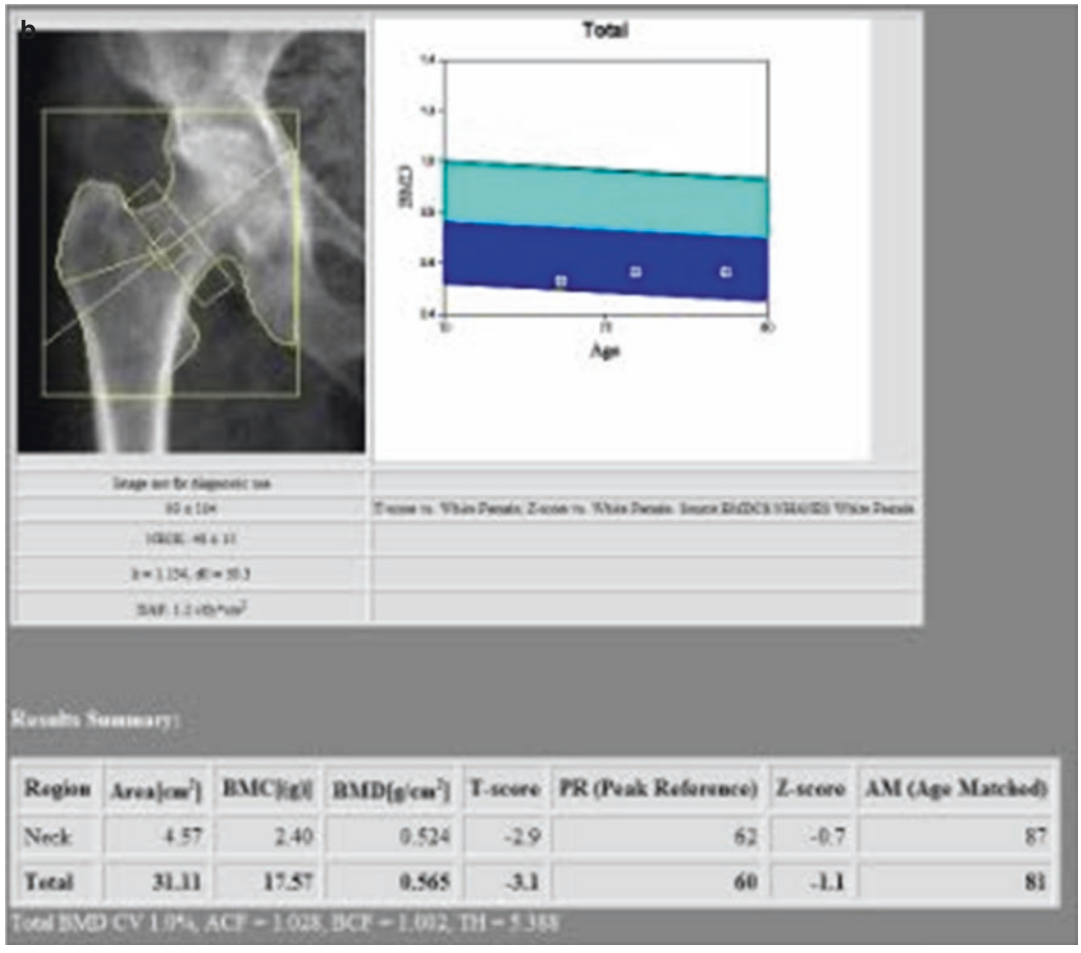

Fig. 8.3 (continued)

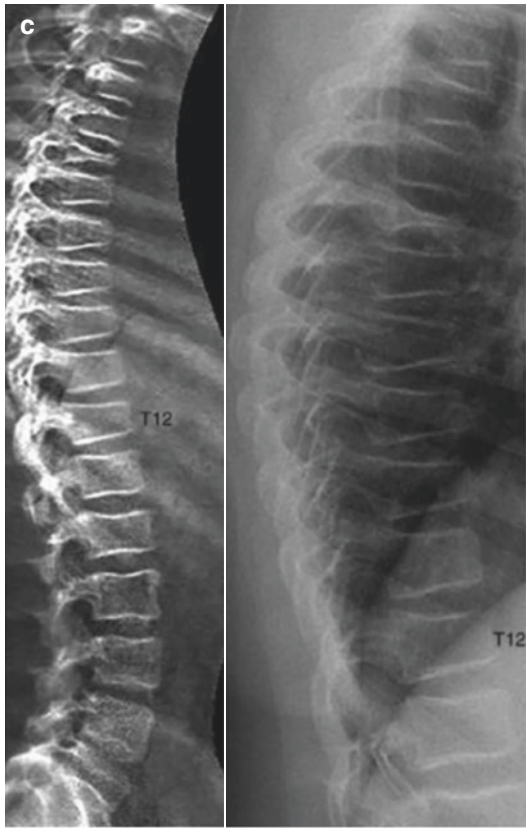

Fig. 8.3 (continued)

the lumbar spine is being compared, then the vertebral levels must be labelled in the same way. If hip or forearm is being compared, the same ROI on the same side must be used. Bone area being compared must be similar.

Interpretation of BMD changes In treated patients who are adherent to therapy, stability or an increase in BMD is an acceptable response. A post hoc analysis of data in 2984 women from the Fracture Intervention Trial (FIT) of alendronate showed that the greatest fracture reduction occurred in those who gained BMD, although those with stable BMD still had fewer fractures than those who lost BMD [43–53]. Loss of BMD more than the LSC is a cause for clinical concern and may be associated with poor adherence to therapy [44–47] or previously unrecognized contributing factors that require additional intervention [48].

Vertebral Fracture Assessment

Vertebral fractures (VFs) are a strong predictor of future fractures of all types [29, 49]. Vertebral fractures are the most common type of fragility fracture, yet approximately two-thirds of vertebral fractures are not clinically detected [30, 50]. Therefore, another valuable evaluation in osteoporosis is vertebral fracture assessment (VFA) on mostly lateral DXA or radiography (Fig. 8.3c). Vertebral fractures can be detected on other modalities such as CT or MRI as well [51]. Vertebral fracture assessment (VFA) by DXA can be done at the time of BMD testing, at greater patient convenience, less cost, and lower radiation exposure than conventional radiography of the spine [52].

Vertebral fracture assessment compares favorably with spine radiographs in detecting moderate and severe vertebral fractures, but it does not perform as well for diagnosing mild Vertebral fractures [53, 54]. In one study of women age 65 years and older, the sensitivity and specificity of vertebral fracture assessment for detecting moderate and severe vertebral fracture assessment was 87–93% and 93–95%, respectively [53].

Identification of previously undetected vertebral fractures may change the diagnostic classification, fracture risk profile, and clinical management [55–57]. The ISCD has published guidelines addressing the potential indications for Vertebral fracture assessment (Table 8.3) [55]. Several radiological scoring methods exist, each using different criteria for diagnosing and grading fractures. These assessment methods for osteoporotic vertebral fractures including quantitative morphometry (QM) analyses have been reviewed extensively elsewhere [58]. Frequently used are methods based on (semi) QM evaluating vertebral height [59] or the algorithm-based qualitative (ABQ) method [60] mainly judging endplate integrity regardless of vertebral height reduction.

However, while all vertebral fractures are deformities, not all vertebral deformities are fractures. There are a number of differential diagnoses that have to be considered in individuals with vertebral deformities, such as Scheuermann's disease and degenerative changes [60–62]. Scheuermann's disease is a form of osteochondrosis of the spine of

unknown etiology characterized by increased posterior rounding of the thoracic spine in association with structural deformity of the vertebral elements [63, 64]. However, merely measuring vertebral heights in clinical practice frequently leads to misdiagnosis of fracture in non-osteoporotic conditions including Scheuermann's disease [64]. Simultaneous assessment of vertebral heights together with endplate integrity may correctly differentiate these cases. A clear and correct fracture definition is crucial, because vertebral fractures form an integral part of clinical decision making to initiate anti-osteoporotic drugs or to switch to more potent and expensive agents in case of fractures under current therapy [65, 66].

Table 8.3 The International Society for Clinical Densitometry (ISCD) indications for vertebral fracture assessment

Lateral spine imaging with standard radiography or densitometric VFA is indicated when T-score is <−1.0 and one or more of the following is present:
Women age ≥70 years or men age ≥80 years
Historical height loss >4 cm (>1.5 inches)
Self-reported but undocumented prior vertebral fracture
Glucocorticoid therapy equivalent to ≥5 mg of prednisone or equivalent per day for ≥3 months

ISCD International Society for Clinical Densitometry, *VFA* vertebral fracture assessment

Trabecular bone score (TBS) is a gray-level textural measurement that can be extracted from a dual-energy X-ray absorptiometry (DXA) image of the lumbar spine with proprietary software; it captures information related to bone microarchitecture that provides an assessment of fracture risk that is independent of bone density [67] (Fig. 8.4).

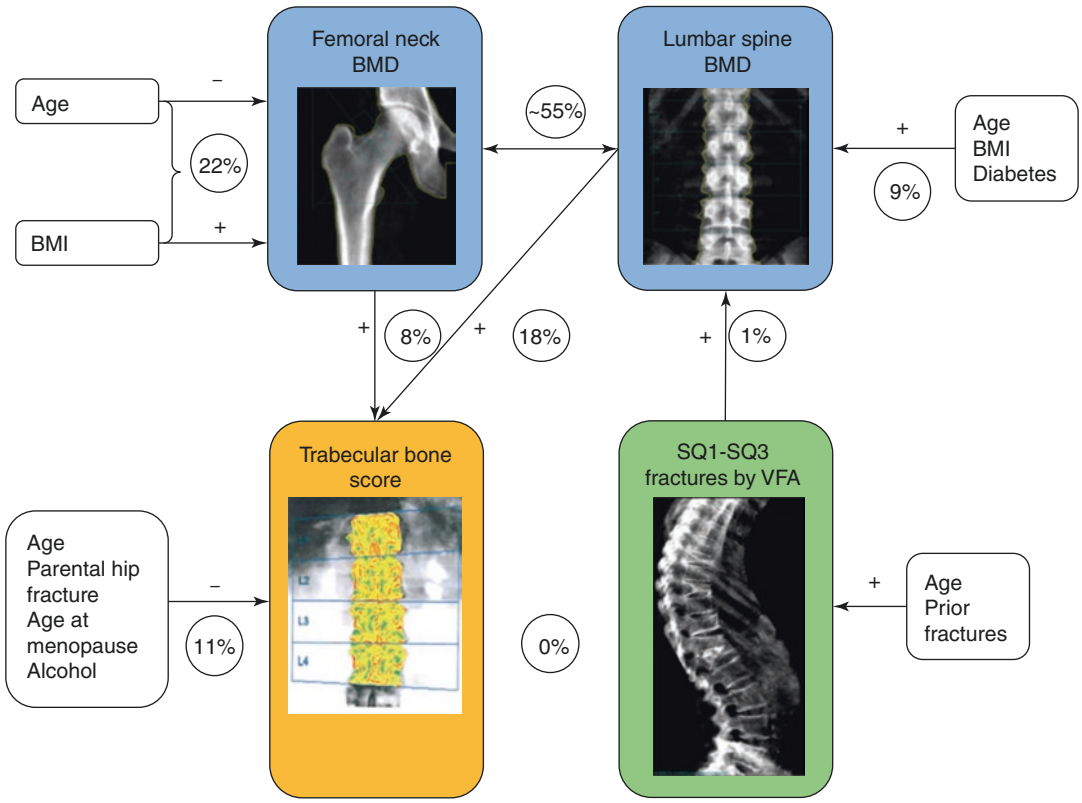

Fig. 8.4 Associations between femoral neck and lumbar spine bone mineral density (BMD), trabecular bone score (TBS), and vertebral fractures on VFA (SQ1-SQ3) with attributed variance of their determinants. BMI body mass index. (Quoted under open access scheme from Borgen et al. [225], under the terms of the Creative Commons Attribution)

Previous studies have shown that TBS predicts fracture in postmenopausal women and older men. TBS is currently used in conjunction with BMD values to enhance the predictive ability of the widely used Fracture Risk Assessment tool (FRAX®), a calculator used to assess an individual's 10-year risk of major osteoporotic fracture.

In a large study, a team of international researchers have validated the predictive ability of TBS using individual-level data of 17,809 men and women from 14 studies worldwide. They aimed to validate the contribution of TBS to fracture risk prediction, independent of FRAX, and to examine the impact of applying TBS adjustment to FRAX probabilities. The study results revealed that:

- TBS was consistently an independent contributor to the assessment of fracture risk and that the relationship with other risk factors was robust across sex, diverse races, fracture incidences, and geographical regions.
- The combination of TBS with the clinical risk factors (including BMD) showed enhanced gradients of risk for hip and non-hip major osteoporotic fractures compared with TBS or the FRAX risk factors alone.

In 2018, the Spanish Society of Bone Research and Mineral Metabolism (SEIOMM) concluded its project and published a review of the scientific evidence on the clinical use of TBS [68] presenting its official positions of the TBS. Three questions were addressed: 1. Can TBS be used to assess the risk of fracture in clinical practice? 2. Can TBS be used to monitor patients with osteoporosis? 3. In what diseases is TBS especially useful? The recommendations for these questions are summarized in Table 8.4 [69].

DXA Additional Parameters

In recent years, several additional quantitative parameters have been described that can be extracted from existing DXA imaging data. For example, hip structural analysis can be performed on DXA images [70–72]. Parameters that can be derived include cross-sectional area (CSA), cross-sectional moment of inertia (CSMI), and the section modulus. Using appropriate assumptions, endocortical width and the cortical thickness can be estimated (35). Cross-sectional moment of inertia (CSMI), as an estimation of the resistance

Table 8.4 The recommendations of the Spanish Society of Bone Research and Mineral Metabolism regarding trabecular bone score [68]

Question	Clinical use	Level of evidence/degree of recommendation
1. Can TBS be used to assess the risk of fracture in clinical practice?	TBS can be used to assess the risk of vertebral fracture, femur and global fragility in women and men from 50 years of age	Level of evidence: 2 ++ Degree of recommendation: B
	TBS can be used in conjunction with BMD to assess vertebral, femur and global fragility in men and women from 50 years of age	Level of evidence: 2 ++ Degree of recommendation: B
2. Can TBS be used to monitor patients with osteoporosis?	The TBS can be used to evaluate changes over time	Level of evidence: 2+ Degree of recommendation: C
	TBS does not improve BMD in the assessment of the effect of treatment over time It should not be used in the assessment of response to bisphosphonates	Evidence level: 2 ++ Degree of recommendation: B
3. In what diseases is TBS especially useful?	TBS can be used to assess the risk of fracture in subjects with diabetes TBS can be used to assess the risk of fracture in subjects treated with glucocorticoids TBS can be used for the clinical orientation of subjects suffering from hypo and hyperparathyroidism TBS can be used for the diagnostic orientation of patients in the presence of osteoarthritis	Level of evidence: 2+

of bone to bending, is calculated according to the formula: ([periosteal diameter/2]^4 − [medullary diameter/2]^4) × π/4 [73]. Section modulus is calculated as CSMI divided by the greater of the measured distances from the center of mass to the medial or lateral surface and is a measure of bending and torsional strength [74].

Quantitative Computed Tomography (QCT)

Originally, QCT was developed as a methodology using single thick (around 10 mm) CT image slices angled to sample the vertebrae and to avoid the cortical end plates. However, this mode of operation has now been largely superseded by the use of volume images covering regions of interest at the spine or hip.

For patients undergoing screening CT colonography (CTC), a potential opportunity exists for concurrent BMD screening by QCT without the need for any additional imaging, radiation exposure, or patient time [75]. In addition, there are a number of indications for CT imaging for which there is a large overlap between the need for a CT scan and a patient having risk factors for osteoporosis. By utilizing volume-based QCT methodology rather than the older single-slice protocols, use may also be made of these CT images for BMD measurement by QCT [76, 77]. Such dual use of CT images could increase screening rates or, alternatively, preclude the need for DXA screening in some individuals.

Clinical Applications of QCT

QCT has long been considered as the gold standard for acquiring subject-specific, volumetric BMD in vivo. In QCT, bone is modeled as a specimen composed of water and mineral. Voxel-wise BMD is computed by comparing the Hounsfield unit of each voxel with those from calibration standards with known CHA densities. Previous literature has shown strong associations between apparent bone density (mass of bone without the marrow divided by bone volume including the pores) and bone mechanical properties (e.g., elastic modulus and yield strength) using material testing techniques. Hence, with a conversion from QCT-based BMD to apparent bone density (5), voxel-wise mechanical properties of the bone of interest can be derived. Furthermore, a heterogeneous bone finite element (FE) model can be generated by assigning region-specific mechanical properties to the QCT-based bony mesh and consequently the fracture risk under mechanical loading can be computed. However, as soft tissues exhibit little signal on QCT, such approach becomes challenging when structuring both bone and soft tissues in FE models (e.g., models of the patellofemoral joint) [78].

Previous studies combining standard CT imaging and QCT have generally focused on BMD measurement at the lumbar spine [79] for which QCT provides a volumetric BMD measure of the trabecular vertebral bone in isolation. This can have an advantage of superior sensitivity due to the higher turnover rate of trabecular bone [80], but QCT T-scores on average are somewhat lower than DXA T-scores for the same age, and the established World Health Organization (WHO) classification of osteoporosis by DXA T-score is not appropriate [81]. By contrast, at the proximal femur, QCT three-dimensional (3D) data may be used to derive a projectional two-dimensional (2D) image of the proximal femur, and this image may be analyzed using standard DXA region of interests (ROIs) to determine DXA equivalent "computed tomography X-ray absorptiometry (CTXA)" areal BMD (aBMD) values in g/cm^2 [82]. Using this method, the WHO T-score classifications may be applied and the aBMD measures may be included in FRAX calculations.

The workflow associated with such dual use of CT scans may be improved using "phantomless" or "asynchronous" calibration methods, so that the BMD measurement does not need to be planned in advance of the CT scan. In addition, using such methods, it is possible to make use of archived CT scans retrospectively [83]. Finally, the use of intravenous (IV) contrast-enhanced CT images for QCT is usually contraindicated and a measurement bias has been shown at the spine

[84]. However, some recent studies suggest that for measurements made at the hip, the measurement difference due to contrast enhancement may not be clinically significant, further widening the utility of CT scans for BMD measurement [85]. Quantitative computed tomography and opportunistic bone density screening by dual use of computed tomography scans was reviewed in a recent article published by Brett and Brown [86].

Standard QCT

QCT may be performed on any CT scanner with the use of a calibration phantom and dedicated analysis software. The patient is usually examined in the supine position, lying on the phantom, usually with a water- or gel-filled cushion between the phantom and patient to avoid CT reconstruction. Calibration phantoms are required to transform the attenuation measured in Hounsfield units into BMD values. When the patient and phantom are examined at the same time, the process may be described as "simultaneous calibration." There are 3 the most frequently used calibration phantoms for this purpose: 1. the solid-state Canne-Genant phantom (Mindways Software Inc., Austin, TX, USA) (this contains five potassium phosphate-equivalent density phases); 2. the five-phase solid state calcium hydroxyapatite phantoms; and 3. the phantom developed by Kalender et al. [87] (this utilizes two calcium hydroxyapatite phases. This phantom is used by Siemens for their commercial QCT product). However, BMD measurements from different types of calibration phantoms are not interchangeable, unless a cross-calibration calculation is performed.

Single-Slice QCT

Single-slice QCT was the original QCT methodology, which was developed on single-slice CT scanners for trabecular BMD measurements at the lumbar spine. Using the standard methodology, single sections of three to four consecutive vertebrae from T11 to L4 are scanned [88–94]. A typical acquisition involves 10-mm slice thickness with a gantry tilt used to derive mid-vertebral sections parallel to the vertebral end plates. The gantry tilt is selected interactively by the technologist from the lateral scout view.

Single-slice QCT protocols generally have radiation doses that are higher than those of DXA, although these doses are smaller than many other radiographic procedures. Low-dose protocols using 80 kVp (or 120 kVp) and 120 mAs (or 150–200 mAs) result in effective doses of less than 200 uSv [88]. By way of comparison, DXA has radiation doses in the order of 10–15 uSv for the spine and hip. However, QCT has lower exposure doses than many other standard radiology procedures: an anteroposterior lumbar spine radiograph has a dose of 700 uSv and a standard abdominal CT has an exposure dose of the order of 8000 uSv [89].

Although radiation exposure dose can be substantially lower with single-slice QCT compared with volumetric QCT (vQCT) (Fig. 8.5), which is described in the following section, a substantial disadvantage with single-slice BMD analysis by 2D QCT is the lower precision compared with that of DXA (1.5–4% vs. 1%), which results in a larger least significant change required to detect significant changes in BMD (6–11% vs. 3%). This, however, is partially offset by the fact that metabolic activity of trabecular bone is higher and that even lower precision single-slice QCT is usually adequate to monitor longitudinal changes that are in the same range as those found with DXA [90].

Volumetric QCT

vQCT or 3D QCT has increased precision and is easier to perform compared with single-slice QCT. A contiguous volume with a slice thickness of 1–3 mm with no CT gantry tilt is typically scanned. At the lumbar spine, protocols usually include only two vertebrae between T11 and L4, often L1 and L2, to reduce dose while achieving measurement precision noninferior or superior to that reported for single-slice QCT. Typical values are in the order of 80–120 kVp and between 50

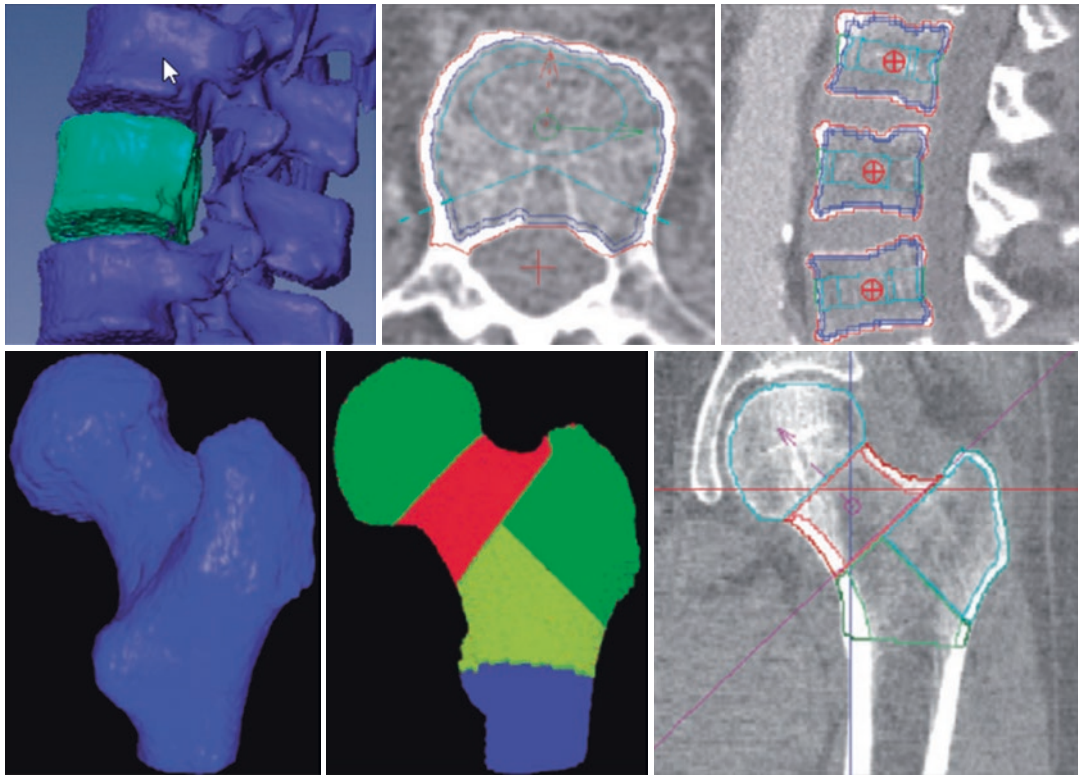

Fig. 8.5 The vQCT of the spine (top panel) and hip (bottom panel) may be used to analyze BMD in various bone compartments and to accurately measure BMD and geometry. Top left: segmented vertebral body selected for analysis with r moved processes. Top center and right: integral (red) and peeled trabecular volumes of interest [VOI] (dark blue) along with the traditional elliptical and Pacman VOIs (light blue). Bottom left: segmented proximal femur. Bottom centre and right: analysis VOIs in the hip. (Quoted under open access scheme from Genant et al. [226], under the terms of the Creative Commons Attribution)

and 200 mAs. Using these parameters, the dose has been estimated using pharmaceutical clinical trials protocols with 1-mm slice width to be as high as 1.5 mSv for the spine and 2.5e3 mSv for the hip [88].

At the spine, QCT provides a volumetric BMD measure of the trabecular vertebral bone in isolation. This can have an advantage of superior sensitivity because of the higher turnover rate of trabecular bone [80] and can also avoid the confounding effects of joint-space narrowing, osteophytes, aortic calcification, and other extraosseous calcification that can artificially raise a DXA spine BMD measurement [91–93]. However, the measurement of isolated trabecular bone means that QCT T-scores are somewhat lower, on average, than DXA T-scores for the same age [10], and the established WHO classification of osteoporosis by DXA T-score is not appropriate. To facilitate the interpretation of QCT spine results, the American College of Radiology has in 2008 and 2013 published guidelines for the performance of QCT [94]; based on these guidelines, volumetric trabecular BMD values from 120 mg/cm^3 to 80 mg/cm^3 are defined as osteopenia and BMD values less than 80 mg/cm^3 as osteoporosis.

High-Resolution Peripheral Quantitative CT (HR-)pQCT)

HR-pQCT is applied to the tibia or (distal) radius with simultaneous scanning of a hydroxyapatite calibration phantom, obtaining measurements within trabecular and cortical compartments

[16]. In cortical bone, standard analysis comprises cortical thickness (Ct.Th) in mm, cortical porosity (Ct.Po) as a percentage relative to the cortical pore volume (Ct.Po.V), and cortical bone volume (Ct.BV) in mm^3 [95, 96]. It has been shown that with increasing age most bone loss is cortical due to predominantly intracortical remodelling [97]. This results in increased spatial distribution, number and size of pores [98]. In trabecular bone, standard analysis includes quantifying structural properties of trabecular bone, such as bone volume fraction (BV/TV), which is derived from trabecular BMD (Tb.BMD), average number of trabeculae (Tb.N), average trabecular thickness (Tb.Th), and average trabecular separation (Tb.Sp) [99]. Associations have been demonstrated for different HR-pQCT measurements at the tibia and radius for vertebral and any-type of fractures [100–104] (Fig. 8.6).

Volumetric assessments with HR-pQCT also have added value in complex phenotypes such as diabetic bone disease. DXA-based studies showed that type 2 diabetes patients with worse glycemic control have paradoxically higher BMD and thicker femoral cortices in narrower bones in spite of a higher fracture risk [105]. A study using HR-pQCT reported that the cortical porosity in type 2 diabetic patients was up to twice that of controls at the radius [96]. This supports the hypothesis that an inefficient redistribution of bone mass, accumulation of microcracks, and cortical porosity reflecting impaired bone repair give rise to fragility in apparently "strong" bones on 2D assessments in inadequately controlled diabetes. Subsequently, Patsch et al. showed in a four-group comparison of type 2 diabetes patients with and without fragility fractures to controls with and without fractures that cortical porosity is specific to those type 2 diabetes patients that fracture [106]. Moreover, an innovative investigation utilizing in vivo microindentation testing of the tibia showed that patients with type 2 diabetes have reduced serum markers of bone turnover and lower bone material strength than controls [107]. In the same study, the average glycemic level over the previous 10 years was negatively correlated with bone material strength. It would be desirable to investigate

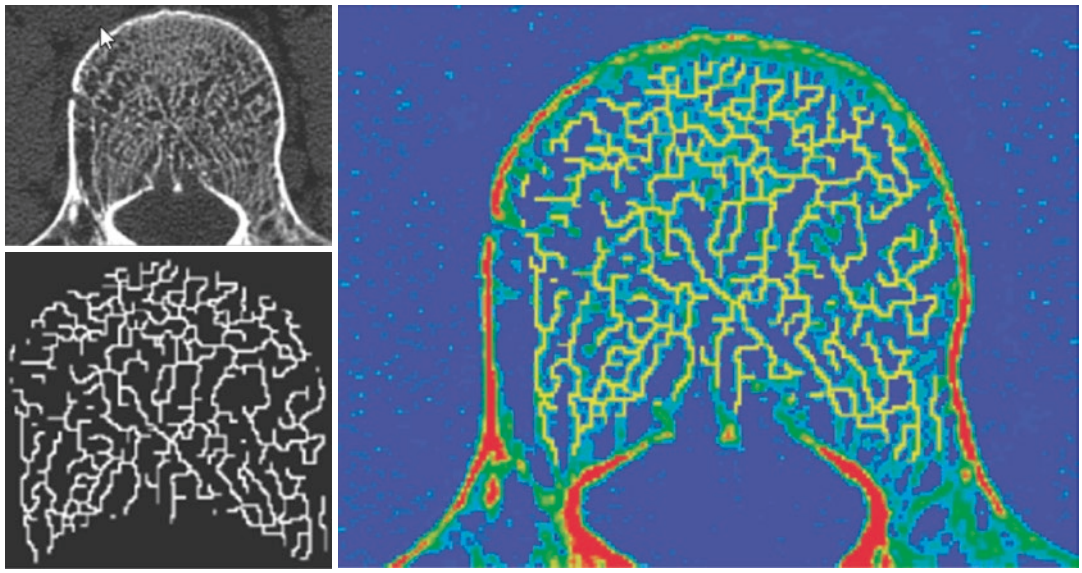

Fig. 8.6 Example of image processing of hrCT images. Trabecular structure can be approximated if individual trabeculae are well separated. The upper left shows the original hrCT spine image, followed on the lower left by the "binarized" and "skeletonized" image processed into single-pixel-thick trabeculae displayed in white against black of the surrounding marrow and followed on the right by a "colorized" version for which quantitative image processing can be undertaken. (Quoted under open access scheme from Genant et al. [226], under the terms of the Creative Commons Attribution)

these phenomena with (pQ)CT on a larger population scale. Medical evidence is still too limited to warrant large-scale implementation of CT in clinical practice at this point [108, 109]. In the future, diagnostics and therapeutics may separately target cortical versus trabecular bone compartments.

Projectional QCT: Hip

By contrast, at the proximal femur, 3D QCT data may be used to derive a projectional 2D image of the proximal femur, and this image may be analyzed using standard DXA ROIs to determine DXA-equivalent CTXA aBMD values in g/cm^2. Because the correlations between these calculated BMD values of the proximal femur and those obtained by DXA are extremely high, the WHO T-score classifications may be applied [106]. The precision of projectional hip BMD values has been found to be slightly better than DXA in the same patients, probably because of hip rotation being performed by software rather than at the time of acquisition. Areal CTXA BMD measurements from hip QCT are included in the FRAX tool [107], and hip BMD conversion equations are available between Hologic and Lunar DXA and QCT. In addition, the 2008 and 2013 American College of Radiology QCT Practice Guidelines state that QCT at the hip also provides aBMD with DXA equivalent T-scores.

Discordance in Diagnosis of Osteoporosis by QCT and DXA

The BMD results measured by DXA and QCT cannot be compared directly, and sometimes, the diagnosis indicated by BMD findings differs between the two techniques. Therefore, this discordance may impact on the diagnosis and therapeutic plan in an individual person. Primarily, DXA scan expresses the results as areal density, including both cortical bone and trabecular bone. Quantitative computed tomography (QCT) is a truly three-dimensional technique for quantifying volumetric trabecular bone density that is not affected by spine degeneration and abdominal aortic calcification [108].

Therefore, some possible causes for the occurrence of discordance can be summarized as: (1) The DXA measurement includes both cortical and trabecular bone, whereas QCT quantifies the trabecular bone density. Trabecular bone is known to have a more rapid rate of age-related loss than cortical bone. This may diminish the sensitivity of DXA for assessing osteoporosis [109–112]. (2) The BMD measurement by QCT is in the central plane of the vertebral body (a thick slice of 9 mm). The measured results may be affected by an uneven distribution of trabecular bone in the whole vertebral body. (3) Previous studies have shown that spinal degeneration and abdominal aortic calcification may be associated with the overestimation of BMD and the underestimation of osteoporosis by posterior-anterior spine DXA [113–117]. Given the effect on lumbar spine DXA BMD, some researchers have suggested that DXA of the hip should be used for identification of osteoporosis particularly in the elderly [118].

Ultrasound Scanning

Unfortunately, DXA cannot be employed for population mass screenings because of important intrinsic limitations, including ionizing radiation exposure, high costs, and unavailability in primary care settings. In order to overcome these limitations, several alternative approaches based on ultrasound (US) technologies have been proposed, with the aim of exploiting their numerous potential benefits. Proposed quantitative ultrasound (QUS) methods have several potential advantages over DXA (absence of ionizing radiation, portable machines, lower cost), but as yet there is no widespread consensus regarding their accuracy in identifying osteoporotic patients [16, 119–122]. Nevertheless, commercially available US devices for bone characterization and osteoporosis diagnosis can be presently applied only to peripheral sites (e.g., calcaneus), with a limited clinical effectiveness [122–126]. In this context, the latest research frontier is represented by

the development of an US approach to osteoporosis diagnosis that is applicable on femoral neck [127–129] and/or lumbar spine [130, 131].

Technically, the most common QUS devices employ through transmission measurements to provide parameters such as broadband ultrasound (US) attenuation, speed of sound, and stiffness index. Recently, some experimental studies have reported the potential of ultrasonic backscattering as a new method for diagnosing osteoporosis, exploring the possible usefulness of parameters such as backscatter coefficient [132, 133], apparent integrated backscatter (AIB) [134, 135], frequency slope of apparent backscatter and time slope of apparent backscatter [136], spectral centroid shift [137], broadband ultrasound backscatter [138], integrated reflection coefficient, mean of backscatter difference spectrum, and slope of backscatter difference spectrum [129]. The overall conclusions that can be drawn from the reported articles are that US backscatter parameters, mostly measured in vitro on excised human bone samples, have appreciable correlations with BMD, and experimental data often support the idea that backscatter measurements may also provide an assessment of bone micro-architecture. However, despite preliminary encouraging in vivo results reported by a few pilot studies [137], the backscatter approach has still remained at an early stage of research and generally suffers from the lack of appropriate clinical validation.

A possible way to improve this situation could be the development of US-based approaches for non-ionizing BMD measurements at the reference anatomic sites. In fact, although the correlation between peripheral QUS parameters and DXA-measured central BMD (i.e., spinal or femoral) is typically poor, site-matched correlations between DXA-measured BMD and corresponding QUS estimates are generally much stronger [139]. Therefore, an improved diagnostic outcome could be expected from US measurements on the reference central sites. On the basis of these considerations, proximal femur has become the target of several recent experimental investigations involving QUS approaches [140–143] that obtained encouraging results. At the spine, Garra et al. [137] assessed the potential of "in vivo" US measurement of a spine diagnostic parameter on humans in which spectral centroid shift was measured on vertebral bodies L3 and L4 of nine female volunteers employing a 2.5-MHz phased-array US probe.

However, in this context, the current official position of the International Society for Clinical Densitometry (ISCD) regarding QUS is that the only validated skeletal site for the clinical use of QUS in osteoporosis management is the heel; validated heel QUS devices predict fragility fractures in patients. Age 65 year, in conjunction with clinical risk factors, can be used to identify a population at very low fracture probability in which no further diagnostic evaluation may be necessary [144]. However, ISCD also specifies that DXA measurements at the spine and femur are the preferred choice for therapeutic decisions and should be used in place of QUS if possible, and in particular, QUS cannot be used for therapeutic monitoring purposes (ISCD 2013) [136].

MRI

In contrast to QCT, MRI can potentially be used for volumetric BMD calculations without losing soft tissue signals. However, quantifying BMD using MRI is challenging, mainly due to the low proton signals in mineral (6). Over the past two decades, several MRI techniques enhancing the phosphorus signals have been developed for BMD calculations. High-resolution (HR) MRI may help in assessing the bone structure whether directly or indirectly. However, in comparison to both DXA and CT, MRI has some pros and cons. On one hand, MRI is relatively more costly and time-consuming and produces a lower spatial resolution than CT. On the other hand, a major advantage for MRI is that it does not represent ionizing radiation risk. Applying MRI to assess for bone mineral density status was recently reviewed by Oei et al. [145]. The next section will summarize these techniques. In addition, the great potential of MRI for detailed characterization of bone at the microarchitectural and molecular level will be also discussed.

As histomorphometry is the best and only method for the direct analysis of bone cells and their activities, it has been considered the gold standard for bone assessment [146, 147]. However, particularly in the clinical setting, bone biopsies are rarely used to diagnose and manage patients with osteoporosis, because of their invasiveness [148]. Molecular imaging, the in vivo characterization and measurement of biological processes at the cellular and molecular level is being hailed as the next great advance for imaging [149]. MRI has been proposed as a non-invasive tool that enable bone architecture analysis. However, technical improvements in MRI are necessary for human application, particularly with regard to maximizing signal-to-noise ratio and spatial resolution within clinically acceptable scan times. This is a prerequisite for the introduction into large-scale population imaging studies and clinical practice in the future to aid the analysis of a large variety of musculoskeletal disorders including osteoporosis.

Inferences can be made about trabecular bone structure from HR-MRI. Osteoporosis patients with and without fractures compared to individuals without osteoporosis have been evaluated for different MRI-derived texture parameters of bone, and differences between these groups were demonstrated at the distal radius and calcaneus [150–152]. One of the few MRI-based studies in diabetic bone disease reported greater trabecular heterogeneity in subjects with type 2 diabetes mellitus than in healthy controls [153]. More MRI studies in diabetic bone disease are necessary given the recent insights regarding the impact of diabetes on bone quality.

Indirect MRI methods used for evaluation of the bone structure include MRI spectroscopy aiming to visualize the osseous structure or the changes in the structure at a molecular level without the need of contrast agents. Proton-magnetic resonance spectroscopy (1H-MRS) is considered the MRI gold standard for bone marrow fat quantification. Point-resolved spectroscopy (PRESS) and stimulated echo acquisition mode (STEAM) single-voxel 1H-MRS pulse sequences have been commonly used for the characterization of the fat spectrum in the bone marrow at the pelvis, spine, and hip [154]. Images are acquired using dedicated coils to detect and quantify frequency signals of water, lipids, and other metabolites. Measures are expressed as universal ppm (parts per million) units with evaluation of areas under the peaks. In addition to qualitative interpretation, (semi-)quantitative analysis is in use such as scaling of ratios to unsuppressed water or to noise [155, 156]. Increased emphasis on quantitative assessment instead of qualitative dichotomization of metabolite content by MRS has been advocated [157]. Measurement quality and awareness of possible artifacts are important in MRS [158], and adequate distinction of the molecular peaks and regions of interest can be technically challenging [154]; corrections can be applied to minimize confounding effects [159].

Direct MRI methods include chemical shift imaging, diffusion-weighted imaging, and perfusion MRI. Chemical shift imaging aims to separately detect protons that process with similar yet slightly different frequencies, namely, those of water and fat [160]. A study evaluating the reproducibility of signal intensity index (SII) measurements in healthy volunteers with MRI systems from different vendors and with different field strengths, found intra- and inter-observer correlation coefficients ranging from 0.82 to 0.98 [161]. In osteoporosis, the few studies performed until now have primarily assessed the bone marrow [162–164]. Diffusion-weighted imaging measures the Brownian motion of water at a microscopic level and provides information on cellularity and cellular integrity expressed in the apparent diffusion coefficient (ADC) [160]. A review article discussing diffusion-weighted imaging in musculoskeletal radiology has been published recently [165]. Similar to chemical shift imaging, most studies carried out using diffusion-weighted imaging in osteoporosis have focused on the bone marrow [166–168]. A few studies reported diffusion-weighted MR imaging parameters to be associated with BMD [169, 170]. One study has examined ADC values before and after vertebroplasty and found that high preoperative ADC was predictive of the occurrence of new compression fractures [171]; therefore replication studies are necessary. As far as perfu-

sion imaging is concerned, different perfusion imaging methods are used; of which the dynamic contrast-enhanced MRI (DCE-MRI) technique is the most commonly implemented [160]. Possible analytical approaches to DCE-MRI data include time-intensity curves, enhancement patterns over time and pharmacokinetic modelling approaches to quantify blood flow. Quantitative outcomes of diffusion-weighted imaging and dynamic contrast-enhanced MRI have been reported to be different between acute osteoporotic vertebral fractures from normal appearing vertebrae [172]. Furthermore, maximum enhancement [E(max)] and enhancement slope [E(slope)] are significantly decreased in osteoporosis at least in the femurs and vertebrae [173–177]. Quantitative parameters of blood flow were studied with DCE-MRI in osteoporotic patients with acute vertebral fracture compared to a control group [178]. Plasma flow (mL/100 mL/min) quantifies the volume of plasma flowing through the region of interest per unit time; plasma volume (mL/100 mL) corresponds to the volume of the plasma per tissue volume in the region of interest, and extraction flow (mL/100 mL/min) characterizes the net flow between the plasma and the interstitial space (extracellular and extravascular space). These perfusion parameters were decreased in normal-appearing vertebral bone marrow of osteoporosis patients compared to controls, but they were found to increase in acute vertebral fractures.

A shortcoming of MRI is that, due to its short T2 relaxation time, no signal from cortical bone is acquired with conventional MRI pulse sequences [179]. Hence, sequences with ultrashort echo time are needed to capture signals of those tissues which exhibit short T2 (e.g., cortical bones, tendons, ligaments, menisci, and myelin) [180]. This may be overcome with novel ultrashort or zero time to echo (UTE/ZTE) MRI techniques. 1H, being the most abundant isotope of hydrogen, is present in bone water and these signals can be acquired by aforementioned techniques. The 1H signal arises from different pools, distinguishable by their relaxation times. Relatively free water within large pores has the longest T2 relaxation times; water in small pores has greater surface to volume ratios, experiences greater surface relaxation, and thus has a shorter T2 relaxation time [181]. Protons bound to bone matrix are more tightly restricted in movement and have shorter T2 relaxation times. A variety of UTE pulse sequences have been developed capable of depicting signal from different water pools in bone (Fig. 8.7) and quantitating the amount of water by means of T2* relaxometry. The field is making steps in translating experience from animal and cadaveric experiments to in vivo human studies [182–185]. As bone water is present

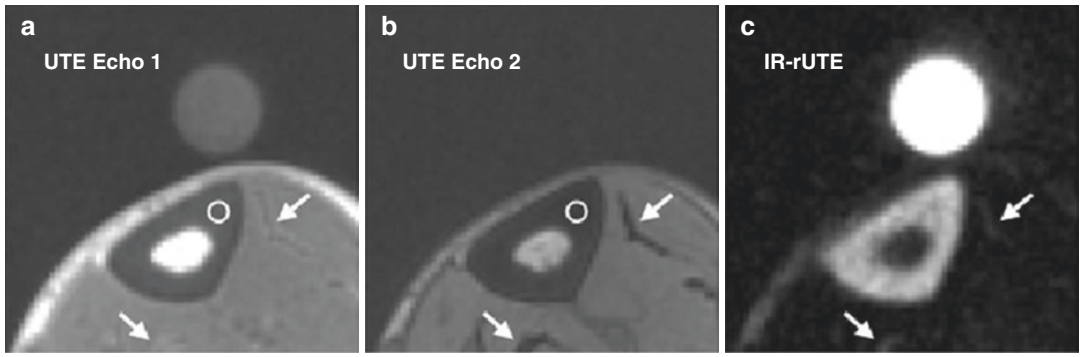

Fig. 8.7 Total and bound water images of cortical bone. Bone water images from a 48 y/o male subject reconstructed from (**a**) first and (**b**) second echo of the dual-echo UTE sequence; (**c**) BW image from the IR-rUTE sequence. Note that in (**c**), surrounding soft tissues as well as bone marrow within the medullary cavity is selectively suppressed via adiabatic inversion, leaving only short-T2 1H density calibration sample and water tightly bound to collagen matrix. Image intensity measured from the circular ROI is noticeably higher in the first echo (0.32 versus 0.03 in the second echo). Also note similar intensity properties of the fasciae (arrows). (Quoted under open access scheme from Zhao et al. [227])

mainly in the pore system of bone, this parameter provides a surrogate measure for porosity, and it has been demonstrated that cortical bone water concentration is greater in postmenopausal women than in premenopausal women [186].

Bone Marrow Fat Imaging

In diseases such as osteoporosis and diabetic bone disease, bone marrow fat has been reported to be affected [187]. The bone marrow fat volume can be measured [188]. Further, bone marrow fat composition can be examined, regarding presence and types of hydrogen bonds, where unsaturated fats contain at least one double bond and saturated fats have the maximum number of hydrogens bonded to carbons. This can be evaluated with *MRS*, dual energy QCT [189, 190], T1-weighted and occasionally T2-weighted MRI [191]. The average coefficient of variation for vertebral bone marrow fat fraction on spectroscopy has been reported at 1.7% (97). The correlation between the marrow fat fraction obtained with MRS and that obtained with dual-energy CT has been reported as high as $r = 0.91$ [192]. Vertebral marrow fat content is significantly increased in osteoporosis compared to osteopenia or normal bone density as evaluated by higher fat fractions on MRS and lower ADC by diffusion weighted MR [193]. An ancillary study in the population-based Age Gene/Environment Susceptibility (AGES) cohort found that higher marrow fat assessed by MRS correlated with lower trabecular BMD in women and higher marrow fat was associated with prevalent vertebral fracture in men [194]. Validation of these results should be pursued.

Dixon quantitative chemical shift MRI (QCSI) relies on phase shifts created by fat-water resonance frequency differences to separate water from fat [195]. Studies have reported good reproducibility for Dixon QCSI for measuring the bone marrow fat fraction in the L1–L4 vertebral bodies and this measurement seems independent of DXA-BMD [196].

A small study in subjects with disuse osteoporosis has demonstrated morphological changes in the bone marrow at the lower limb such as reinforcement of trabecular lines, subchondral fat content, signal intensity, and vasculature [197]. Further quantitative texture analysis on this subject in larger samples may be worthwhile.

Combined QCT and MRS studies have demonstrated that the prevalence of fragility fractures is associated with lower unsaturation levels and higher saturation levels of bone marrow fat, in which the participants with diabetes with fractures have the lowest marrow unsaturation and highest saturation [198]. In contrast to controls without diabetes, higher mean vertebral bone marrow fat content is significantly correlated with visceral adipose tissue and HbA1C in persons with type 2 diabetes, representing worse metabolic profiles [199]. The concept of high-saturated fat-associated adipose inflammation and insulin resistance has been proposed; however, underlying molecular mechanisms remain to be elucidated.

Positron Emission Tomography (PET)

Application of PET/CT in the field of osteoporosis is still limited. In certain clinical fracture cases where CT and MRI images are inconclusive in differentiating benign from malignant pathologies, PET/CT can be acquired, which can also discover additional skeletal or extra-skeletal metastases [200]. The standardized uptake value (SUV), a dimensionless parameter, is commonly used as a relative measure of F-fluorodeoxyglucose (FDG) tissue uptake with correction for the amount of injected FDG and the patient size [201]. Further, bone fracture healing can be visualized by PET/CT, but this has predominantly been studied in animal models [202–205]. Zooming in further, in 18F-Fluoride PET scanning, it is believed that PET intensity reflects the activities of osteoblasts and osteoclasts, and at least in animal experiments, microdamage can be detected [206]. Regional bone perfusion and turnover studies with bone turnover markers as a reference have been performed comparing different skeletal sites in treatment-naïve and patients

with osteoporosis on treatment with various anti-osteoporotic agents [207–213]. The long-term precision reflected by the coefficients of variation (12.2–26.6%) and intraclass correlation (0.44–0.85) for 18F-Fluoride PET parameters has been reported to be equivalent to that observed for biochemical bone turnover markers [214]. It has been hypothesized that PET/CT may be useful in atypical femoral fracture patients, but supportive research data is needed [215].

No reports on the utilization of PET/MRI in osteoporosis have been published to date. Neither has diabetic bone disease been studied with PET/MRI in humans; a small study comparing diabetic and healthy pigs found a significant inverse correlation between vertebral bone marrow glucose uptake and fat content [216]. Nonetheless, the first PET/MRI studies to detect and characterize osseous metabolic abnormalities in osteoarthritis are being done where PET/MRI may detect metabolic abnormalities in subchondral bone, which appear normal on MRI [217]. Development of MRI quantitative imaging techniques is an exciting area of research deserving further explorations.

Bioengineering: Using an Electronic Stethoscope and Machine Learning to Detect Osteoporosis from Percussion Responses

One can tap on the surface of a structure or material to determine its solidity. Similarly, percussion or tapping techniques are used by doctors in clinical examinations to determine density or cavity and assess certain conditions of the thorax and abdomen [218]. They can also be used for assessing conditions in other parts of the body. Percussion sound transmitted through bones, listened through the chest using a stethoscope, was reported to be used to detect osteoporosis [219]. A close correlation between bone resonant frequencies and the BMD was confirmed recently [220]. The lowest resonant frequency of tibia and other physiological information were mapped onto the fracture risk assessment tool (FRAX) algorithm to give a diagnosis of osteoporosis [221]. Recently, a machine learning method was recently proposed to differentiate vibro-acoustic signals and detect osteoporosis [222]. The method illustrated in Fig. 8.8 involves as follows: A clinician taps on a patient's proximal tibia bone with a Taylor reflex hammer, and an electronic stethoscope picks up the induced sound at the midpoint and/or the distal end of the tibia. The signal is transmitted via a Bluetooth data link to a computer for further signal processing and pattern recognition, leading eventually to a diagnostic decision. By utilizing common clinical devices and apparatus, the method has considerable potential to be used by primary care providers as a screening test for whole populations, thus enabling early detection of osteoporosis (Fig. 8.7).

The diagnostic decision-making mechanism of the proposed method is based on statistical machine learning from a large number of recordings. The machine learning algorithm maps the

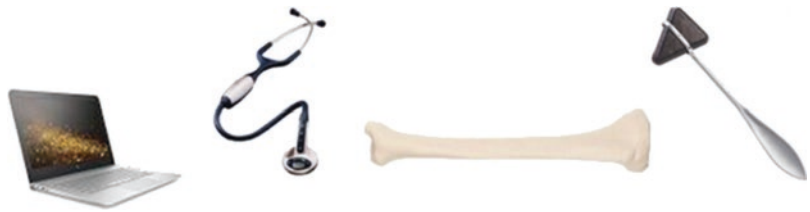

Fig. 8.8 Components of the Electronic Stethoscope and Machine Learning tool for the diagnosis of osteoporosis: illustration of a practical method for an osteoporosis screening testing. (Quoted under open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/) from: Scanlan et al. [228])

individual impulse responses to a continuous output, which is then split into two classes: healthy (OK) and osteoporotic (OP). This is based on the doctors' diagnoses of the patients, taking into account DXA T-scores and other physiological parameters and aspects. The lowest resonant frequency is closely related to the bending stiffness of the bone and, therefore, the quality of the bone [222, 223]. Clear correlation relationships between resonant frequencies of long bones and whole body BMDs have recently been confirmed [220] (Fig. 8.9).

Impulse responses acquired in vivo using percussion techniques have artifacts: The Taylor

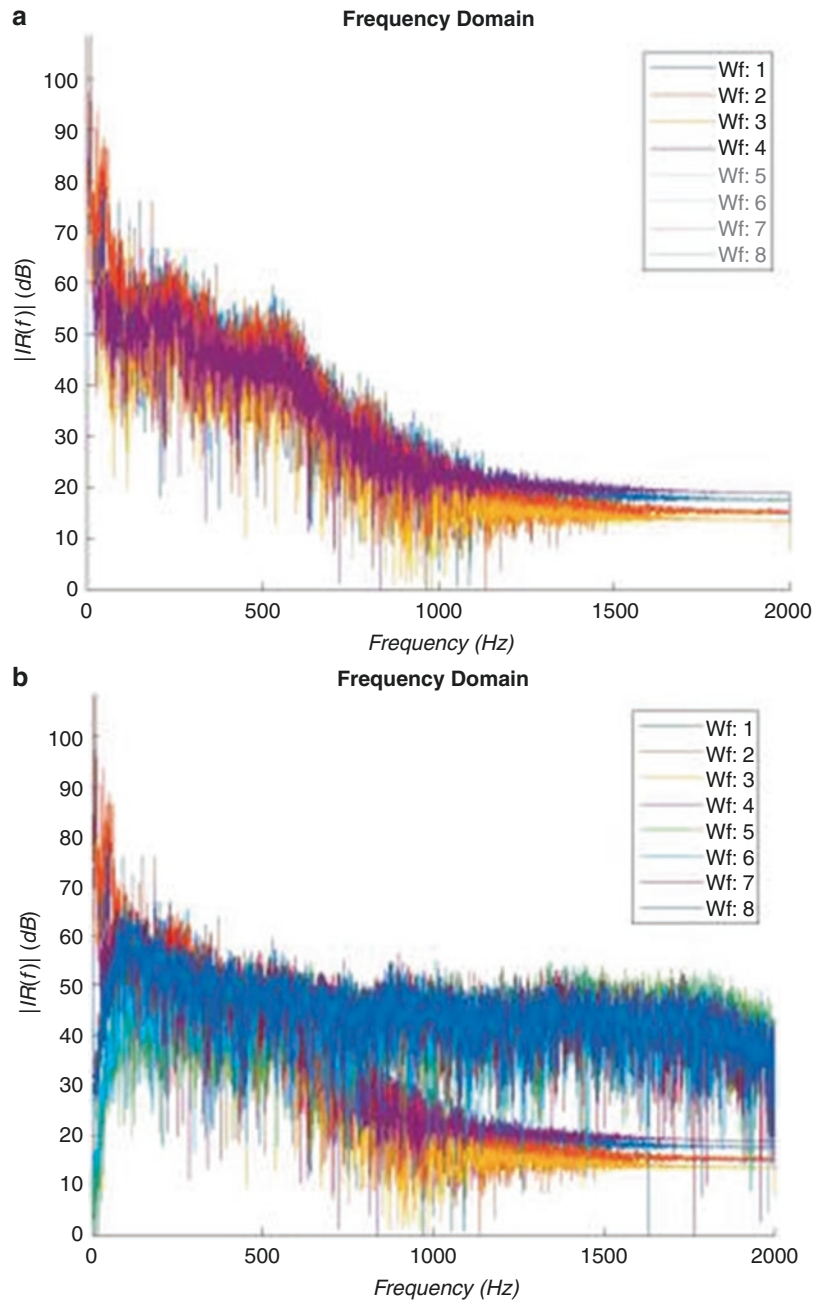

Fig. 8.9 (**a**) Frequency response of stethoscope from a noise signal. (**b**) Overplayed stethoscope and accelerometer signals, Tracks 1–4: stethoscope; Tracks 5–8: accelerometer. (Quoted under open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/) from: Scanlan et al. [228])

reflex hammer has a semi-rigid rubber head and the soft-tissue layers introduce a damping effect. Therefore, the impulse responses include convolved components of these damping/soft layers, which vary considerably in a population. Feature extraction methods that can de-convolve complex signals might be beneficial. Machine learning may be expected to learn from a large number of examples to disregard these components found in signals.

In conclusion, this chapter reviewed the importance of osteoporosis imaging both in diagnosis and management. It also summarized quantitative imaging methods in osteoporosis, where current clinical practice most frequently utilizes assessments from DXA and conventional radiography. QCT has the unique ability to provide information on anatomical morphology and get many quantitative parameters about bone health with a single scan, without causing pain due to movement especially in the elderly and those with fractures (such as identifying the details of vertebral fractures). Correct interpretation is vital as treatment decisions are taken based on these outcomes. Further technical developments are ongoing to expand the richness of data obtained from these modalities. Finally, potentially novel application of quantitative parameters from ultrasound, CT, MRI, and PET is underway in clinical and research settings. However, in this context, the current official position of the International Society for Clinical Densitometry (ISCD) and DXA measurements at the spine and femur are the preferred choice for therapeutic decisions and should be used in standard clinical practice.

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9 The Challenges and Limitations of Osteoporosis Diagnosis

Yasser El Miedany

Introduction

Osteoporosis is a progressive systemic skeletal disease characterized by reduced bone mass leading to bone fragility and higher risk of fractures. The number of osteoporotic fractures is increasing worldwide resulting in a global major public health issue [1]. Osteoporosis is the most common reason among the elderly for nontraumatic or low-energy-induced fractures [2], which represents the main clinical consequence of the disease. Around the world, one in three women and one in five men aged 50 years and over are at risk of an osteoporotic fracture. In fact, an osteoporotic fracture is estimated to occur every 3 seconds [3].

Since age is the dominant risk factor for osteoporotic fractures, roughly 90% of the fragility fractures occur in patients 60 years and over, and the fracture rate is world widely expected to increase, as the number of older adults is rising [4, 5]. The most common fractures associated with osteoporosis occur at the hip, spine, and wrist. Osteoporotic fractures can result in serious consequences including increased morbidity, disability, pain, and mortality. Of particular concern are vertebral (spinal) and hip fractures. Relatively uncomplicated wrist fractures are usually associated with devastating pain and mild disability (and sometimes to limitations in daily activities/work) [6], while severe fractures, such as hip fractures, usually lead to hospital admissions and operative procedures, which may be complicated by infection, myocardial infarction, thromboembolism, and delirium [7]. In addition, patients with hip fractures may have persistent postoperative limitations in walking and daily living, and more importantly, mortality risk is increased [8, 9]. In concordance, vertebral fractures can result in serious consequences, including loss of height, intense back pain, and deformity (sometimes called Dowager's hump). Such serious complications as well as morbidities have highlighted the importance of osteoporosis as a disease of a major health concern.

Notwithstanding its high prevalence, osteoporosis is often underdiagnosed and undertreated. This was documented in several reports and meta-analysis that describe an inadequacy in diagnosis and treatment of osteoporosis worldwide [10–14], particularly in the first few months after fragility fracture, where the risk for a subsequent fracture is substantially increased and, consequently, treatment is vitally important [15]. Even when the diagnosis is made and the decision is taken to treat, there are remaining challenges in implementing therapy for osteoporosis. This highlighted the fact that in spite of the availability of several therapeutic agents to treat osteoporosis and prevent fractures, there remain

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challenges and multiple unmet needs in the field of osteoporosis and fracture care.

This chapter will discuss how the concept of quality has emerged and its impact on the patients' management. It will also discuss the challenges to osteoporosis diagnosis and management including the challenges of underdiagnosis (even after fractures), the scanning process, patient awareness, as well as the missed falls risk assessment.

Challenge 1: Underdiagnosis of Osteoporosis (Even after Fractures)

The underdiagnosis and under-treatment of osteoporosis represents a substantial healthcare problem. Data from Medicare claims for 1999 to 2000 showed that only 30% of eligible women age 65 and older had a bone density test [16], despite recognition by many organizations that fracture risk is high and DXA is indicated in this population [17–19]. An adult with any fracture [20], even one due to trauma [21], may have osteoporosis, may be at risk of future fractures, and should be considered for further evaluation. Vertebral fractures, the most prevalent type of osteoporotic fracture, are commonly underrecognized and underreported [22, 23], perhaps because they tend to be silent in its initial stages, thereby missing an opportunity to identify and treat a patient at high risk. On the other hand, clinical vertebral fractures are those that come to clinical attention because of symptoms and then are appropriately diagnosed. While morphometric vertebral fractures are those detected by an imaging study regardless of symptoms, only about one-third of all vertebral fractures are clinically apparent [24].

Few other chronic diseases have received the unacceptance of therapies to the magnitude that pervades osteoporosis care. The annual cost in the USA of caring for osteoporotic-related fractures parallels or exceeds the annual cost for myocardial infarction, breast cancer, and/or cerebrovascular accidents [25–27]. In addition, in a large study in Manitoba, Canada, the ratio of the total annual costs of either prevalent or incident osteoporotic-related fractures exceeds the same ratio calculation for many other serious chronic diseases [28]. Equally disturbing are data showing that the percentage of patients receiving a registered therapy for osteoporosis, even after sustaining a hip fracture, has declined in the USA from 41% in 2001 to 21% in 2011 [26]. Finally, the leading cause of the loss of independence in men or women 70 years of age and older is fractures due to falls at home [29–31].

As early as 2005, reports [32, 33] revealed that 10.2% of women age 67 and older with a fracture were tested for osteoporosis within the following 6 months. Patients discharged from the hospital after hip fractures are commonly not diagnosed with or treated for osteoporosis [34, 35] although the risk of future fractures is very high [36]. Inpatient consultation with a medical specialist has not consistently improved osteoporosis care, with some reports of no effect and others suggesting a modest benefit [37, 38].

There are many opinions regarding the decline in the diagnosis and treatment of osteoporosis. In this author's opinion, the three major reasons are:

1. The decline in bone mineral density testing by dual-energy X-ray absorptiometry (DXA) in non-facility-designated DXA sites (e.g., private practices) [39–42].
2. The underappreciation of the seriousness of all osteoporotic fractures, including asymptomatic vertebral compression fractures, and the failure to ensure that patients admitted to hospital facilities with osteoporotic fractures are directed into an osteoporosis management plan to prevent a second fracture [43–49]. Even if the DXA scan is requested, it is frequently carried out after the patient's discharge, and usually the patients are not referred to a specialized bone health clinic.
3. Primary care physicians are often overburdened with clinical, administrative, and regulatory responsibilities that leave little time to consider a silent disease that increases the risk of an event that may occur far in the future.
4. Acute fractures are often treated by an orthopedist or emergency department specialist who is not responsible for long-term care and

prevention of future fractures. The primary care physician may not become aware of the fracture until long after it has occurred.

5. The fear that has been imbedded in the minds of patients as well as many physicians concerning the safety of bisphosphonates, e.g., their association with osteonecrosis of the jaw and/or atypical subtrochanteric femur fractures (AFFs) [50, 51].

Another factor that is local to the USA is the plans published by the Centers for Medicare & Medicaid Services (CMS) to significantly reduce reimbursement for dual-energy X-ray absorptiometry (DXA), performed as a hospital outpatient service in the 2017 as reported in the Hospital Outpatient Prospective Payment System (HOPPS). If finalized, by 2023 it will cut payment for the DXA testing by 37%. The reduction follows a 75% decline in reimbursement for DXA performed in physicians' offices since 2006 (the rate was $140 in 2007 and dropped to $42 in 2018). The anticipated consequences are as follows: fewer patients will be diagnosed with osteoporosis, fewer patients will be treated, and more fractures will occur, with fracture-related healthcare expenses far exceeding the savings from fewer DXA tests and fewer prescriptions for drugs to reduce fracture risk [52–54].

The International Society for Clinical Densitometry (ISCD) and multiple other professional societies involved in osteoporosis patient management and research have recently supported a bill in the Congress (Increasing Access to Osteoporosis Testing for Medicare Beneficiaries Act of 2015, HR 2461, 114th Congress) to set a flat and common floor for all DXA providers nationwide of $98/test [55]. There is also a large imbalance in costs for osteoporosis management. One example is the measurement of serum 25-hydroxyvitamin D, an important test for osteoporosis management that is reimbursed at approximately $200, whereas payment for DXA, a test with wide applications for diagnosis, risk assessment, and monitoring of treatments, has a meagre payment that is two-thirds lower than the payment needed just to break even on the cost of doing DXA.

Strategies for improving osteoporosis diagnosis (Table 9.1) include (1) appointing an advocate who would help in identifying the high-risk population. Given the many demands placed on primary care physicians or accident and emergency departments, who may not have time to focus on osteoporosis, it may be helpful to appoint staff as "advocates" for skeletal health. This could be a medical assistant, nurse, or healthcare educator who is charged with alerting the physician when bone mineral density testing is needed or who could perhaps be given the authority to order DXA scanning and blood checks for bone profile (calcium, phosphorus, alkaline phosphatase, as well as vitamin D serum level) based on pre-approved criteria/questionnaires [56].

Changing the healthcare approach may be a more effective way to improve clinical outcomes than changing the actions of individual physicians. Disease management programs that institutionalize pathways of care for osteoporosis have been shown to be promising [57, 58]. Similarly, post-fracture intervention programs may provide an opportunity to better manage patients at very high risk of future fractures [59, 60].

To assure patient access to diagnostic services for assessment of skeletal health, advocates are focusing on legislation to restore DXA reimbursement to a level that would allow outpatient DXA facilities to avoid financial losses and continue operating [61]. This possibility may be aided by grassroots support from concerned phy-

Table 9.1 Approaches to improve osteoporosis diagnosis (managing OP challenges and strategies)

Challenge	Strategy
Personnel	Appointing an advocate in the standard clinical setting
Identification	Set up criteria to identify people with imminent fracture risk/high-risk falls
	Software to identify people with low-trauma fracture
Limited resources	Assessing fracture risk without BMD (e.g., FRAX)
Management	Set up a disease management program
Support	Lobby with legislators
Standard of care	Implementing guidelines for osteoporosis management

sicians and from patients likely to be harmed by limited access to DXA testing because of fewer instruments in operation and greater distances to travel to reach them. The largest US patient advocate organization for osteoporosis care, the National Osteoporosis Foundation (www.nof.org), is leading a drive to educate legislators on the value of bone density testing and to pass corrective legislation. In June 2019, the American College of Rheumatology representatives attended advocacy meetings in Washington, D.C., to support legislation for the Increasing Access to Osteoporosis Testing for Medicare Beneficiaries Act (H.R. 2693/S. 283). If passed, this would set the minimum for Medicare reimbursement at $98, ensuring bone density testing can be performed for more patients. The CMS has raised the reimbursement rate for DXA testing in the hospital setting, but the ACR would like to see rates raised in the private practice setting as well [62].

Identifying people with imminent fracture risk or high possibility of having a fall is important to stratify population and prioritize the need for DXA scanning. The patients who get the greatest reduction in fracture risk with drug therapy are those who have the highest baseline risk of fracture [63]. An estimate of fracture risk is therefore important in determining which patients to treat. While bone mineral density is an excellent predictor of fracture risk, density combined with clinical risk factors for fracture is a better predictor than density or clinical risk factors alone. Tools like FRAX [64] or Q-fracture [65] can help identifying with high fracture probability even without DXA scanning.

Clinician's Guide to Prevention and Treatment of Osteoporosis is of great help to harmonize osteoporosis treatment nationally/internationally. There are several treatment recommendations available such as those published by National Osteoporosis Foundation in the USA, NICE [66]/NOGG in England [67], French recommendations [68], etc. Most of these documents address postmenopausal women and men age 50 and older of all ethnic groups and are intended for use by clinicians in making decisions in the care of individual patients. The recommendations should provide a general framework for management but should not be taken as rigid standards of practice but rather as a framework for making clinical decisions with consideration of the needs of each individual patient.

Challenges 2: From T-Score to Bone Strength and Quality

Studies of osteoporosis epidemiology and its drug treatments have challenged the concept that denser bone means stronger bone. Bone strength or resistance to fracture is not easily measured by routine densitometry, being a function of both density and quality [69]. DXA scanners generate two-dimensional images of complex three-dimensional structures and report bone density as the quotient of the bone mineral content divided by the bone area. An obvious pitfall of this method is that a larger bone will convey superior strength but may in fact have the same bone density as a smaller bone [70]. Bone quality is a composite of properties that make bone resist fracture. These include biomechanics (including microarchitecture and accumulated microscopic damage), the quality of collagen, mineral crystal size, and bone turnover. The determinants of bone strength are complex but can be divided into four basic components (Fig. 9.1): size, shape, architecture, and composition. Bone has a unique ability to coordinately adjust these traits. This results in a structure that is sufficiently stiff to resist habitual loads but minimizes mass, keeping the overall energy of movement to a minimum. The overall strength of a bone depends on the proportion of cortical and trabecular tissues, their morphologies and their material properties, and the interactions among these traits. An individual's unique genetic program also contributes to bone strength; it is estimated that up to 70% of ultimate bone strength and structure is genetically determined [71].

Studying the characteristics of bone structure reveals that bone is comprised of a dense cortical shell that surrounds a spongy trabecular bone network. The periosteal diameter combined with the endosteal diameter determines cortical thick-

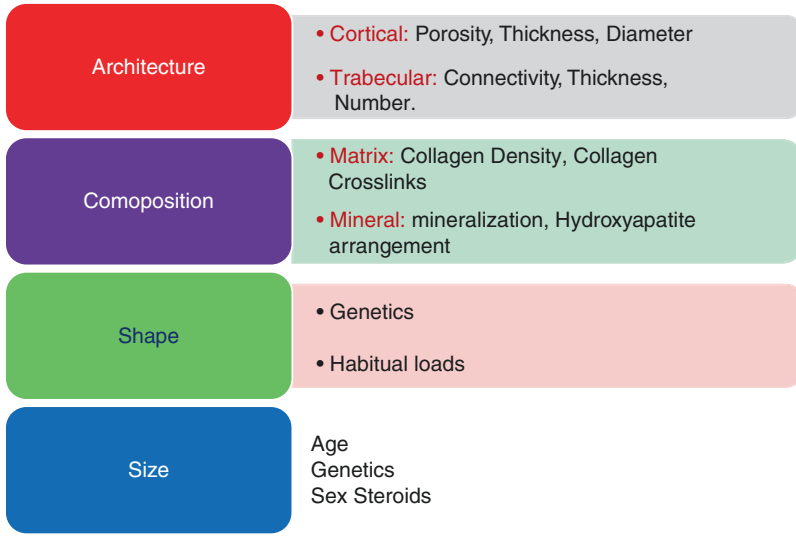

Fig. 9.1 Determinants of bone strength. Bone strength is a product of the complex interactions of different skeletal criteria. The interplay of several structural components including both cortical and trabecular factors represents the basis of the bone architecture. Cortical thickness, diameter, and porosity contribute to cortical strength, whereas the number, the thickness, and the connectivity of plates and rods determine trabecular bone strength. It is difficult to assess for bone composition non-invasively, as it relies on the bone matrix strength which is based on the degree of collagen cross-links and the collagen density. While the bone size increases with age and with puberty, ultimate bone size also has a large genetic contribution. The interaction of genetics and habitual loading determines bone shape

ness. The size of bone along with cortical thickness and porosity significantly contribute to bone strength. The inner trabecular compartment contains a network of plates and rods that also contribute to bone strength (Fig. 9.2) [70].

The bone architecture plays an important role in determining the bone strength. The trabecular arrangement combined with cortical bone thickness and porosity provides a scaffold that is significantly stronger than an equal mass of solid bone. The trabecular bone scaffold within the marrow space is composed of plates and rods (Fig. 9.3) with a higher plate/rod ratio conferring strength. With aging, plates become more rod-like, and plate connectivity with the rods declines, all of which contributes to lower bone strength and stiffness [71].

The proportion of cortical and trabecular bone varies depending on the location. For example, the ultradistal radius is approximately 25% cortical and 75% trabecular bone. The proximal 1/3 radius is primarily all cortical bone [70]. Furthermore, the arrangement of trabecular bone is strategic to provide maximal strength. This is especially evident in the femoral neck [72, 73]. The ability of the inferior cortex and compressive arcade to resist compressive loads, combined with the superior cortex and tensile arcade to resist tensile loads, provides maximal strength and flexibility (Fig. 9.2). Failure of this cooperative network is the reason for femoral neck fractures. Thus, efforts to maintain strength by applying more or greater loads to stimulate bone formation may make the bone stronger for daily loads. Unfortunately, upon losing appreciable bone mass in the femur (e.g., tensile arcade), it remains unclear whether an exercise program will be able to restore lost tissue.

Cortical porosity is another layer that defines cortical strength independent of cortical size. Heightened osteoclast resorption expands existing Haversian canals, creating large macropores and leading to the progressive thinning of the cortical tissue that is capable of bearing load. With age, pore volume increases, but pore number remains relatively constant [74]. It is mechani-

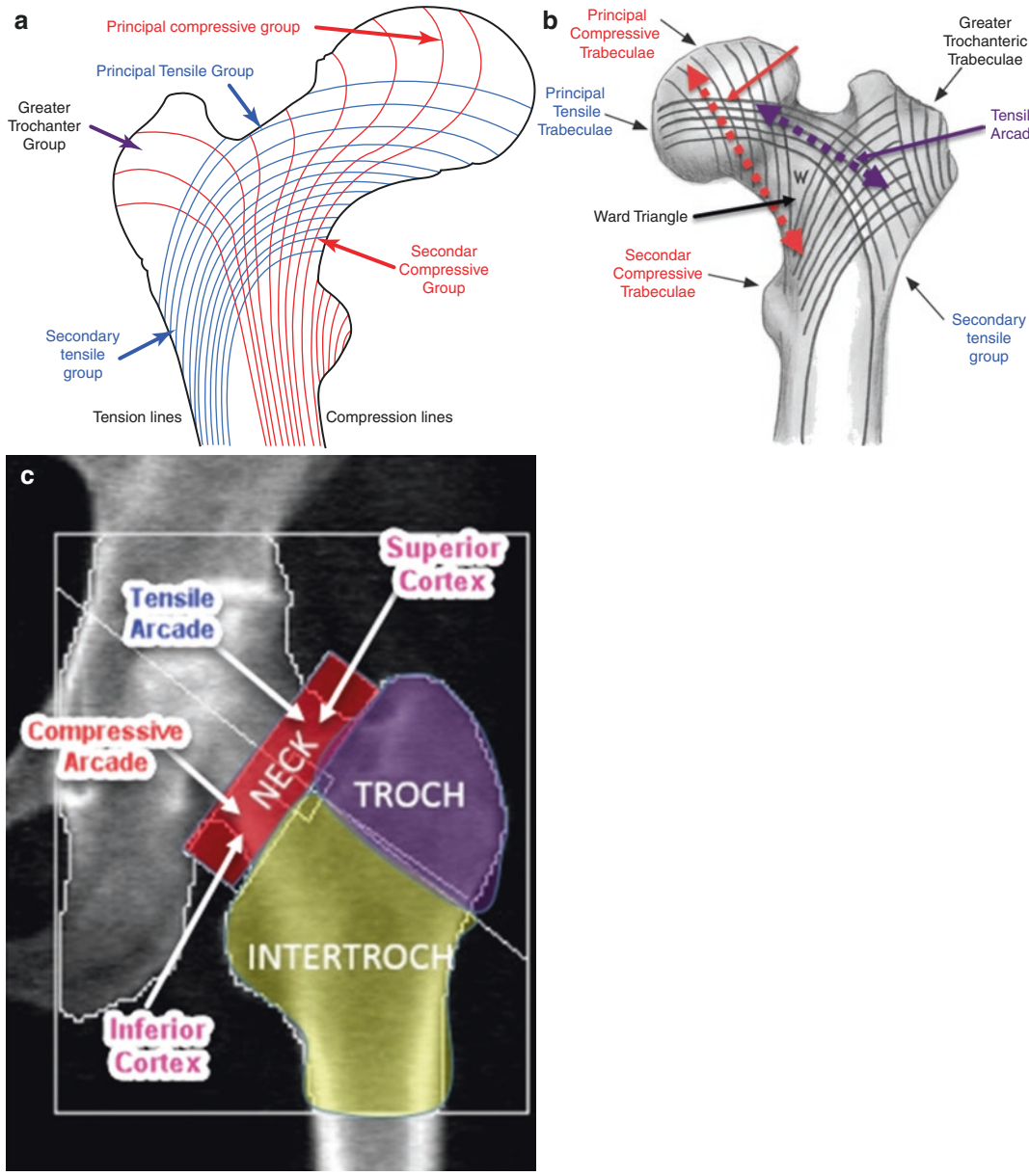

Fig. 9.2 (**a**) Strategic arrangement of cortical and trabecular bone. Trabecular bones are grouped into primary and secondary compressive and tensile groups. (**b**) With standing, the femoral neck experiences compress forces on the inferior surface and tensile forces on the superior surface. Compressive loads are reinforced with a compressive arcade composed of a thickened inferior cortex and an additional trabecular network. The tensile arcade is reinforced with a network of trabecular bone. These reinforcements are combined with lateral and medial cortices that provide additional reinforcements against side-to-side forces. (**c**) The critical aspects of femoral neck strength superimposed onto a hip DXA scan image

cally fortuitous that the resorptive process begins near the endocortical surface. The proximate location of these macropores minimizes the impact on bone strength compared to pores created closer to the periosteal surface [75–77]. Despite this biomechanically favorable location of bone loss, cortical porosity is a strong predictor of fracture especially in the cortical rich area

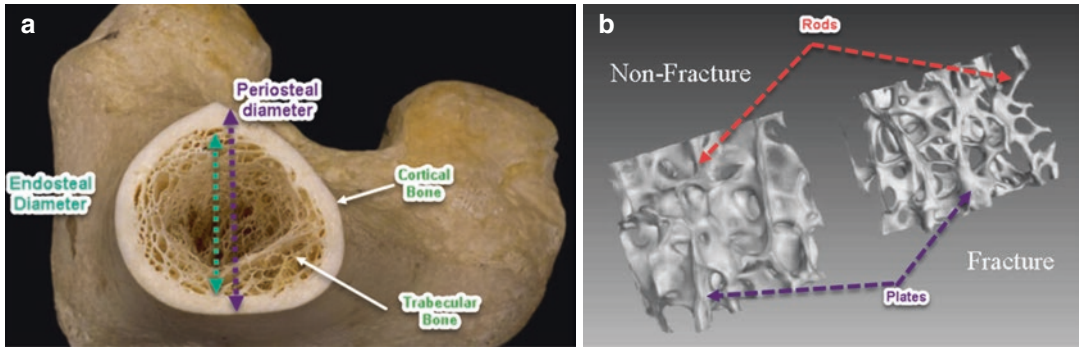

Fig. 9.3 (**a**) Structural characteristics of bone. Bone is comprised of a dense cortical shell that surrounds a spongy trabecular bone network. The periosteal diameter (purple) combined with the endosteal diameter (green) determines cortical thickness. The size of bone along with cortical thickness and porosity significantly contributes to bone strength. (**b**) The inner trabecular compartment contains a network of plates and rods that also contribute to bone strength

of the forearm [78]. Osteoclast resorption and resultant porosity of the trabecular bone surface also contribute to bone fragility.

The term of bone quality became popular in the early 1990s, when paradoxes in the treatment of osteoporosis challenged the generally accepted orthodoxy that bone density itself was the best way to assess strength of bone [69]. Bone quality was originally defined as the factors contributing to strength that are not explained by BMD. From a clinical perspective, this definition provides a name to unexplained factors. Operationally, bone quality is described as an amalgamation of all the factors that determine how well the skeleton can resist fracturing. From an engineering perspective, this definition makes little sense as it does not provide a definable biomechanical pathway linking strength to physical bone traits and ultimately to the underlying biology [79]. The composition of bone, the regular arrangement of collagen, the degree of cross-linking of adjacent collagen fibrils and mineral to protein matrix ratio all contribute to bone quality. The first inkling of the discrepancy between density and strength arose with the use of sodium fluoride to treat osteoporosis. Although sodium fluoride produced large increases in bone mass (and therefore in density), the strength of the bone did not parallel this change [80, 81]. In fact, fluoride made bone more brittle, because it changed the quality of the mineral and rendered it more susceptible to fracturing. High serum fluoride levels increased the vertebral fracture rate despite higher bone density [81]. On the other hand, diseases such as Paget's disease, diabetes mellitus, and osteogenesis imperfecta and long-term use of glucocorticoids contribute to poor bone quality. Another example of decreased bone quality is stress fractures that occur due to repetitive damage. High bone turnover is also another component that leads to poor bone quality. Bone turnover markers have been reported to be predictive of fracture risk that is independent of BMD [82–84]. Clinical tests to assess bone quality are currently being developed but are not available for routine clinical use.

As mentioned earlier, DXA images are a two-dimensional (vertical and horizontal) condensation of a three-dimensional structure. Therefore, bone thickness is not measured in this scan. The BMC measured reflects the amount of cortical and trabecular tissue present within a structure that acts to attenuate the X-ray signal; bones attenuate the signal to a greater degree resulting in a higher gray value and BMC measure. Bone area is a measure of the size of the region of interest (ROI). For the hip, the ROI width is fixed, and thus variation in bone area reflects differences in external bone size. Nevertheless, attempts to correct this size-related problem have demonstrated little additional benefit in predicting fracture risk beyond standard measurement of areal BMD

[85]. Furthermore, the ratio of these two variables provides a measure of the mass density but not a measure of morphology or material properties. Consequently, BMD does not differentiate whether the variation in BMD arises from differences in cortical mass, trabecular mass, or external bone size.

It may be expected that women, uniformly, lose endosteal and trabecular bone in a similar pattern. Recent data however suggest that the pattern of bone loss with aging in women is not uniform [86]. Bone shape and size at the menopause transition may in fact have a critical role in determining long-term bone loss with aging. Women with narrower femoral necks experienced modest decreases in BMC compared to those with wider femoral necks. But, women with narrow femoral necks also had larger increases in femoral neck area compared to women with wider femoral necks. BMD is the quotient of the BMC divided by the area. Because the larger increase in the denominator (area) in women with narrow femoral necks is similarly matched by the larger decrease in the numerator (BMC) in women with wide femoral necks, the result is that both groups have similar losses in BMD over time but for very different reasons. In addition to the previous discussion regarding how most fragility fractures occur in persons with T-scores > − 2.5, this example illustrates another limitation of DXA scanning to accurately predict bone strength and fracture risk [71].

Changes in Density Account Partially for the Decrease in Fractures

Clinical studies showed that the drugs approved for treating osteoporosis prevented fractures better than we would expect from their effects on bone density. The increases in density ranged from about half a percent with vitamin D to over 10% with high doses of teriparatide (Forteo), while the decreases in the risk of vertebral fractures ranged from 23% to 69% (Table 9.2) [87, 88]. Cummings et al. [12, 89], reviewing data from the Fracture Intervention Trial [90], estimated that the change in bone density with alendronate (Fosamax) 5 mg explained only 16% (95% confidence interval 11–27%) of the reduction in spinal fracture risk. With raloxifene (Evista), only 4% of the reduction in vertebral fracture risk is ascribable to the changes in density—96% is unexplained [91].

In a number of clinical trials, antiresorptive drugs of various classes started to reduce the risk

Table 9.2 Modest increases in bone density vs large decreases in fracture risk [data quoted from References 93–100]

Drug	% increase in spinal density (spine)	% decrease in new fractures (absolute reduction)		% decrease in new fractures Relative reduction	
		Vertebral	Nonvertebral	Vertebral	Nonvertebral
Vitamin D	0.4			37	
Calcium	1.7			23	
Raloxifene (more)	2.5	3.5	0.8	35	8.6
Ibandronate		4.9	NA	62	NA
Risedronate (Actonel)	4.5	5	0.4	36	19.7
Alendronate (Fosamax)	6.1	7.1	1.1	47.1	50.8
Zoledronate	6.7	7.3	1.1	70	44
Denosumab (freedom)	5.92	4.8	1.5	67.5	18.8
Teriparatide (Forteo) 20 μg	9.7	9.3	3.5	65.3	52.9

The reduction in absolute fracture risk is defined as fracture incidence in the placebo group minus fracture incidence in the treatment group. The reduction in absolute risk can also be used to calculate the number needed to treat to prevent the occurrence of the event being considered (in this case, the fracture). This is defined as the inverse of the reduction in absolute risk (expressed as a raw value and not as a percentage)

of fractures before the increases in bone density reached their maximum. Raloxifene significantly reduces the incidence of fractures within 6 to 12 months of starting treatment, whereas the maximal increase in spinal bone density of 2% to 3% is seen at 3 years [92]. This type of information further supported the discordance of density and bone strength and underscored the concept that drug therapy affects other factors in bone physiology.

Challenge 3: The Scanning Process

As DXA scan is, an areal, rather than a true volumetric density, as the depth of the bones cannot be taken into account with a single posteroanterior projection. As fracture development depends on factors in addition to BMD (if the patient falls, the nature of the fall, and the patient's response to the fall, besides other determinants of bone quality), it is impossible for BMD techniques to help completely discriminate between patients who have fractures and those who do not. However, the lower the BMD, the more at risk the patient is for sustaining a fracture [101]. Although the ionizing radiation from DXA scanners is low, regulations for ionizing radiation apply to their installation and operation. Dedicated and highly motivated technical staff with appropriate training can ensure proper patient positioning and precise results. However, all centers involved in clinical DXA scanning and interpretation should be aware of pitfalls that may lead to errors in evaluation and both false-positive and false-negative results. These pitfalls are related to (a) the scanner and its software, (b) the technologist and his or her positioning of the patient and analysis of the scans, and (c) various patient-related artifacts.

Proper calibration should be performed to minimize scanner-related pitfalls. Phantoms need to be scanned following the manufacturer's guidelines, typically at least once a week. If significant shifts or drifts are found in plotted and reviewed phantom data, the scanner should be serviced prior to scanning any more patients. Furthermore, all DXA images should be carefully assessed for patient positioning, scan analysis, and artifacts. Common pitfalls in patient positioning include improper centering of the lumbar spine and abduction or external rotation of the hip. In the spine, common analytic pitfalls are related to numbering of the vertebrae, placement of intervertebral markers, and detection of bone edges. In the hip, analytic pitfalls are related to the placement of femoral ROIs and the detection of bone edges. Common anatomic artifacts found on DXA images of the lumbar spine originate from degenerative disk disease, compression fractures, postsurgical defects, and overlying atherosclerotic calcifications. Moreover, some artifacts may be caused by implantable devices such as stents and vena cava filters, overlying gastrointestinal contrast material, lumbar hardware, vertebroplasty cement, and external objects (e.g., piercings, bra clips, and metallic buttons). Anatomic artifacts found on DXA images of the hip include osteoarthritis, heterotopic ossification, and large panniculus. Wallets, keys, coins, surgical hardware, and motion artefact may also be seen. Patient motion results in blurring or irregular contour of the bone margins on DXA images and may affect the analysis [102–104].

Different manufacturers use different edge detection algorithms and analyze different ROIs for evaluation of the hip. Consequently, results from different scanners are not interchangeable. In longitudinal studies, it is vital to use the same scanner and software program. After all, an interpreting physician should treat the DXA image with the same care given to any other X-ray image [105].

Challenge 4: Patient Awareness

A US observational study of women experiencing a first hip fracture between 2008 and 2013 showed that only 17% and 23% had evidence of osteoporosis assessment and/or treatment within 6 or 12 months of their fractures, respectively [106]. Results from a recently published survey of untreated postmenopausal women with osteoporosis and their physicians reported that patients themselves decided against pharmacological

treatment in at least half of the cases of non-treatment.

NOF commissioned a pilot Patient Oriented Value™ (POV) report [107] to investigate how patients valued and prioritized various attributes associated with osteoporosis therapy across the treatment journey, including side effects, affordability, mechanism of action, and cost, in their treatment decisions. NOF first connected with several patient advocacy organizations in the aging and bone health field to review the current process for how value frameworks are developed. The organization then surveyed patients and caregivers about the preferences that drive treatment decisions and persistence to gain a better understanding of the patient-related factors perpetuating the care gap in diagnosing and managing this chronic disease. Some key findings from the survey included the following:

- Individuals at risk for an osteoporotic fracture are primarily concerned that a fracture will trigger loss of the ability to live independently.
- Individuals reporting an unwillingness to consider treatment were overwhelmingly likely to have expressed concern with, or to have experienced, treatment side effects.
- Participants across the risk spectrum for an osteoporotic fracture identified dual mode of action, i.e., having both anabolic (bone building) and antiresorptive (slowing bone breakdown) capability as the most desirable attribute of a treatment. Interestingly, participants said low out-of-pocket cost was the attribute least likely to drive their treatment decision.
- Formulation and dosing frequency preferences were unexpectedly divergent, underscoring the importance of ensuring that individuals at greatest risk of osteoporotic fracture have sufficient options to enable access to a treatment to which they will adhere.

The Patient Oriented Value™ (POV) report underscores the importance of patient-centered care in determining value of treatment, particularly when value analyses are used to determine who gets access to particular treatments. Patient information is a key component of effective self-management [108] and specifically in relation to osteoporosis and fracture prevention. Information and education interventions have been shown to improve outcomes including health-directed behaviors and positive as well as active engagement in life, skill and technique acquisition, social integration, and support [109]. Patient education centers on the assumption that patients who are better informed about their condition and management will be more likely to adopt positive health behaviors [110] and will therefore improve, maintain, or slow deterioration of their health status [111]. However, this viewpoint of patient education does not acknowledge the role of patient opinions and choice and implies that health professionals set the education agenda and define optimal health behaviors [112].

Patients are often dissatisfied with the information they receive from health professionals. A recent national survey of 1088 supporters of the National Osteoporosis Society (NOS) rated "easy access to information from health professionals" as the number one research priority for osteoporosis and fracture out of 40 domains [113]. The focus groups that preceded this survey emphasized the importance, yet the relative lack, of information given by healthcare professionals early on in the participant's pathway, e.g., at time of diagnosis, and in ongoing consultations with primary care clinicians [114].

A recent review [115] has been carried out aiming at understanding the information needs of patients with osteoporosis and/or fragility fractures in order to refine research questions in this area, which is a priority for patients. The findings illustrate that one size does not fit all with a wide range of needs and preferences regarding information, as might be expected. However, the finding that core information needs prevail regarding the nature of osteoporosis, including the relationship with aging and pain, the purpose of drug treatment, and the nature of non-pharmacological treatment, is of concern. A number of barriers were identified, including the perceived knowledge and attitudes of health professionals, the

context in which information is given, and the nature of resources supporting information exchange. Finally, it was revealed that unmet information needs can have far-reaching consequences in terms of adherence to treatment, relationships with health professionals, and augmenting the physical and psychosocial morbidity associated with the condition.

In an earlier study, Wluka et al. conducted an extensive review of health information needs across a range of musculoskeletal conditions [116]. Outcomes revealed that, in concordance with osteoporosis patients, people living with rheumatoid arthritis and osteoarthritis also want to know more about the nature of the condition. Osteoporosis and osteoarthritis are often got mixed up as a process of aging. However, the results of the work illustrated the negative impact on engagement with treatment if patients (and/or their clinicians) attribute their condition solely to aging [116, 117]. The finding that fracture risk assessments were questioned aligns with large multicenter epidemiological study that demonstrates that postmenopausal women most at risk underestimate their own fracture risk [118].

Other factors identified influencing whether information needs are met include the observation that some reported health information were too complex for some patients to understand, indicating low health literacy, which is likely to be a major contributor to unmet need. Health literacy is defined as the personal characteristics and social resources needed for individuals and communities to access, understand, appraise, and use information and services to make decisions about health; in the UK, the majority of patient health information is too complex for 43% of the population who have limited health literacy [119, 120].

Another point to be considered also is the clinicians' perception of osteoporosis and that the disease is not of interest to them. Few qualitative research studies were carried out exploring the perceptions of primary care providers regarding osteoporosis, but the limited evidence available does suggest that the condition may carry a low priority when compared to other long-term conditions such as cardiovascular disease [121] and that these clinicians may have their own educational needs regarding osteoporosis [122]. Furthermore, research with primary and secondary care clinicians suggests they underestimate the impact of the condition on their patients [123]. Not all the patients' information needs should be met by clinicians or specifically doctors. Former studies reported how people use allied health professionals, e.g., pharmacists and dieticians, their social networks, and other organizations to gain information. Participants expressed great satisfaction with information resources available from third sector organizations such as the Royal Osteoporosis Society (ROS) [114].

How best to improve patients' awareness and communicate fracture risk is not well established; although treatment decision aids which communicate fracture risk have been shown to improve rates of treatment adherence in small studies, they have not been qualitatively evaluated [124–126]. Unique to osteoporosis is the need for more education and support around long-term treatment, to improve communication around the monitoring of the so-called silent disease and the effects of treatment. Also, the information giving in healthcare settings may need to be given a greater priority and be consistent with that given in other contexts. In standard practice, primary and secondary care services might consider the follow-up pathways for these patients and how these pathways are communicated to patients. Organizations and other providers should produce more information leaflets relating to osteoporosis and osteoporosis medication to ensure that material is easily understandable to those with limited health literacy. Online tools can be also helpful and easily accessible [127].

Challenge 5: The Missed Falls Risk Assessment

Estimating absolute fracture risk is intuitively attractive, focusing on actual fractures rather than proxies such as bone mineral density or relative risks of fracture. But it has a fundamental conceptual flaw: fewer than one in three hip fractures

are attributable to bone fragility [128]. Fractures are traumatic events induced by falls, mostly in frail older adults [129].

Incidence of hip fracture in women rises 44-fold from the age of 55 to 85, and the effect of aging is 11-fold greater than that of reduced bone mineral density [130, 131]. About a third of generally healthy people aged ≥65 fall at least once a year [132], and this proportion increases to a half by age 80 [133]. The question "Do you have impaired balance?" can predict about 40% of all hip fractures [134], whereas osteoporosis predicts less than 30%. Aging does result in bone fragility, but without a fall, even fragile hips do not fracture [135].

In spite of its importance in the occurrence of fractures, falls risk assessment is not included in standard measures of osteoporosis/fracture risk assessment. Falls is not included in the FRAX risk assessment tool. This represents a major challenge in the assessment of probability of fractures.

Risk factors for falls are multiple and related, and the likelihood of a fall increases with the increasing number of risk factors [136]. Intrinsic risk factors comprise age-related changes in all components of the sensory, cognitive, and neuromuscular systems related to the control of postural stability, as well as diseases affecting any of these systems, functional and cognitive deficits, and the use of psychoactive drugs. Extrinsic risk factors include the environment or activities that can disturb the postural stability [137]. Because both the risk of falling and the rate of falls can be reduced using management programs or exercises following the application of multifactorial screening tools [138, 139], primary to secondary prevention actions are preferred to reduce the burden of falls in the older population [140, 141].

Fall risk assessment (FRA) methods are an effective, systematic approach aiming at reducing the falls incidence and related morbidity [141–143]. A considerable number of methods are available, most of them have cutoff values for stratification of risk of falling [144]. The most popular falls risk tools are Berg Balance Scale, polypharmacy, Falls Risk Assessment Score, Fall Risk Assessment Tool, Fall Efficiency Scale, and Posturography.

The Berg Balance Scale (BBS) This tools quantifies the dynamic postural stability—a person's ability to control the projection of the body's center of mass over a base of support while transitioning from a dynamic to a static state [145]. The BBS is composed of 14 items covering functional tasks common to everyday life; each item is categorized on an ordinal scale according to the degree of difficulty: 0 (unable to perform the task) to 4 (performs the task independently) [146]. The participants were classified as high (0–46 points) or low (47–56 points) risk of falling (sensitivity = 88.2%, specificity = 76.5%) [147].

Polypharmacy, i.e., the concomitant use of more than five drugs of classes benzodiazepines, antidepressants, antipsychotics, and antiepileptics [148], was used to classified the participants as at high (≥5 medications) or low (<5 medications) risk of falling (sensitivity = 49%, specificity = 67%) [149].

The Falls Risk Assessment Score (FRAS) is a questionnaire containing five questions that addressed clinical variables that were easily evaluated in the clinical practice. FRAS ranges from 0 to 6.5 points, with higher scores indicating a greater risk of sustaining a fall. The score for each item was >1 fall in the last 12 months ("yes" = 2); slow walking speed/change in gait ("yes" = 1.5); loss of balance ("yes" = 1); poor sight ("yes" = 1); weak hand grip ("yes" = 1); and age (0.02 per year increase from 60 years old). Participants were classified as at high (>3.5 points) or low (≤3.5 points) risk of falling (sensitivity = 96.2%, specificity = 86.0%) [150].

The Fall Risk Assessment Tool (FRAT-up) expresses the probability of falling in 12 months [151]. The FRAT-up questionnaire contains 28 items, with the possibility of leaving blank fields because it embeds prevalence information on individual risk factors [152]. The risk factors considered herein to estimate the FRAT-up were rheumatic disease, Parkinson's disease, use of sedatives, living alone, suffering any pain, use of a walking aid, dizziness or unsteadiness last year, urinary incontinence last year, use of antiepileptics, history of previous falls, fear of falling,

history of previous strokes, sex, use of antihypertensives, diabetes, number of drugs used by the participant, age, and hearing impairment. The reported accuracy was 64.2% [152]. Due to the lack of reported cutoff point, the value of FRAT-up is >0.31 (considering the embedded prevalence for all the factors of the model) as high risk of falling and low risk of falling otherwise.

The Falls Efficacy Scale (FES) measures the concern for falling when performing activities of daily-living indoors and at the community level [153]. We used the Portuguese-Brazil version of the FES-I instrument, which has both high internal consistency (Cronbach's $\alpha = 0.93$) and reliability (ICC = 0.84 to 0.91). The questionnaire assesses the concern about the possibility of falling when performing 16 activities, each with scores of 1–4. The cutoff point was 23 points or more to discriminate participants at high or low risk of fall (sensitivity = 47%, specificity = 66%) [154].

Posturography quantifies the static postural stability—a person's ability to control the projection of the body's center of mass over a static base of support [146]. Signal acquisition was performed using one Wii Balance Board (WBB) portable force platform (Nintendo Company Limited, Japan) controlled by a custom-built software (Lab-VIEW 2014, National Instruments, USA). WBB is a valid and reliable instrument to assess static postural balance in elderlies [155]. The protocol followed international recommendations for posturography [156]. The experiment consisted of trials of static postural tasks characterized by feet apart or together and eyes open or closed, summing up four trials.

Posturography data was processed for regularization of the sampling frequency, downsampled to 50 Hz, and truncated to 55 s to increase the accuracy of the calculated variables [157]. We used the cutoff value for classifying fallers and non-fallers using the Romberg quotient, calculated as the ratio between eyes closed and eyes open values [158] of the anteroposterior range of center-of-pressure displacement. The chosen cutoff value discriminates between prospective non-fallers and prospective single fallers without a 6-month fall history using signals acquired from two WBB (high risk: RQ AP range <1.64); sensitivity = 81.8%, specificity = 59.6%) [159].

However, while falls are common and increasingly recognized as a leading cause of disability and mortality [160–162], little attention is given to assessment of fall risk when bone density is being measured in older individuals. This is important because if bone density alone is used to determine fracture risk, another potential major determinant of fracture, i.e., fall risk, is being overlooked. Indeed the importance of considering falls and osteoporosis management together in fracture risk assessment and prevention has been highlighted in England and Wales by the National Service Framework for Older People [162]. Earlier studies [163, 164] revealed that both bone density and fall risk could be easily measured in women referred for open access bone densitometry [165]. Using simple screening tests for falls is essential to determine fracture risk in older people. Subsequent management to reduce fracture risk should be individualized for each patient.

In conclusion, there is a gap between clinical knowledge in osteoporosis and its application in the standard practice. Notwithstanding its high prevalence, osteoporosis is often underdiagnosed and undertreated. Moreover, even when the diagnosis is made and the decision is taken to treat, there are remaining challenges in implementing therapy for osteoporosis. This chapter reviewed several challenges to osteoporosis diagnosis as well as the basic principles of bone biomechanics aiming at advancing clinical management of fragility fractures and improving bone quality.

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Best Practice Recommendations for DXA Scans and Reports

10

Yasser El Miedany

Introduction

Bone mineral density (BMD) testing is a key component in the management of patients with osteoporosis. Dual-energy X-ray absorptiometry (DXA) is a quantitative radiological procedure for measuring the bone mineral density (BMD), a major determinant of bone strength (1). Indeed, assessing BMD by DXA is a component of osteoporosis treatment guidelines in several countries all over the world [3–6]. However, DXA measurements are used not only to diagnose osteoporosis but also to monitor changes in BMD over time and estimate fracture risk and are often integral to therapeutic intervention recommendations. The World Health Organization (WHO) has established DXA as the best densitometric technique for assessing BMD in postmenopausal women and based the definitions of osteopenia and osteoporosis on its results. Furthermore, current guidance on fracture risk assessment adopted by the WHO (the fracture risk assessment algorithm (FRAX)) [7] includes femoral neck BMD measurement by DXA as an important risk factor input for fracture risk probability assessment. DXA also has applications beyond BMD testing (Table 10.1), including vertebral fracture assessment (12), analysis of body composition (13), hip structural analysis (14), and trabecular bone score determination (15). Furthermore, physicians rely on DXA measurements to manage patients with skeletal disorders.

Poor quality DXA acquisition/analysis and/or incorrect reporting of the results may result in the ordering of unnecessary diagnostic procedures, failing to order the required tests, or inappropriately starting, stopping, or changing treatment. Such errors in clinical practice are unfortunately common, sometimes costly, and potentially harmful to patients (16–21). DXA scans in growing children and adolescents are particularly challenging, and errors are common with respect to both data acquisition and interpretation (22). These errors can lead to the inappropriate initiation of therapeutic agents, many of which have unknown side effects in pediatric patients, and other inappropriate management decisions.

This chapter will discuss the basic principles of DXA scanning, how to collect local reference data, falls risk, and the role of healthcare professionals (physicians, radiographer, as well as practice and osteoporosis nurse specialist) in the DXA scanning service. It will expand to discuss reporting of DXA scans for both adults and children as well as errors in standard practice. Glossary is included in the chapter including examples of preassessment questionnaires as well as the elements to be considered when reporting DXA scans. The objective is to provide the responsible healthcare professional with suf-

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Table 10.1 Uses of DXA scanning in bone health assessment

Based on BMD measurement	Beyond BMD measurement
Assessment of BMD status and level of bone mineral content (diagnose osteopenia/osteoporosis) Estimate fracture risk Therapeutic intervention recommendations Monitor changes in BMD: Over time In response to therapy Measurement of BMD at multiple skeletal sites	Assessment of vertebral morphometry/vertebral fractures Analysis of body composition Hip structural analysis Trabecular bone score determination Evaluation of bone-prosthetic counterface (assessment of bone around prosthetic implants)

ficient information and guidance so that the most informed management decision can be made.

Basic Principles of DXA Scanning

Basically, DXA is a quantitative radiological procedure for measuring bone mineral density. Several different types of DXA systems are available, but they all operate on similar principles. A radiation source is aimed at a radiation detector placed directly opposite to the site to be measured. The patient is placed on a table in the path of the radiation beam. The source/detector assembly is then scanned across the measurement region. The attenuation of the radiation beam is determined and is related to the BMD [9, 10]. However, based on the fact that DXA scanners use two X-ray energies in the presence of three types of tissue, namely, bone mineral, lean tissue, and adipose tissue, there are considerable errors arising from the inhomogeneous distribution of adipose tissue in the human body [11]. Earlier studies [12–14] suggested that BMD measurement errors are in the range of 5–8%.

DXA technology can measure virtually any skeletal site; however, in standard practice, the clinical use has been focused on the lumbar spine, proximal femur, forearm, and total body [15]. DXA systems are available either as full table systems (capable of multiple skeletal measurements, including the spine and hip) or as peripheral systems (limited to measuring the peripheral skeleton). Because of their ability to measure the BMD at skeletal sites of greatest clinical interest, full table DXA systems are the current clinical choice for osteoporosis assessment. Peripheral DXA systems are characterized by being portable and less expensive than full table systems, yet they are more frequently used for screening and early risk assessment; but they cannot be used to monitor response to therapy. Spine and proximal femur scans represent the majority of the clinical measurements performed using DXA. Most full table DXA systems are able to perform additional scans, including lateral spine BMD measurements, body composition study, vertebral morphometry, measurements of children and infants BMD, assessment of bone around prosthetic implants, small animal studies, and measurements of excised bone specimens. However, for children measurement, the exam should be undertaken by clinicians skilled in interpretation of scans in children in centers that have an adapted pediatric software [16]. A glossary of DXA terminology and common acronyms is provided in Table 10.2 [16].

Best Practice of DXA

Over time, densitometer calibration may change due to degradation of the components (e.g., X-ray tube and detector), moving the instrument to a different location, or a variety of other factors. The skills of a DXA technologist may improve with experience or worsen over time, or a highly proficient technologist may leave and be replaced by one who is less skilled. Similarly, a physician involved may be dedicated to very high DXA quality or may view DXA as a sideline to other responsibilities. For all of these reasons, the reliability of DXA measurements and reports is sometimes in doubt, thereby having potential adverse effects on the management of patients [16, 17, 19].

Table 10.2 Glossary of terminology and definitions used in DXA scanning process

Terminology	Definition
Acquisition	The process of positioning and scanning the patient on the DXA table
Calibration	The process of correcting differences between known reference values and actual measured DXA values
Analysis	Assessing and correcting, if necessary, computer default selections for bone edges, regions of interest, and intervertebral space markers; selecting reference databases; and generating data for interpretation
Artifact	Internal or external factors that can alter the DXA measurements
Fracture risk assessment tool	A validated system for estimating fracture risk in populations
Interpretation	The process of reviewing the images and data of a DXA scan to provide a diagnosis, assessment of fracture risk, and comparison with any previous studies while recognizing limitations, if any, in the quality of the test
Least significant change	The amount by which one BMD value must differ from another in order for the difference to be statistically significant at a 95% level of confidence (i.e., the smallest change in BMD that is statistically significant)
Phantom	A standardized object with known BMD that is measured regularly to assess the stability of DXA measurements
Precision assessment	The methodology of scanning multiple patients more than once that provides the data for calculating the lease significant change
Reference database	Data for mean BMD and standard deviation of a defined population that is used to calculate T-scores and Z-scores
Region of interest	A standardized portion of bone(s) for measuring BMD
Reporting	The translation of data from acquisition and analysis into a clinically useful report
Shewhart plot	A graph for recording serial phantom measurements to determine the stability of the DXA system
Sievert	A derived unit of ionizing radiation dose; 1 Sv = 100 rem (Roentgen equivalent man)
Standard operating procedures	A document that provides necessary information for DXA usage for each DXA facility
T-score	The standard deviation difference between a patient's BMD and that of a young adult reference population
Z-score	The standard deviation difference between a patient's BMD and that of an age-, sex-, and ethnicity-matched reference population
TBLH	Total body less head, assessment of the entire body minus the head region
Certification	Validation that an individual has acquired a basic level of knowledge on bone densitometry
Accreditation of a certification program	Declaration by a neutral third party that the program meets national and/or international standards for development, implementation, and maintenance of the certification program
Accreditation of a DXA facility	A process through which a DXA facility is validated as providing quality bone density tests

In order to compare serial BMD studies on the same device, precision assessment conducted according to well-recognized standards is necessary to calculate the precision error and least significant change (LSC). Precision error is inherent in the BMD measurement itself and is largely dependent on the skill of the technologist in placing the patient in the same position for different scans. Precision represents the reproducibility of the BMD measurement and is typically calculated by measuring BMD in 15 patients 3 times or 30 patients twice on the same day, repositioning the patient after each scan. The least significant change (LSC), a value that is derived from the precision calculation, is the smallest BMD change that is statistically significant with a 95% level of confidence. Unfortunately, many DXA facilities have not done precision assessment, and quantitative comparison of BMD measurements cannot, therefore, be performed. Furthermore, there is often a lack of adherence to manufacturers' recommendations for device maintenance and quality control, and the education and training of bone densitometry technologists and interpreters vary widely. For all these

reasons, mistakes in BMD testing are commonly seen, sometimes with adverse effects on patient care [19].

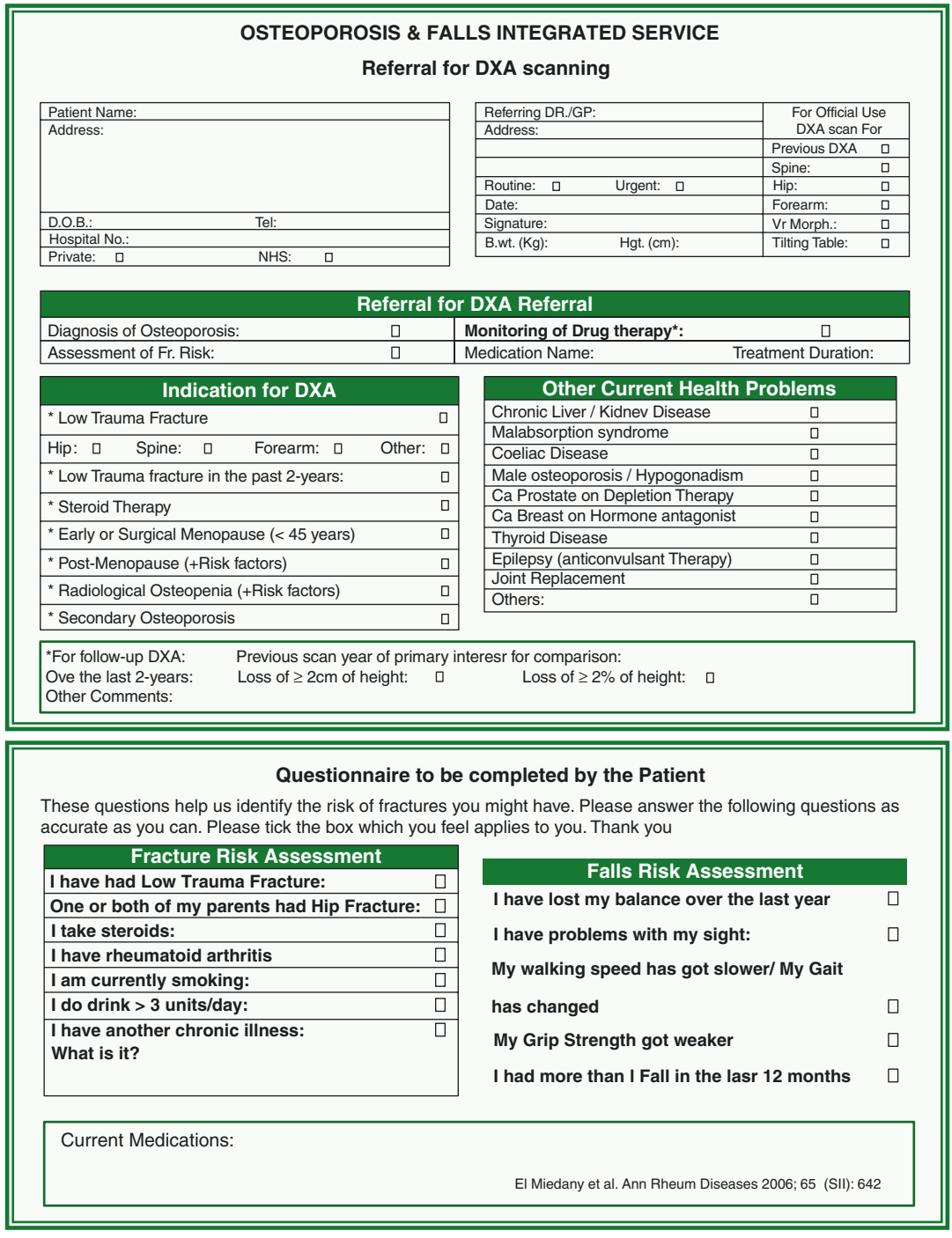
How to Collect Local Reference Data

As the standardization of the diagnosis of osteoporosis is with a single reference database as outlined by WHO criteria, local reference values are primarily valuable for body composition analysis and in younger (pediatric) populations for determining Z-scores. Local reference values can be defined as either "healthy," "representative," or "normal." Unfortunately, there are no standard definitions for these terms. For example, the BMDCS study is a healthy cohort that excluded all children with bone disease, children taking any medications that may affect bone density, children with multiple fractures, etc. [18]. The NHANES III study is a representative cohort of women recruited randomly by postal code throughout the USA, regardless of health status [19].

This guide for obtaining normative ranges was modeled after an investigator's guide used by one of the manufacturers. The number of subjects and the age distributions have been based on statistical justifications. If the investigator deviates substantially from this protocol, statistical power and relevance may be lost, especially if collecting fewer numbers. The following describes the procedures for adult reference data collections. The investigator will need to recruit a minimum of 300 participants for each group desired, separated by sex and ethnicity. For example, adequately describing two distinct ethnic groups for both sexes requires 1200 participants (i.e., 50 subjects for each decade, sex, and ethnicity between 20 and 80 years old). The investigator will also need to capture all biological information. A QC phantom scan needs to be performed at least on the days that the subject is scanned but preferably three times a week to daily. The measurements and regions of interest (ROIs) the investigator acquires are dependent on their needs. If the need is exclusively for bone density, assessment in adults, spine, hip, and forearm DXA is appropriate. For body composition studies, whole body needs to be included. Each site is measured once for each subject, and the results are recorded on the Case Record Form (CRF). The Case Record Form (CRF) can then be sent to a statistician for analysis [20].

Demographics, medical history, and drug therapies should be noted on a completed patient information questionnaire as shown in Fig. 10.1. There is some debate as to the statistical method used to evaluate reference data. The simplest analysis is to calculate a population mean and SD for each 10-year age group. Z-scores can then be generated by comparing a patient's measure to the decade reference values. Others have suggested that a quinquennial analysis of the means offers better resolution for separating pre- and postmenopausal women than other fitting approaches [21]. Regression models can be used to achieve more age resolution and stability in the Z-score values through each decade. Several approaches can be used; nonlinear and piecewise linear models have been used in the past. For a nonlinear model, the measure is plotted against age. The highest order regression (i.e., age, age2, age3) yielding a significant improvement over the next lower order regression model should be considered as the basis for the final reference data equation. Z-scores are then calculated using this equation to generate the measure mean and SD for the patient's age. The SEE is used for the average SD across the entire age range (the SEE is an example of a root mean square error. The SEE tells us something about the accuracy of the predictions). However, this assumes that the distributions around the mean values are normal.

The most sophisticated approach is to take skew into account in the distributions around the mean values. Cole has developed a model and software that calculate percentile curves without assumptions of how normal the distribution is. This method, called LMS, is a fitting procedure that employs three cubic splines to generate centile estimates for age or size-related growth [22]. T. Cole offers a free program to perform this type of analysis (http://homepage.mac.com/tjcole/FileSharing1.html). The L curve, a Box–Cox



OSTEOPOROSIS & FALLS INTEGRATED SERVICE

Referral for DXA scanning

Patient Name:	
Address:	
D.O.B.:	Tel:
Hospital No.:	
Private: ☐	NHS: ☐

Referring DR./GP:	For Official Use DXA scan For
Address:	Previous DXA ☐
	Spine: ☐
Routine: ☐ Urgent: ☐	Hip: ☐
Date:	Forearm: ☐
Signature:	Vr Morph.: ☐
B.wt. (Kg): Hgt. (cm):	Tilting Table: ☐

Referral for DXA Referral			
Diagnosis of Osteoporosis:	☐	**Monitoring of Drug therapy*:**	☐
Assessment of Fr. Risk:	☐	Medication Name:	Treatment Duration:

Indication for DXA	
* Low Trauma Fracture	☐
Hip: ☐ Spine: ☐ Forearm: ☐ Other: ☐	
* Low Trauma fracture in the past 2-years:	☐
* Steroid Therapy	☐
* Early or Surgical Menopause (< 45 years)	☐
* Post-Menopause (+Risk factors)	☐
* Radiological Osteopenia (+Risk factors)	☐
* Secondary Osteoporosis	☐

Other Current Health Problems	
Chronic Liver / Kidnev Disease	☐
Malabsorption syndrome	☐
Coeliac Disease	☐
Male osteoporosis / Hypogonadism	☐
Ca Prostate on Depletion Therapy	☐
Ca Breast on Hormone antagonist	☐
Thyroid Disease	☐
Epilepsy (anticonvulsant Therapy)	☐
Joint Replacement	☐
Others:	☐

*For follow-up DXA: Previous scan year of primary interesr for comparison:
Ove the last 2-years: Loss of ≥ 2cm of height: ☐ Loss of ≥ 2% of height: ☐
Other Comments:

Questionnaire to be completed by the Patient

These questions help us identify the risk of fractures you might have. Please answer the following questions as accurate as you can. Please tick the box which you feel applies to you. Thank you

Fracture Risk Assessment	
I have had Low Trauma Fracture:	☐
One or both of my parents had Hip Fracture:	☐
I take steroids:	☐
I have rheumatoid arthritis	☐
I am currently smoking:	☐
I do drink > 3 units/day:	☐
I have another chronic illness: What is it?	☐

Falls Risk Assessment	
I have lost my balance over the last year	☐
I have problems with my sight:	☐
My walking speed has got slower/ My Gait has changed	☐
My Grip Strength got weaker	☐
I had more than I Fall in the lasr 12 months	☐

Current Medications:

El Miedany et al. Ann Rheum Diseases 2006; 65 (SII): 642

Fig. 10.1 Template for DXA scan referral form

power transformation of the measured variable, characterizes skewness; the M curve is the median for the measure (e.g., aBMD); and the *S* curve represents the CV (coefficients of variation) of the measure. *Z*-scores and centiles can be generated from the *L*, *M*, and *S* values. To obtain a

Z-score for an individual subject, the following equation is used:

$$Z = \left[\left(\text{Measurement} / M\right)L - 1\right] / \left(L \times S\right)$$

where the measurement represents the result from a DXA scan (aBMD, BMC, PCTFM, etc.) and *L*, *M*, and *S* are age-specific values. Similarly, the centiles for age are obtained using the equation:

$$\text{Centile} = M\left(1 + L \times S \times Z\right)1 / L$$

where *L*, *M*, and *S* are for the required age and sex and *Z* is the standard normal deviate for the corresponding centile (e.g., for the 50th centile, *Z* = 0). Examples of this type of reference data curve are the CDC growth charts (the CDC growth charts are used for children age 2 years and older in the USA) [23] and the children's aBMD and BMC reference data curves by Kalkwarf [18].

Role of Healthcare Professionals in the DXA Scanning Service

The physician in charge The physician who is responsible for supervising a DXA facility, interpreting the DXA results, and signing off on the report must have sufficient training to assure that the data are correct and that interpretation and reporting conform to current standards in the field [38]. Expert opinion recommends providing referring clinicians with precise interpretation of all DXA scan results and subsequent guidance for patient management. Current practice is inconsistent, and guidance may be vague, so that the many specialists (including nurses, GPs, gerontologists, gynecologists, orthopedic surgeons, etc.) who are involved in referring patients for bone densitometry may be unclear as to how best to act on the results. Skills, knowledge about, and interest in the significance of DXA findings and which investigations and interventions are appropriate vary across these different disciplines.

Globally, requirements for training, performing, and interpreting DXA scans by healthcare professionals are variable [24]. Local regulation in the USA does not require any specific qualifications for DXA interpretation [25], despite the important technical aspects of the test. US Medicare regulations only require some qualifications of supervising physicians in independent diagnostic testing facilities [26], but not in hospital facilities or private clinical practices. In Canada, three provinces currently have a requirement for International Society for Clinical Densitometry (ISCD) certification for physicians who are reporting or supervising a DXA facility. In Brazil, certification by the Brazilian College of Radiology and Diagnostic Imaging (Colégio Brasileiro de Radiologia e Diagnóstico por Imagem) is required for any physician to perform DXA acquisition, analysis, and reporting.

Many scans are reported by registered healthcare professionals (e.g., radiologists, radiographers, physicians, nurses, etc.), whether medically qualified or not, who may not have direct experience in the management of osteoporosis and metabolic bone disease. Furthermore, many reporting healthcare professionals have not had formal training in DXA methodology or image interpretation and do not themselves operate a scanner. They therefore need to be made aware of the subtleties of interpretation; the significance of artifacts and abnormalities; and the importance of correct positioning when comparing scans [27]. In addition, there may be a need to make the referrer aware of other factors in the patient's clinical history that may modulate the patient's fracture risk or that may influence the application of clinical guidance or the necessity for further investigations or follow-up scans. Hence, there is a need to identify and address the educational and training needs of healthcare professionals in this area and for a standard to be established to set the learning outcomes.

Practice nurses and general practitioners In the primary care setting, practice nurses play an essential part in the delivery of quality primary care, and due to the increasing shift of care from acute to primary, they have a growing responsibility in management of long-term conditions including osteoporosis. Effective fracture preven-

tion is best addressed via a whole system response to the challenge of identifying fragility fractures. Practice nurses and general practitioners are well placed to identify fragility fractures, assess patients for osteoporosis, treat them, and monitor their adherence to treatment, thereby preventing further disabling and costly fractures. The role the practice nurses in the primary care setting was outlined by the royal osteoporosis society [28].

Identifying patients at risk of osteoporosis is one of the tasks that can be handled by practice nurses, who can screen patients for risk factors for osteoporosis, including family history, low BMI, coeliac disease, rheumatoid arthritis, smoking, or heavy drinking. Similarly, with the relevant knowledge, practice nurses can identify patients treated with medications that put them at greater risk of osteoporosis such as steroids, antiepileptic drugs, as well as hormone antagonist/depletion therapies used for breast cancer treatments such as aromatase inhibitors and prostate cancer drugs. Similarly, practice nurses and general practitioners can play a part in low-trauma fracture prevention by identifying all people over 50 years of age with a fracture in their practice and referring them to a fracture liaison service (FLS) for osteoporosis assessment. This should include all fragility fractures excluding face and skull. If a practice nurse sees a patient who has had a fragility fracture after the age of 50 who has not had a DXA scan or an assessment for osteoporosis, then this should be flagged up for consideration. The general practitioner or practice nurse can conduct both an online FRAX assessment and a dietary assessment for calcium intake, refer the patient for a DXA scan if appropriate, or start bone-sparing medication. Where the patient is complex, and where oral treatments have not been tolerated or successful, they can be referred to rheumatology or the local fracture liaison service (FLS).

Furthermore, practice nurses can play a vital role in the identification of osteoporotic vertebral fractures in primary care where most vertebral fractures will present as acute onset back pain with no obvious trauma. Without an assessment for osteoporosis, these fractures are otherwise easily missed. Action to identify and treat vertebral fractures by the practice nurse can quickly modify the patient's risk of future debilitating fractures. If a practice nurse reviewed a patient with risk factors for osteoporosis, acute onset of back pain, and no obvious trauma and/or loss of height or receives a CT/MRI or X-ray report that highlights a vertebral fracture, then it should be highlighted to the GP as a matter of priority for assessment. The patient should be sent for a DXA scan.

Lastly, follow-up of all patients to check adherence to treatment is central, both to achieving best practice standards and realizing the clinical and cost benefits of fracture prevention. Practice nurses are well placed to do this, especially for complex patients and where there is no fracture liaison service (FLS) in place. Patients will benefit from a good working relationship between their practice nurse and the local osteoporosis service or fracture liaison service (FLS).

On the other hand, setting up specialized nurse-led osteoporosis in the hospitals/secondary care was also reported to be of value for rapid assessment and management of patients living with osteoporosis, particularly those who sustain acute fractures. An earlier study revealed that adopting specialized nurse-led osteoporosis vertebral fracture service identified patients at risk, allowed for accurate diagnosis, and shortened the time of assessment and management [29].

Radiographers

Radiographers working as part of a DXA service should have a robust knowledge of the DXA scanning techniques, risks, pitfalls, as well as national guidance for best practice. Furthermore, radiographers are required to bring particular skills to DXA and osteoporosis services. In addition to acquiring images, they have a responsibility for safeguarding adults and children. Some patients present with special requirements such as mobility difficulties; therefore, radiographers need to understand the principals of safe manual handling to protect themselves and others. DXA services may be provided in remote or mobile

locations, and radiographers should understand the challenges presented by lone working in terms of the safety and well-being of themselves and their patients [30].

A DXA scan generally takes 15 to 20 minutes, with the standard World Health Organization (WHO) recommended sites for measurement being the lumbar spine, unilateral or bilateral proximal femoral, and, in some cases, the forearm [31]. The use of DXA vertebral fracture assessment (VFA) scans provide a low-dose visual assessment of vertebrae from the fourth thoracic vertebra (upper spine) to the level of the fourth or fifth lumbar vertebra (lower spine) for fractures in patients meeting scan criteria [32, 33]. Since a much lower dose of ionizing radiation is used for VFA scans in comparison to thoracolumbar spine radiographs, these scans can be undertaken on those who present clinical risk(s) for osteoporosis, even in the absence of a strong clinical suspicion of fracture [34].

Consistent positioning and technique are of particular importance in DXA to ensure reproducibility, accuracy, and precision for patients having follow-up scans. Radiographic positioning is a tactile skill, and radiographers should be aware of consent [35] and chaperone [36] policies and procedures. Practical aspects of the exposure such as pillow height and patient leg height as well as post processing techniques all influence the diagnostic result. Radiographers need to understand avoidable and unavoidable artifacts and the impact these may have on BMD. From time to time, DXA images may demonstrate incidental findings that require action. Radiographers should view the DXA images and should have the knowledge, skills, and competence to follow the correct procedure for communication of findings in accordance with the reporting standards [37].

Falls Service

Falls and osteoporosis go hand in hand to result in fractures, and as such, a falls prevention agenda needs to be high on the priority list for the healthcare professionals dealing with bone health issues as well as service managers. Tendency to fall has been identified as a predominant non-skeletal predictor of fragility fractures in the elderly [38]. It has been reported that about 90% of hip fractures involve falls [39]. Kaptoge et al. [40] found in the prospective multinational European Prospective Osteoporosis Study (EPOS) that BMD appeared to be less important in explaining variations in incidence of upper limb fractures in women across diverse populations in Europe, compared with the effect of location-specific risks of falling and factors that may be associated with the likelihood of falling. The nature of the fall likely determines the type of fracture, while bone density and factors that increase or attenuate the force of impact of the fall determine whether a fracture will occur when a faller lands on a particular bone [39]. The majority of falls in old age likely result from a combination of factors relating to aging and poor health, such as decrease in muscle strength and function, gait disorders, and loss of balance [41]. Epilepsy, use of seizure medication, Parkinson's disease, and wearing corrective lenses are factors that tend to be associated with increased risk of pelvis fracture in men and women [42].

Identifying frequent fallers and referral to appropriate services is a key addition to the scanning and diagnostic services. Setting up integrated "Osteoporosis and Falls" services would help to manage those patients at high risk of falls and prevent further fractures [38]. Making every contact count (MEEC), which is an evidence-based approach to improving people's health and well-being by helping them change their behavior, can be used as a framework to underpin the bone health service [44]. Identifying falls risk factors, early in the management pathway, help protecting them and preventing further falling over. Patients can be screened for falls risk. Several questionnaires have been developed and are available [45, 46]. As a result of widening the focus in fracture prevention to include both osteoporosis and falls, some centers implemented a combined fracture and falls risk in one referral form for DXA scanning [47], which would also be included in the DXA scan reporting as recommendations for high falls risk management.

DXA Scanning in Standard Clinical Practice

Referring for DXA Scanning

BMD consultation requests should include patient demographics, the indication for BMD testing, factors of relevance to the scan assessment (joint replacement, bone surgery, or bone disease in scan regions), osteoporosis medication history, factors of relevance to fracture risk determination in patients 50 years of age or older (fragility fracture history, glucocorticoid history), and any other pertinent medical information [48–50]. History of recent fractures in the last 2 years is also important to highlight the probability of imminent fracture risk. On referring a patient for DXA, the FRAX® tool should be used to estimate the patient's 10-year fracture probability to decide whether DXA referral would be helpful. Even if the fracture risk is very high, it is helpful to know BMD in order to assess how well the patient is likely to respond to drug therapy and as a baseline to monitor progress. In most cases, it is clinically appropriate and feasible to send a patient over the age of 75 years for a DXA scanning. It is also advisable to include the falls risk as well as the possibility of sustaining an imminent fracture risk [51]. An example of a comprehensive DXA scan referral form is shown in Fig. 10.1.

On follow-up scans done on patients receiving osteoporosis drug therapy, it is particularly helpful if BMD requests indicate the scan year of primary interest for comparison, with details of current osteoporosis drug therapy and duration [52, 53]. While this level of information is often not provided, a thorough patient history from the referring physician is to be encouraged [48–50].

Pre-scan Assessment

DXA is contraindicated in patients for whom it is unlikely to alter clinical decisions, as well as in women who are or might be pregnant. If the patient has received recent radio-opaque contrast material or radioactive compounds, DXA should be postponed until such material no longer represents a potential confounding factor. Calcium supplements should not be taken on the same day before the DXA procedure, as an unabsorbed calcium tablet located in a scanned area might affect the BMD measurement. A patient whose weight exceeds the limit for the DXA table (typically about 130 kg for older instruments; 180–200 kg for others) should not be put on the table in case of damage to the table frame or injury to the patient. Therefore, the patient should be screened before having the DXA scan carried out. Patient questionnaires are usually the best approach for pre-scanning assessment. A template questionnaire that acquires the appropriate information necessary for BMD testing in adults (defined as those 18 years of age or over) is presented in Fig. 10.2. This can either be filled in by the patients while sitting in the waiting area or posted to the patient to be completed either online or paper format [54, 55]. The questionnaire should then be checked by trained facility staff. Alternatively, history can be directly taken by facility staff. The specific items on the questionnaire are intended to collect the minimum information needed to analyze a BMD scan and determine absolute fracture risk in those aged 50 years and over [48, 49]. Additional history items that are of relevance to individual patients should also be collected, such as menopausal history, medication history, and illnesses [42–44].

Reporting DXA Scans

Acquisition and accurate interpretation of bone densitometry scans are necessary first steps towards any clinical assessment process. The DXA report fulfils the role of transmitting data clearly to the clinician. A timely, concise, and informative report is essential to relay the DXA findings and to avoid costly and potentially dangerous misinterpretations by physicians unfamiliar with densitometry data.

Reports generated using the DXA manufacturer's proprietary software have advanced significantly since X-ray-based bone densitometers were

Patient Questionnaire*

Please complete this questionnaire while waiting for your bone mineral density test. This document will be reviewed with you. A staff member will measure your height and weight.

Name: _____ Date: / /20

Date of Birth: / / Female □ Male □

If you answer yes to any of the following 3 questions, please speak to the receptionist immediately:

1. Is there any chance that you are pregnant? Yes □ No □
2. Have you had a barium enema or barium drink in the last 2 weeks? Yes □ No □
3. Have you had a nuclear medicine scan or x-ray dye in the last week? Yes □ No □
4. Have you had hyperparathyroidism or a high calcium level in your blood? Yes □ No □
5. Have you ever had surgery of the spine or hips? Yes □ No □

The following information will help us to assess your personal status.

4. Have you ever had a bone density test before? Yes □ No □

If yes, when and where? ……..

5. Have you had a recent change in your body weight? Yes □ No □

If yes, how many kilograms…….. lost over how many months …….

6. Your height when you were in your late teens or early twenties: ……

7. Have you had a broken bone in the last 2-years? Yes □ No □

Which bone: …… When: ……

8. Apart from any recent fracture in the last 2-years, Have you ever broken a bone? Yes □ No □

Bone Broken	Simple Fall?	If not a simple fall, please describe the circumstances	Age when this occurred

The following information will help us to assess for your future risk of fracture, please tick:

Fracture Risk Assessment	
I have had Low Trauma Fracture:	☐
One or both of my parents had Hip fracture:	☐
I take steroids:	☐
I have rheumatoid arthritis	☐
I am currently smoking:	☐

Fig. 10.2 Template for pre-DXA scan assessment questionnaire

I do drink > 3 units/day:	☐
I have another chronic illness: **What is it?**	☐

The following information will help us assess your risk of falls:

Falls Risk Assessment	
I have lost my balance over the last year	☐
I have problems with my sight:	☐
My walking speed has got slower/ My Gait has changed	☐
My Grip Strength got weaker	☐
I had more than 1 Fall in the last 12 months	☐

7. Have you taken steroid pills (such as prednisone or cortisone) for more than 3 months in the last 12 months? Yes ☐ No ☐
If yes, are you currently taking steroid pills? Yes ☐ No ☐
How long have you been taking them?……What is your current dose?……
What is the reason you take steroid pills?……

8. Have you ever been treated with medication(s) for osteoporosis? Yes ☐ No ☐
If yes, which medication(s) and for how long: ……
……
……

9. Are you currently receiving or have you previously received any of the following medications?

Medications for	Yes	No	For How Long?
Seizures or epilepsy			
Chemotherapy for cancer			
Prostate cancer			
Breast cancer			
Preventing organ transplant rejection			

10. Have you been diagnosed with any of the following conditions?

Chronic kidney disease	Yes	when	comments
Chronic liver disease			
Hyperthyroidism			
Hyperprolactinemia			
Premonpausal amenorrhea (excluding pregnancy)			
Oophorectomy in women under 50-years			
Hypogonadism			
Systemic Lupus erythematosus			
Ankylosing spondylitis			
Paget's disease			
Coeliac disease			
cancer			
Established osteoporosis			

Fig. 10.2 (continued)

11. Have you been treated with any of the following medications?

	Yes	Currently?	If currently, for how long?
Hormone Replacement Therapy			
Steroids over 50mg/day			
Anti-seizure medication			
Tamoxifen			
Raloxifene (Evista)			
Testosterone			
Alendronate			
Risedronate			
Parathyroid hormone			
Zoledronate			
Denosumab			
Calcium supplements			
Vitamin D supplements			

For women only:

12. Are you still having menstrual periods? Yes □ No □

13. Before the menopause, did you ever miss your periods for 6 months or more, besides during pregnancy? Yes □ No □

14. Have you had your menopause? Yes □ No □ If yes, at what age? ……..

15. Have you had a hysterectomy? Yes □ No □ If yes, at what age? ……..

16. Have you had both of your ovaries removed? Yes □ No □ If yes, at what age? ……

*this is a modified questionnaire that has been developed based on the sample provided by the International Society for Clinical Densitometry at http://www.iscd.org

Fig. 10.2 (continued)

widely marketed in the late 1980s. Typically, these reports provide basic patient demographic data and a graphical image of the skeletal scan, as well as numeric data for bone area (BA), bone mineral content (BMC), and bone mineral density (BMD) for each region (and sub-regions). Additionally, the patient's BMD data are compared with reference data derived from healthy controls to generate standard deviation scores: Z-scores represent comparisons with age-matched norms and T-scores comparisons with young adults.

Regardless of the age of the subject, most of the standard software provided by the manufacturer automatically reports both the T-scores and the resulting diagnoses of osteopenia or osteoporosis, as established by the World Health Organization (WHO) [1, 2]. The software-generated reports appear to provide a comprehensive clinical evaluation of the results sufficient to estimate risk for osteoporosis. However, interpretation based solely on these computer-generated reports is inappropriate and often misleading when interpreting the DXA results. It is crucial that the software generated report be modified and supplemented by a formal written report provided by an expert experienced in interpreting densitometry outcomes.

Report Targets

The clinical DXA report has six main purposes (Table 10.3). Typically, the report is sent only to the referring physician. However, some knowledgeable families may also request a copy of the report; therefore, it is best to provide definitions of all technical and clinical terminology used and to provide an objective, non-judgmental review.

Similar to other clinical reports, the technical DXA report has basic elements (Table 10.4),

Table 10.3 Main purposes of the DXA scan report

Expected targets of DXA scan reporting
To present the numeric data in a concise, organized, and easily understood fashion to the referring physician
To provide a rough X-ray picture of the scanned area which would allow identifying any pitfalls of the scanning process
To provide enough technical information to allow for comparison to subsequent DXA studies or to those studies done at other sites
To provide a preliminary interpretation of the findings in a clinical context
To provide estimation of the fracture probability
Recommendations for patient's management

Table 10.4 International Society for Clinical Densitometry (ISCD) guidelines for DXA reporting nomenclature

Measure	Decimal places	Example
BMD (g/cm^2)	3	0.725
T-score	1	−1.7
Z-score	1	−2.1
BMC, spine, or hip scan (g)	2	27.61
BMC, whole-body scan (g)	0	1652
Bone area, spine, or hip scan (cm^2)	2	44.66
Bone area, whole-body scan (cm^2)	0	1850

which include (1) patient demographics, (2) a brief medical history, (3) test results, (4) technical comments, and (5) interpretation and recommendations. Each element will be described in detail below, and data that are typically included in each section are elucidated. The formal report and advice regarding management should be written and signed by a qualified, knowledgeable experienced physician in the field [55].

Demographics

Typically, the report includes basic patient demographics and anthropometrics. Demographics should include patient name, date of birth, gender, healthcare number/hospital number or other identifier, height, weight, scan date, report date, name of the referring physician, name of the reporting physician, and BMD facility name and location [49, 50]. Weight and height should be measured at the BMD facility [48, 49]. It is very important to document patient height and weight because DXA measures "areal" and not true volumetric BMD. Neither values reported by the patient nor measurements provided by other medical practitioners should be used, other than in exceptional circumstances where it is not possible to carry out the measurements (such as if the patient cannot stand). If height or weight data were not measured directly by the BMD facility, this should be indicated in the report.

Weight can be measured with either a mechanical or an electronic scale that is medical grade. Facilities are encouraged to use wall-mounted height measuring devices, referred to as stadiometers, and to use standardized positioning of patients. It is also encouraged that three height measurements be made, with repositioning between each measurement, and the average used as the height value. The reason for this is that, just as with bone density quantitation, height measurements have significant precision error and this is minimized by averaging several assessments [56, 57] (in some centers, this height measurement methodology is a recommendation and is not a requirement for accreditation).

The demographic and anthropometric data are helpful in determining if body size is sufficiently above or below the expected range to warrant adjusting DXA results. If warranted, there are a number of recommendations for how to attempt to correct BMD for the size effects [59].

Medical History Used for Risk Determination

The report should include a brief summary of the clinical history relevant to the patient's medical status and the interpretation of the scan. This might include the primary medical diagnosis; history of low-trauma fractures, particularly in the last 2 years; history of underlying medical condition or the use of medications known to affect BMD (e.g., antiepileptics and glucocorticoid therapy); mobility status and falls risk; endocrine abnormalities; pubertal status; surgical-induced menopause; bone age; and fam-

ily history of osteoporosis [48, 49]. Physical activity level, dietary history, and use of vitamin or mineral supplements may also be useful.

Clinical information included in the referral form for DXA scanning improves both the acquisition and the interpretation of bone densitometry. Ideally, the relevant patient's medical history should be obtained and recorded directly from the referring physician. This would be ideal when there is a local bone health service set up. Ideally, there should be an agreed referral form for DXA scan service (e.g., that shown in Fig. 10.1) [58]. The form should include (1) the reason for referring (e.g., for diagnosis of osteoporosis or monitoring of therapy); (2) indication for DXA scanning; (3) other health problems/medications that might affect the patient's bone mineral density; (4) the main items of fracture risk score (e.g., FRAX) highlighting which fracture risk does the patient have; and (5) the patient's falls risk. This will facilitate the process of reporting and assessment of the patient's probability of having another fracture. However, in several occasions, patients are referred for bone densitometry assessment from a variety of clinical departments not familiar with the request form, and pre-scanning relevant medical history may not be readily available. Consequently, a registration questionnaire should be ready at the time of the DXA procedure to be completed by the patient. The technician should review the questionnaire paying attention to details surrounding fracture history, medication and supplement usage, and family history of osteoporosis.

If, for some reason, the questionnaire cannot be adequately completed at the time of examination (e.g., because of a language barrier or difficulty to read or hear), the form can be faxed/emailed to the referring clinic for completion by a qualified staff member familiar with the patient after the DXA procedure is completed.

Test Results

Care must be taken in all technical aspects of how scanning is performed, including adherence to manufacturer protocols, proper positioning, subregion assignment, bone tracing, determination of regions of interest, and quality assurance [49, 50, 59]. A minimum of two skeletal sites should be scanned and reported. The usual sites would be the lumbar spine and the proximal femur [60].

For each skeletal site that is assessed, BMD, BMC, T-score, and Z-score should be included. The ISCD currently recommends calculating T-scores using a uniform sex-matched (white) young adult database for patients of all ethnicities in the USA, recognizing that other countries might use alternative databases according to local requirements [61]. Regarding Z-scores, the ISCD recommends databases that are matched for sex, ethnicity, and age. Although there is no established standard for using or not using weight adjustment for Z-scores, the evidence seems to favor not using weight adjustment [62].

For each skeletal site with a valid scan, reported density results should include absolute BMD (in g/cm^2 to 3 decimal places) and either T-score (to one decimal place) for those 50 years or older or Z-score (to one decimal place) for those under 50 years of age [63] (Table 10.4). For women, T-scores and Z-scores should be derived using the manufacturer's white female reference database. Similarly, for men over age 50 years, T-scores used for diagnostic classification should be derived using a white male reference database; the femoral neck T-score used for risk determination should be derived from a white female reference database, while the spine T-score used to alter the risk category from low to moderate if the value is ≤ -2.5 should be derived from a white male reference database. For men under age 50 years, Z-scores should be derived using a white male reference database. The reference databases and versions should be specified in the report [62].

When analyzing the lumbar spine, L1–L4 should be used unless the decision is made to exclude one or two vertebrae because of technical artifacts. A minimum of two vertebrae should be used. Interpretation should not be based on a single vertebra [49, 59]. If a report includes graphical representation of results, the graph must present data and reference curves for the vertebrae, actually, used in interpretation.

Consideration can be given to excluding a particular vertebra if the T-score of that vertebra is more than one standard deviation greater than the T-score of the vertebra with the next highest value [64]. It is not mandatory that a high-density vertebra be excluded, but it should be evaluated for causes of artifact and a decision made as to whether it should be retained in the vertebral analysis.

For the proximal femur, the left side should be measured unless it is not available and invalid or the right hip was previously measured [49]. Results should be reported for the total hip and femoral neck. If either the spine or hip site is not available or invalid because of artifact, another body site should be substituted. The non-dominant forearm is the site of choice, and the one-third (or 33%) radius should be reported [59]. If the non-dominant forearm is not available or is invalid, the dominant side may be used. If the wrist cannot be measured, total body BMD can be assessed. The head may be included or excluded when analyzing the scan. If the head is excluded, this should be noted in the report. If the spine cannot be measured, and neither forearm nor total body measurements are available, bilateral hip measurements may be made. The two hip measurements should be reported separately, not as an averaged value [64]. When applying hip data to determine the diagnostic category or fracture risk category, the lowest of the relevant values from the two sides should be used. For patients whose weight exceeds the limit of the DXA equipment, bilateral forearm studies may be done unless one side is not available or invalid, although it will not be possible to determine fracture risk [63, 64].

Technical Notes

The report should consider future DXA scanning and allow comparisons with previous and future densitometry studies. Therefore, it should include sufficient information regarding how the DXA was performed and interpreted. Given the fact that there are intrinsic differences between the variable DXA scanners, and the software used for BMD assessment, the manufacturer and model of the instrument should be specified (e.g., Hologic Delphi A/Lunar iDXA). Similarly, the software mode used to acquire and analyze the scan should also be provided (e.g., auto low-density, low-density spine [LDS] software). If the reference data used in the calculation of Z-scores were different from the manufacturer's normative data, it is important that this also be documented.

Careful visual review of each scan, prior to the preparation of the report, should be considered to ensure that artifacts do not affect the data recorded (Fig. 10.3). The report should outline any technical matters encountered during the scanning process. Documentation is important, both for the initial interpretation of the DXA scan and to alert the DXA technologist to these effects in future scan acquisitions. These might include noticeable scoliosis, degenerative disease, vertebral compression fractures, or nonremovable metal artifacts (Table 10.5). Scans with motion artifacts or removable metal objects (e.g., metal from the underwire or clasp of a bra, a belt buckle, a pant zipper, or a belly button ring) should not be reported. These scans should be repeated before the patient leaves the clinic [65].

Diagnostic Category

The diagnostic category is determined using the lowest T-score (for individuals 50 years of age or older) or Z-score (for individuals under 50 years of age) from the available results for the lumbar spine, total hip, femoral neck, one-third (or 33%) radius, and total body (2). The trochanteric region and Ward's region of the proximal femur are not to be used (16). T-scores or Z-scores for diagnostic categorization should be derived using a white female reference database for women and a white male reference database for men. The original WHO criteria are stated in Table 10.6.

The WHO criteria should not be applied to other bone density measures, including QCT of the spine or hip, peripheral densitometry systems using ultrasound, DXA, or other technologies that scan the fingers, metacarpals, or heels [31].

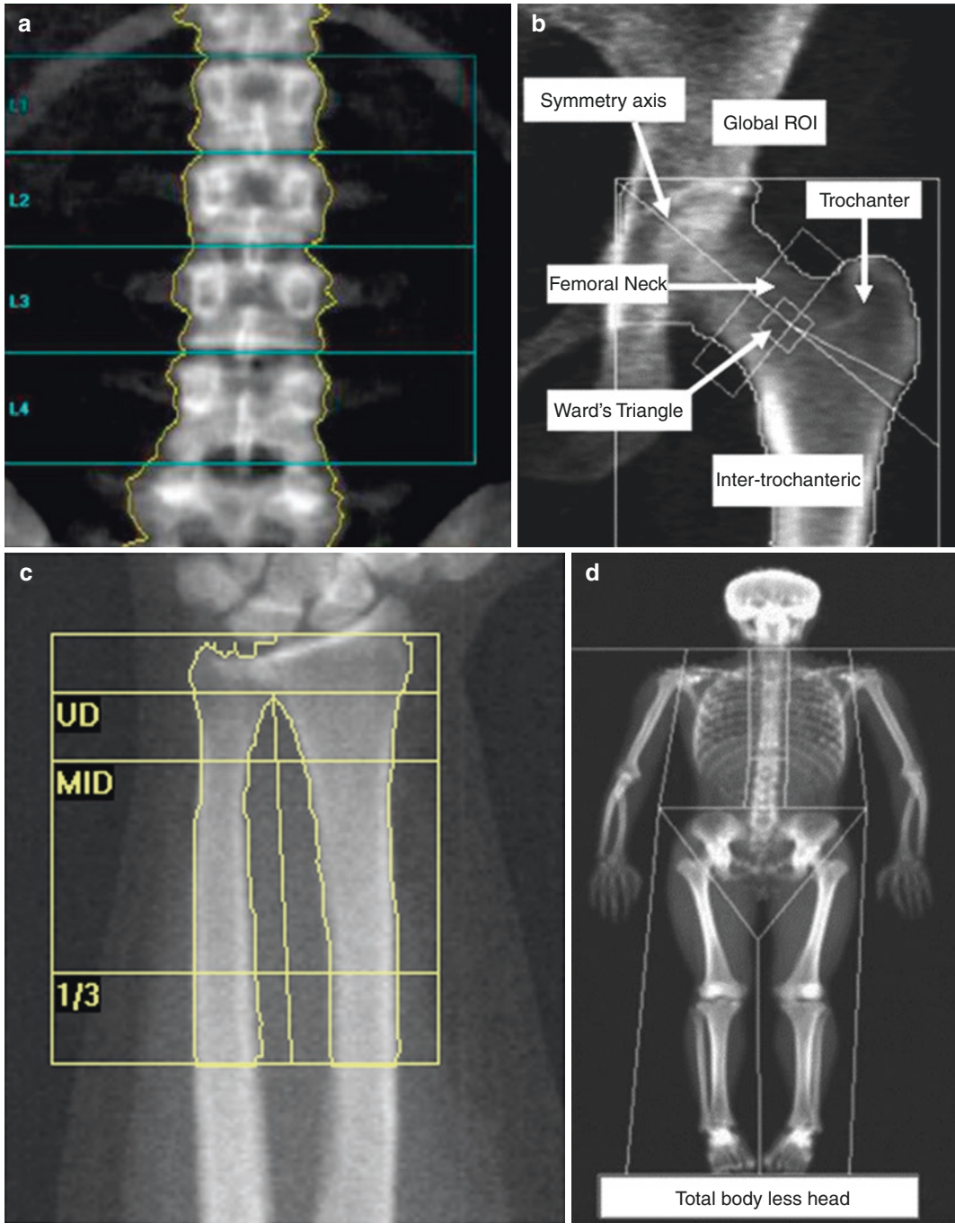


Fig. 10.3 Correct positioning, bony landmarks, and analysis of the L1–L4 spine (**a**), proximal femur (**b**), distal radius (**c**), and total body less head for pediatric age group (**d**)

Fracture Risk

The absolute fracture risk category should be reported for men and women 50 years of age and older. The current WHO guidelines for diagnosing and treating osteoporosis are based on a comprehensive fracture risk model WHO "FRAX." The WHO FRAX algorithm estimates the likeli-

Table 10.5 Examples of technical difficulties noted on DXA scan reports: The presence of artifacts is unavoidable. Familiarity with pitfalls, variants, and recognition of artifacts will lead to better interpretation without erroneous results

Relevant technical matters	
Spine scan	Compression fracture in L1– L4 used for analysis Plate/screws fitted in the lumbar vertebrae/surgical laminectomy Scoliosis in the lumbar region Osteoarthritis noted in L1–L4 used for analysis Aortic calcification, spinal ligament ossification in the lumbar region Previous vertebroplasty in one of the vertebrae Pacemakers
Proximal femur scan	Left hip replacement, right proximal femur scanned Incomplete hip rotation, prominent lesser trochanter
Whole-body scan	Permanent plate/screws in right wrist secondary to fracture Gold crowns on molar teeth
Avoidable artifacts	
Spine scan	Navel ring, pant zipper artifact in L3, L4 Dye from previous scanning
Proximal femur scan	Jeans stud in the rear pocket Metal coin artifact in pocket, interferes with femoral neck
Whole-body scan	Bracelet on left forearm Underwire bra in upper left and right quadrants

Table 10.6 WHO criteria for diagnosing osteoporosis from T-scores [143]. It should be noted that this criterion is exclusively applicable for postmenopausal women and men over 50 and not for younger adults or children

Age 50 years or older		Under age 50 years	
Status	Criteria (T-score)	Status	Criteria (Z-score)
Normal	aBMD is within 1 SD of a "young normal" adult (T-score at −1.0 and above)	Within expected range for age	> −2.0
Low bone mass (osteopenia)	aBMD is between 1 and 2.5 SD below that of a "young normal" adult (T-score between −1 and −2.5)		
Osteoporosis	aBMD is 2.5 SD or more below that of a "young normal" adult (T-score at or below −2.5)	Below expected range for age	≤ −2.0
Severe (established) osteoporosis	T-score at or below −2.5 and one or more fractures		

hood for a person to break a hip or other major bone due to low bone mass or osteoporosis over a period of 10 years. The National Osteoporosis Foundation (NOF) has prepared a clinician's guide to osteoporosis that discusses the details of the FRAX model and the use of fracture risk versus BMD alone (http://www.nof.org/professionals/NOF_Clinicians%20_Guide.pdf). In summary, the major recommendations to the clinician regarding the diagnosis of osteoporosis are outlined in Table 10.7 [66]. The WHO FRAX model is the most common tool used to assess for the fracture risk. Although it was noted that the WHO FRAX algorithm pertains only to individuals that have not been treated for osteoporosis, other studies revealed that in women currently or previously treated for osteoporosis, the FRAX tool can be used to predict fracture probability. Osteoporosis treatment does not annul prediction of fractures. FRAX tool could be of value in guiding clinicians towards the need for continuation or withdrawal of treatment [67].

Interpretation

A narrative section on the interpretation and implications of BMD results should be provided. This should not be a simple restatement of data. The reporting physician should integrate the available information on the patient's specific risk factor, fracture risk probability, falls risk, as well as current medication (when appropriate). Guidance as to therapeutic considerations can also be provided within the context of the local/

Table 10.7 NOF recommendations to the clinician for initiating osteoporosis treatment

For postmenopausal women and men aged 50 and older:

1. Patients should be counseled on the risk of osteoporosis and related fractures
2. Secondary causes should be checked
3. Advice on adequate amounts of calcium (at least 1200 mg/day, including supplements if necessary) and vitamin D (800 to 1000 IU per day of vitamin D3 for individuals at risk of insufficiency) should be given
4. Regular weight-bearing and muscle-strengthening exercises should be recommended to reduce the risk of falls and fractures
5. Patients should be advised to avoid tobacco smoking and excessive alcohol intake
6. For women aged 65 and older and men aged 70 and older, BMD testing should be recommended
7. For postmenopausal women and men aged 50–70, BMD testing should be recommended where there is concern based on their risk factor profile
8. BMD testing should be recommended to those who have suffered a fracture to determine the degree of disease severity
9. Treatment should be initiated in those with hip or vertebral (clinical or morphometric) fractures
10. Therapy should be initiated in those with BMD T-scores <−2.5 at the femoral neck, total hip, or spine by DXA, after appropriate evaluation
11. Treatment should be initiated in postmenopausal women and in men aged 50 and older with low bone mass (T-score −1 to −2.5, osteopenia) at the femoral neck, total hip, or spine and 10-year hip fracture probability ≥3% or a 10-year all major osteoporosis-related fracture probability of ≥20% based on the US-adapted WHO absolute fracture risk model
12. Current FDA-approved pharmacologic options for osteoporosis prevention and/or treatment are bisphosphonates (alendronate, ibandronate, risedronate, and zoledronate), estrogens, and/or hormone therapy, raloxifene, and parathyroid hormone (PTH 1–34)
13. BMD testing performed in DXA centers using accepted quality assurance measures is appropriate for monitoring bone loss (recommendation: every 2 years). For patients on pharmacotherapy, it is typically performed 2 years after initiating therapy and at 2-year intervals thereafter

Physician's guide to prevention and treatment of osteoporosis, National Osteoporosis Foundation, Washington, D.C. (2008) [66]

international osteoporosis guidelines and up to the degree appropriate to the knowledge and experience of the reporting physician [48, 49].

Follow-Up Recommendation

A recommendation should be included for the timing of the next DXA study. The timing of serial testing should be driven by the expected rate of bone loss. The intention of serial monitoring is to provide a sufficient period of time for anticipated changes in density to exceed the precision error of the DXA method, which also renders a stable density informative measure [59].

A guide for the follow-up period is provided in Table 10.8, although this needs to be applied in the context of local recommendations. When indicating recommended timing of the subsequent BMD test, consideration should be given to specifying the year of recommended follow-up rather than a time interval, as this makes the report more readily implementable by referring physicians. For follow-up periods under 2 years, the month of recommended follow-up could also be included.

Limitations

Any structural abnormalities, anatomical variants, artifacts, suboptimal positioning, or other issues impacting on scan reliability and interpretation need to be considered when interpreting BMD results. A judgment needs to be made as to whether these issues render results invalid or impact on the interpretation. Some sources of artifact are preventable, and care should be taken to assess these prior to scanning (such as metal on clothes or in pockets, or recent barium or nuclear medicine studies), either to remove the source of artifact or postpone the scan to a future date. Sources of artifact relevant to the scan should be noted in the report. Skeletal size can affect BMD readings, with larger bones producing falsely high values and smaller bones producing falsely low values [64]. There is no accepted means of correcting for skeletal size, but height or weight outside the normal range should be noted and should be considered in the interpretation of results. Components of the first-time and follow-up adult DXA report are shown in Table 10.9.

Table 10.8 Recommended timing of follow-up DXA bone mineral density testing

Anticipated rate of BMD change	Clinical scenarios	Timing of follow-up
Very high	Moderate to high dose steroids, anabolic agent, hormone antagonist therapy, imminent fracture risk	12 months
High	Osteoporosis drug therapy initiated or changed, low to moderate dose glucocorticoids	1–2 years
Moderate	Therapy with nutritional supplements or lifestyle improvements	1–3 years
Low	Stability documented on nutritional supplements or lifestyle improvements and with no change in clinical status; drug therapy shown to be effective	3–5 years
Very low	Normal results or low fracture risk and no clinical risks	5–10 years

Follow-Up Adult BMD Report

It is common to have follow-up DXA scans requested. This step should reflect the need to have a new scan, which should be also reflected in the repeat BMD report. Consequently, the follow-up adult BMD report should include, in addition to all the components of a first-time adult report, specific new items such as changes in density, statistical parameters relating to measurement error, aspects of interpretation relating density changes to the clinical situation, and definitions relevant to follow-up.

Follow-Up Referral Form

The referral should include the reason for repeating the BMD testing and whether it is to monitor response to therapy or change in the patient's status, e.g., sustaining a fracture. Developing a recent fracture should be highlighted as an imminent fracture risk. Also, the form should include any change in the patient medical status, whether he developed a new medical disorder or taking medication that might affect the bone health status. The

Table 10.9 Main elements of the first-time and follow-up DXA scan report

Components of the first-time adult DXA report
I. Patient and provider information
Patient name
Medical record number
Date of birth
Gender
Scan date
Referring physician
Report date
Reporting physician
Facility name and location
Measured weight, height
Calculated BMI, height, weight
Clinical information
Primary diagnosis
Indications for the scan and other risk factors
Falls history
List of current relevant medications
Inclusion of possible risk factors, including documentation of nontraumatic fractures
History of low-trauma fracture in the last 2 years
Fracture risk probability (without BMD)
Calcium intake or use of calcium supplements
II. Diagnostic category
Test results
Skeletal sites scanned, region of interest (ROI)
BMD in g/cm^2
The T-score and/or Z-score to one decimal point for each ROI
Fracture risk category (if 50 years and over)
Fracture risk probability
Imminent fracture risk
Falls risk assessment outcomes
III. Technical comments
Manufacturer, model of instrument used
Software version
Technical quality of the scans obtained
Limitations of the study (e.g., artifacts, scoliosis)
Reference database used
IV. Interpretation and recommendations
Qualitative assessment of BMD T-score results including specific statements about which diagnostic category the patient falls into
A statement on the fracture risk probability
A note on imminent fracture risk
Interpretation of vertebral fracture assessment scans where performed
Recommendation including general comments as well as the requirement of pharmacological intervention (bone-sparing agent, calcium, and vitamin D3 supplementation + lifestyle advice)
Falls risk assessment outcomes and recommendation of referral to a specialized clinics
Referral to specialist clinic/possible further investigations required
Recommendations for necessity and timing of follow-up DXA scan studies

(continued)

Table 10.9 (continued)

Components of a follow-up adult DXA report
I. Patient and provider information
Patient name
Medical record number
Date of birth
Gender
Scan date
Referring physician
Report date
Reporting physician
Facility name and location
Measured weight, height
Calculated BMI, height, % of weight change
Clinical information
Primary diagnosis
Indications for the scan and other risk factors
Falls history
List of current relevant medications
Date when the patient started current osteoporosis therapy
Inclusion of possible risk factors, including documentation of nontraumatic fractures
History of low-trauma fracture in the last 2 years
Fracture risk probability (without BMD)
Calcium intake or use of calcium supplements
Indication for follow-up DXA scan
Interval fractures, change in clinical status, medications
II. Diagnostic category
Test results
Skeletal sites scanned
BMD, BMC, bone area for each site
BMD T-score and Z-scores for each site
Fracture risk category (if 50 years and over)
Fracture risk probability
Imminent fracture risk
Falls risk outcomes
Changes in BMD
Percentage of BMD change
Percentage in BMD change in comparison to baseline scan, last previous scan, and the results of the scan done just before starting osteoporosis therapy
Statistical significance of BMD change
III. Technical comments
Which previous scans are being used for comparison?
Statement regarding what denotes statistical significance for change in BMD at the center or "least significant change" (LSC)
IV. Interpretation and recommendations
Qualitative assessment of BMD T-score results including specific statements about which diagnostic category the patient falls into
A statement on the fracture risk probability
A note on imminent fracture risk
Interpretation of vertebral fracture assessment scans where performed
Recommendation including general comments as well as the requirement of pharmacological intervention (bone-sparing agent, calcium, and vitamin D3 supplementation + lifestyle advice)
Falls risk assessment outcomes and recommendation of referral to a specialized clinics
Referral to specialist clinic/ possible further investigations required
Recommendations for necessity and timing of follow-up DXA scan studies

referring physician should also highlight if the patient has started taking medication to improve his bone mineral density status and the duration of treatment. Fracture risk probability, without BMD, can also be carried out by the referring physician and recorded in the referral form.

Demographics

Any significant change in height recorded at the BMD facility should be noted. In particular, loss of height exceeding 2 cm over 3 years or less should be emphasized, as this amount of change in height has been shown to have a high predictive value for incident vertebral fractures which might have developed during the monitoring period. Consequently, this may be an indication to do spine radiographs or vertebral morphometry to assess for vertebral fractures [48, 57].

Change in the patient's body weight is another demographic parameter to note, as this may represent an artifactual change in BMD values. Though there is no consensus as to what is the

threshold of change in body weight that can be flagged as being of potential importance as a source of artifact, some physicians suggested the use of percentage change in weight, whereas others recommended the use of absolute change in weight. A suggested threshold is 10% change in weight over the monitoring period. However, each reporting physician must define a weight change threshold and adopt it in all serial reporting, applying it to each pair of BMD measurements for which change in BMD is reported [68].

Fracture Risk Category

All men and women aged 50 years and above should have the absolute fracture risk category reported, regardless of therapy that might be taking. If bone-active drug therapy is currently prescribed and taken by the patient, the fracture risk category should be provided, but the report should include a statement indicating that the risk may be lower than calculated if osteoporosis drug therapy is effective [49, 67].

Changes in Density

Whenever possible, when serial BMD assessments are carried out, it is always preferable to use the same DXA machine. In concordance, it is highly recommended that positioning and subregion assignment must be consistent [59]. Also, the same reference population database should be used for serial studies when possible [64]. If the reference database has to be changed, this should be noted in the report. The description of change in the BMD should include the absolute density change (in g/cm^2, to 3 decimal places) and percentage change (to 1 decimal place) [52]. Percentage change must be derived using absolute density (g/cm^2), not T-scores or Z-scores. An annualized rate of change should be reported, though it may be optional in some locations. The skeletal sites for which changes in density are to be reported are the lumbar spine (using whichever vertebrae are considered valid, with a minimum of two vertebrae) and the total proximal femur (this include neck of the femur and total hip). Other hip sub-regions should not be used. If either the spine or hip is not available, it is permissible to report changes at a single site. If the forearm or total body BMD is being monitored in lieu of the spine or hip, change can be reported for the one-third (or 33%) proximal radius or for the total body BMD. It must be recognized that the change profile at these sites may not be in parallel with changes at the spine and hip and may not correlate as well with drug responses. This will need to be addressed in the interpretation section [69].

Changes in BMD must be reported in relation to (1) the first baseline study on file, (2) the most recent previous BMD study, and (3) the study done closest to the initiation of the current clinical medical management/medication (if any), if this can be confirmed. The latter BMD change is the one of greatest importance for patients on drug therapy; it is also relevant to patients who adopted lifestyle changes and/or started nutritional supplements for bone health. Ideally, the study of primary interest for comparison should be indicated on the requisition by the referring physician, but if it is not provided, the reporting physician is responsible for obtaining this information from the patient's history [52, 64].

On comparison to previous scans, statistical significance must be reported for each BMD skeletal site, indicating whether the difference is considered significant at a 95% level of confidence [50]. The manufacturer's software determination of statistical significance should not be the one to be used (2). Each facility must determine the precision error for each DXA machine and for each skeletal site (including forearm and total body if these sites are measured by the facility and are used for serial monitoring) using the least significant change (LSC) methodology and using this value when determining statistical significance. It is permissible to apply results derived from precision testing on one side (forearm or hip) to serial scans done using the opposite side of the body. A follow-up BMD report should state the least significant change (LSC) in absolute values (g/cm^2 to 3 decimal places) for each skeletal site for which change is reported.

Whenever possible, the same instrument should be used for serial studies on an individual patient. Comparisons between measurements done on different machines can be made only if inter-machine precision between the two devices has been determined [59, 64].

Interpretation

The clinical implications of the change in BMD or fracture risk must be incorporated into the interpretation section of the report [49, 50]. This is of greatest importance for patients receiving osteoporosis drug therapy, where BMD is often being used to assist in monitoring management outcomes. The primary BMD outcome of interest in this circumstance is the net change in density from the time that the current therapeutic regimen was initiated [53].

In general, net gain in BMD is considered positive drug effect while net loss of density is considered as evidence of drug failure. Secondary changes in the BMD profile that may differ from the net change on a drug regimen, such as a change from the most recent prior study, also need to be considered in the interpretation. For serial studies in those not on osteoporosis drug therapies, there are similar implications for the effects of nutritional supplements, lifestyle changes, and exercise regimens [70].

So far, there is insufficient data to define the relationship between the amount of loss in BMD and the resulting change in fracture risk. Rather, the implications of density loss and any changes in the fracture risk probability should be discussed in the interpretation of results. Components of follow-up DXA scan report in adult are shown in Table 10.9.

Table 10.10 Method for adjusting Z-score for bone age or height age

Z-score adjustment for bone age	Z-score adjustment for height age
1. Determine Z-score for all scan sites based on chronological age 2. Perform wrist radiographs and derive bone age 3. Use point estimate of bone age to determine "adjusted birthdate" for patient 4. If bone age differs from chronological age by more than 1 year, change birthdate to "adjusted birthdate" in DXA program and determine adjusted Z-scores for all scan sites 5. Report for all scan sites the Z-scores based on chronological age and the bone age-adjusted Z-scores. If bone age does not differ from chronological age by more than 1 year, this should be noted in the report and a bone age-adjusted Z-score need not be reported	1. Determine Z-score for all scan sites based on chronological age 2. Determine "height age" using growth charts for the child's gender (available at www.cdc.gov/GrowthCharts) 3. Measure height three times and use the average value as patient height 4. Using the patient's height on the vertical axis of the CDC growth chart, locate where this height line intersects the 50th percentile growth curve. Extrapolating to the horizontal axis, determine the age corresponding to the point on the 50th percentile growth curve. This is the patient's "height age" 5. If height age differs from chronological age by more than 1 year, change birthdate to "adjusted birthdate" in DXA program and determine adjusted Z-scores for all scan sites 6. Report for all scan sites the Z-scores based on chronological age and the height age-adjusted Z-scores. If height age does not differ from chronological age by more than 1 year, this should be noted in the report and a height age-adjusted Z-score need not be reported

Pediatric DXA Scanning

The pediatric population is defined as individuals under age 18 years. The components of a first-time pediatric BMD report, in contrast to the adult first-time BMD report, are shown in Table 10.10. In concordance with adults, there are similar components including demographics, machine identification, and limitations [71]. On the other hand, there are differences regarding BMD data and interpretation. This is based on the fact that there are specific definitions which apply to reporting in this age group [72]. There are no guidelines on timing of follow-up studies, so a recommended follow-up date is not mandatory, although may be included at the discretion of the reporting physician. If the referring physician has not relayed the

indications for the scan and the relevant medical history, it is possible to ask the patient, parent, or both to complete a brief registration questionnaire at the time of the DXA procedure. Individual pediatric patient should be collected and may include fracture history, medications, and illnesses. Height and weight measurements in younger children require special devices and procedures. If these are not available, it is acceptable in younger children to use values provided by other medical practitioners. If height or weight were not measured directly by the BMD facility, this should be indicated in the report [71].

Diagnostic Category

For each skeletal site that is assessed, BMD, BMC, and BA (BA: bone area) should be included, as should the corresponding BMD Z-score, to enable the clinician to determine if the measured values are within the expected range for age. BMC and BAs are used to calculate estimates of volumetric BMD (i.e., bone mineral apparent density [BMAD]) and should be included in the report. Reporting BMC and BA also allows the clinician to examine subsequent changes due to bone growth. The current standard for reporting the diagnostic category in the pediatric population is based on the lowest adjusted Z-score from the results for the lumbar spine and total body, using either bone mineral content (BMC) or BMD at the discretion of the reporting physician. The T-score is not to be used in pediatric reporting. If either the spine or total body value is not available or invalid, this should be reported as a limitation. Forearm measurements (one-third or 33% site) may be used if either the spine or total body value is not available, but only if a reference population database is available from which forearm Z-scores can be derived. Proximal femur measurements are not to be used to generate the diagnostic category in the pediatric population, although it may be clinically useful to begin measuring hip density in older adolescents in order to start transition into the adult mode of monitoring [71, 73].

Technical Comments

Care must be taken in all technical aspects of how scanning is performed, including adherence to manufacturer protocols, proper positioning, subregion assignment, bone tracing, determination of regions of interest, and quality assurance. Results should be reported for the lumbar spine and total body, including BMC and BMD for each site. When analyzing the lumbar spine, L1 to L4 should be used unless the decision is made to exclude one or two vertebrae because of technical artifacts [64]. A minimum of two vertebrae should be used. Interpretation should never be based on a single vertebra. If a report includes graphical representation of results, the graph must present data and reference curves for the vertebrae actually used in interpretation. Consideration can be given to excluding a particular vertebra if the Z-score of that vertebra is more than one standard deviation greater than the Z-score of the vertebra with the next highest value. It is not mandatory that the high-density vertebra be excluded, but it should be evaluated for causes of artifact and a decision made as to whether it should be included in the vertebral analysis. In some manufacturers' databases, Z-scores may not be available if vertebrae are excluded. In this circumstance, it is appropriate to include L1 to L4 in order to generate a Z-score, but the interpretation section must address the accuracy of the spine measurement and the ways in which the Z-score may have been perturbed by the abnormal vertebrae. For the total body measurement, the head may be included or excluded on analyzing the scan [72–74]. If the head is excluded, this should be noted in the report. For adolescent patients whose weight exceeds the limit of the DXA equipment, bilateral forearm studies may be done unless one side is not available or invalid, in which case a single side can be measured [71, 72].

For each skeletal site with a valid scan, reported density results should include absolute BMD (in g/cm^2 to 3 decimal places), BMD Z-score (to 1 decimal place), and adjusted BMD Z-score (to 1 decimal place) and BMC (in g, to 2 decimal places), BMC Z-score (to 1 decimal place), and adjusted BMC Z-score (to 1 decimal place) [59].

The Z-score adjustment is done to correct for relative skeletal size or maturation. There is no consensus at this time as to the specific adjustment that should be made, so the nature of the adjustment is at the discretion of the reporting physician. Adjustment can be based on height, weight, body mass index, bone area, bone age, pubertal stage, lean body mass, or a combination of these parameters [77–79]. The method of adjustment should be noted in the report, and if a multivariable method is used, a published reference should be provided.

The assignment of diagnostic category should be based on the adjusted Z-scores using the BMC Z-score, the BMD Z-score, or the lower of the two, at the discretion of the reporting physician. Some manufacturers provide height or weight corrections as part of the DXA software. For those whose DXA software does not provide such corrections, an approach to correcting for bone age or height age is described in Table 10.10. Each method of correction has limitations and constraints, and these need to be considered in the interpretation [64, 71].

Bone area, corrected bone area, and area Z-scores are not required but can be included at the discretion of the reporting physician [79]. All Z-scores are derived using a white female reference database for girls and a white male database for boys. The reference database and version should be specified in the report. If the reference database that is used to generate Z-scores is not one provided by the manufacturer, a published reference should be provided. Z-scores may not be available for certain skeletal sites at young ages and so do not need to be reported [71].

Follow-Up Pediatric DXA Scanning

The components of a follow-up pediatric BMD report are shown in Table 10.11. A follow-up pediatric BMD report should include all of the components of a first-time pediatric report. In addition, items specific to follow-up also need to be described, including changes in density, statistical parameters relating to measurement error, and aspects of interpretation relating to the changes in density.

Changes in Density

When comparing serial assessments, positioning and sub-region assignment must be consistent [78, 79]. The same reference population database

Table 10.11 Suggested elements of pediatric DXA report

Suggested elements of the first-time pediatric DXA report
I. Patient and provider information
Patient name
Medical record number
Date of birth
Gender
Scan date
Referring physician
Report date
Reporting physician
Facility name and location
Measured weight, height
Calculated BMI, height, weight
Clinical information
Primary diagnosis
Indications for the scan and other risk factors
Falls history
List of current relevant medications
Bone age or pubertal stage
Inclusion of possible risk factors, including documentation of nontraumatic fractures
Calcium intake or use of calcium supplements
II. Diagnostic category
Test results
Skeletal sites scanned
BMD, BMC, bone area for each site
BMD Z-scores for each site by chronological age
Adjusted Z-scores for each site by bone age (if available)
III. Technical comments
Manufacturer, model of instrument used
Software version (standard, pediatric, low-density software)
Technical quality of the scans obtained
Limitations of the study (e.g., artifacts, scoliosis)
Pediatric reference source(s) used
IV. Interpretation and recommendations
Qualitative assessment of BMD Z-score results including specific statements about which diagnostic category the patient falls into
Recommendation including general comments as well as the requirement of pharmacological intervention
Recommendations for necessity and timing of follow-up DXA scan studies
Components of a follow-up pediatric DXA report

(continued)

Table 10.11 (continued)

I. Patient and provider information
Patient name
Medical record number
Date of birth
Gender
Scan date
Referring physician
Report date
Reporting physician
Facility name and location
Measured weight, height
Calculated BMI, height, weight % or Z-scores
Primary diagnosis, indications for test
List of current relevant medications
Bone age or pubertal stage
Inclusion of possible risk factors, including documentation of nontraumatic fractures
Calcium intake or use of calcium supplements
Indication for follow-up DXA scan
Interval fractures, change in clinical status, medications
II. Test results
Skeletal sites scanned
BMD, BMC, bone area for each site
BMD Z-scores for each site by chronological age
Adjusted Z-scores for each site by bone age (if available)
Annualized change in BMC, BMD
Percentage of BMC change
Change in Z-scores
Statistical significance of BMC change
III. Technical comments
Which previous scans are being used for comparison?
Statement regarding what denotes statistical significance for change in BMD at the center or "least significant change" (LSC)
Recommendation for necessity and timing of follow-up DXA scan

Modified from Refs. [4, 8] and itself Ellen Fung reporting DXA scan

***Note*.** The elements in plain print are considered standard at most densitometry centers. Those in *italics* are provided as suggestions

DXA dual-energy x-ray absorptiometry, *BMI* body mass index, *BMD* bone mineral density, *BMC* bone mineral content

should be used for serial studies whenever possible. If the reference population database must be changed, this should be noted in the report. The description of density change should include the absolute density change (in g/cm2, to 3 decimal places), percentage change (to 1 decimal place, derived using absolute density, not Z-scores), change in Z-score, and change in adjusted Z-score [59, 64]. Annualized rates of change may be reported, but this is optional [79]. The skeletal sites for which changes in density are to be reported are the lumbar spine (using whichever vertebrae are considered valid, with a minimum of two vertebrae) and the total body [71, 72]. If the forearm is being monitored in lieu of the spine or total body, change can be reported for the one-third or 33% proximal radius [78]. It must be recognized that the change profile at the forearm may not parallel changes at the spine and total body and may not correlate as well with drug responses. This will need to be addressed in the interpretation section, if applicable.

Changes in density must be reported in relation to (1) the first study on file and (2) the most recent previous study. Pediatric osteoporosis drug treatment regimens are not well defined, and if information is not provided by the referring physician, it can be difficult to ascertain the timing of the BMD study corresponding to the initiation of a clinical treatment regimen. It is therefore not mandatory at this time that changes be reported in relation to the initiation of treatment. This can be provided at the discretion of the reporting physician if it is felt that an appropriate comparison study can be defined in relation to treatment.

Statistical significance must be reported for each BMD skeletal site comparison, indicating whether the difference is considered significant at a 95% level of confidence. The manufacturer's software determination of statistical significance is not to be used. Each facility must determine precision error for each DXA machine and for each skeletal site (including forearm if this site is measured by the facility and used for serial monitoring) using the LSC methodology and use this value when determining statistical significance [64]. It is permissible to apply results derived from precision testing of the forearm on one side to serial scans done using the opposite side of the body. Facilities are encouraged to derive precision using pediatric age subjects, particularly facilities that perform only pediatric clinical tests. In the absence of data proving that precision differs between adults and children, however, it is accept-

able at this time for all facilities to use precision derived from adult subjects. If precision is derived using adult subjects, this should be noted in the report. A follow-up pediatric BMD report should state the LSC in absolute values (g/cm^2 to 3 decimal places for BMD, g to 2 decimal places for BMC) for each skeletal site for which change is reported and for both BMD and BMC. Whenever possible, the same instrument should be used for serial studies on an individual patient. Comparisons between measurements done on different machines can be made only if inter-machine precision between the two devices has been determined [59, 64]. Table 10.12 shows the common mistakes in DXA scanning and BMD assessment.

There is no accepted methodology, so far, for evaluating statistical significance of Z-score differences at different time points. The change in Z-score between comparison BMD studies should be noted. An opinion as to whether the difference is clinically meaningful should be incorporated into the interpretation section. It is not necessary to report changes in either height or weight.

In conclusion, a timely, concise, and informative DXA report is essential to relay densitometry findings and to avoid costly and potentially dangerous misinterpretations by referring physicians unfamiliar with interpreting densitometry data.

Table 10.12 Common mistakes in DXA scanning and BMD assessment

Category	Error	Example
Referral	Request DXA scan for inappropriate subject	Healthy menstruating 30 years old female without any risk factor
	Not requesting DXA scan for the subject at risk	Older adult 70 years old who sustained distal forearm fracture
Quality control	Failure to follow the system maintenance recommendations	No service of the scanner has been requested.
	Failure to carry out the phantom measurement	No record of phantom scanning
	No identification of the correct significant change in calibration	Quantitative comparison of the BMD cannot be carried out if the least significant change is not calculated
	No assessment of the precision error and failure to calculate the least significant change	
Acquisition	Inaccurate positioning of the patient	Spine not parallel to edges of DXA table or hip not sufficiently internally rotated
	Improper scan mode	Scan mode may alter BMD and is manually or automatically selected, depending on the instrument used
	Incorrect skeletal site	BMD measured at hip with total hip replacement
	Artifacts not removed from scanned area	Spine scanned when patient is wearing underwired bra or has belly button ring in place
	Wrong demographic information	Man entered as woman, or incorrect date of birth/age used
Analysis	No reviewing or correction of improper default	Large osteophyte is included in area of measured spine
	Identification of bone edges and regions of interest	Helpful markers are the iliac crest, usually at the L4–L5 interspace, and lowest set of ribs, usually at T12
	Inaccurate labeling of vertebral bodies	

Table 10.12 (continued)

Category	Error	Example
Interpretation	Wrong application of WHO diagnostic T-score criteria and ISCD Official Positions	Reporting T-scores in a healthy premenopausal woman and applying the WHO diagnostic criteria may result in faulty assessment of fracture risk
	Wrong BMD comparison	LSC not known, different instruments used, different bone area scanned, different labeling of vertebral bodies, left hip compared with right hip, comparing T-scores instead of BMD, different scan modes
	Stating that bone has been lost when there is only one BMD test	Bone loss can only be identified when serial BMD tests have been done and the LSC is known
	Incorrect representation of fracture risk	Expressing fracture risk as relative risk will overestimate fracture probability if the comparator population is at low fracture risk

- Enough information should be provided in the report to allow for comparison to previous and subsequent DXA studies.
- The technical DXA report typically has five basic elements: (1) patient demographics, (2) a brief medical history, (3) test results, (4) technical comments, and (5) interpretationand recommendations.
- Medical history information should be obtained ideally from the referring physician, or otherwise from the patient or parent. Key information to include in the report are primary medical diagnosis, use of medications known to affect bone, fracture history and whenavailable, pubertal status, bone age, focused dietary, and physical activity histories.
- Careful review of the DXA scan images must be made prior to reporting of results toavoid misinterpretation of the findings based on artifacts in the scan field.

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Pitfalls in DXA Scanning

11

Abdellah El Maghraoui

Abbreviations

BMC	Bone mineral content
BMD	Bone mineral density
CV	Coefficient of variation
DXA	Dual-energy X-ray absorptiometry
IOF	International Osteoporosis Foundation
ISCD	International Society for Clinical Densitometry
LSC	Least significant change
PE	Precision error
ROI	Region of interest
SD	Standard deviation
SDD	Smallest detectable difference
TBS	Trabecular bone score
VFA	Vertebral fracture assessment
WHO	World Health Organization

Osteoporosis is a metabolic bone disorder defined as a disease of increased skeletal fragility and susceptibility to fracture accompanied by low bone mineral density (BMD) and microarchitectural deterioration. It is a common disease with a spectrum ranging from asymptomatic bone loss to disabling hip fracture. Dual-energy X-ray absorptiometry (DXA) is recognized as the reference method to measure BMD with acceptable accuracy errors and good precision and reproducibility [1]. The World Health Organization (WHO) experts has recommended DXA as the best densitometric technique for assessing BMD in postmenopausal women and based the definitions of osteopenia and osteoporosis on its results [2, 3]. DXA allows accurate diagnosis of osteoporosis, estimation of fracture risk, and monitoring of patients undergoing treatment. Additional features of DXA include measurement of BMD at multiple skeletal sites, safety of performance, short investigation time, and ease of use [4–6]. A DXA measurement can be completed in about 5 minutes with minimal radiation exposure (about one-tenth that of a standard chest X-ray). Moreover, DXA machines offer the opportunity to assess vertebral fractures, body composition, and even abdominal aortic calcification which may be very useful in some patients [7].

Principle of DXA Scanning

Several different types of DXA systems are available, but they all operate on similar principles. A radiation source is aimed at a radiation detector placed directly opposite the site to be measured. The patient is placed on a table in the path of the radiation beam. The source/detector assembly is then scanned across the measurement region. The

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attenuation of the radiation beam is determined and is related to the BMD [8, 9]. Because DXA scanners use two X-ray energies in the presence of three types of tissue (bone mineral, lean tissue, and adipose tissue), there are considerable errors arising from the inhomogeneous distribution of adipose tissue in the human body [10] (which can be studied either through cadaver studies [11], CT imaging to delineate the distribution of adipose tissue external to bone [12], or MRI to measure the percentage of marrow fat inside bone [13]).

DXA technology can measure virtually any skeletal site, but clinical use has been concentrated on the lumbar spine, proximal femur, forearm, and total body [6]. DXA systems are available either as full table systems (capable of multiple skeletal measurements, including the spine and hip) or as peripheral systems (limited to measuring the peripheral skeleton). Because of their versatility, and the ability to measure the skeletal sites of greatest clinical interest, full table DXA systems are the current clinical choice for osteoporosis assessment. Peripheral DXA systems, portable and less expensive than full table systems, are more frequently used as screening and early risk assessment tools; they cannot be used for treatments follow-up. Spine and proximal femur scans represent the majority of the clinical measurements performed using DXA. Most full table DXA systems are able to perform additional scans, including lateral spine BMD measurements, body composition study, assessment of vertebral fractures, measurements of children and infants, assessment of bone around prosthetic implants, small animal studies, and measurements of excised bone specimens. However, for children measurement, the exam should be undertaken by clinicians skilled in interpretation of scans in children in centers that have an adapted pediatric software.

Early DXA systems used a pencil beam geometry and a single detector, which was scanned across the measurement region. Modern full table DXA scanners use a fan-beam source and multiple detectors, which are swept across the measurement region. Fan beam provides the advantage of decreased scan times compared to single-beam systems, but these machines typically cost more because of the need for multiple X-ray detectors. Fan-beam systems use either a single-view or multiview mode to image the skeleton [14].

In clinical practice, BMD measurements are widely used to diagnose osteoporosis, and measurement in bone mass is commonly used as a surrogate for fracture risk [15]. BMD is the measured parameter and allows the calculation of the bone mineral content (BMC) in grams and the two-dimensional projected area in cm^2 of the bone(s) being measured; thus the units of BMD are g/cm^2. The BMD values (in g/cm^2) are not used for diagnosing osteoporosis. Instead, a working group of the WHO proposed to define osteoporosis on the basis of the T-score (which is the difference between the measured BMD and the mean value of young adults, expressed in standard deviations (SD) for a normal population of the same gender and ethnicity) [16]. Despite its limitations, this definition, which concerns only postmenopausal women and men over 50, is currently applied worldwide. Thus, the WHO diagnostic criteria for osteoporosis define osteoporosis in terms of a T-score below −2.5 and osteopenia when T-score is between −2.5 and −1.

The T-score is calculated using the formula: (patient's BMD - young normal mean)/SD of young normal. For example, if a patient has a BMD of 0.700 g/cm^2, the young normal mean is 1.000 g/cm^2, and the young normal standard deviation is 0.100 g/cm^2, then this patient's T-score would be (0.700–1.000)/0.100, or −0.300/0.100, or −3.0 [16]. A T-score of 0 is equal to the young normal mean value, −1.0 is 1 SD low, −2.0 is 2 SD low, etc. Although the WHO classification was not intended to be applied to individual patients, it works well to define "normal" (T-score −1.0 and above) and "osteoporosis" (T-score −2.5 and below). Several large studies have shown an unacceptably high risk of fracture in postmenopausal women who have T-scores of −2.5 and below. Thus, this threshold is the cornerstone of the patient's assessment. For the therapeutic decisions, however, other risk factors are considered such as prevalent fractures, age, and the risk of falls.

In addition to the T-scores, DXA reports also provide Z-scores, which are calculated similarly to the T-score, except that the patient's BMD is compared with an age-matched (and race- and gender-matched) mean, and the result expressed as a standard deviation score [16]. In premenopausal women, a low Z-score (below −2.0) indicates that bone density is lower than expected and should trigger a search for an underlying cause.

In all cases, physicians must keep in mind to actively look for secondary osteoporosis in front of low BMD value, either by thorough history taking or with biochemical studies before stating about postmenopausal osteoporosis.

Contraindications

There are no absolute contraindications to performing DXA. However, in some situations, the exam may be of little value (artifacts or difficulties in interpretation):

- Recently administered gastrointestinal contrast or radionuclides.
- Severe degenerative changes or fracture deformity in the measurement area.
- Implants, hardware, devices, or other foreign material in the measurement area.
- The patient's inability to attain correct position and/or remain motionless for the measurement.
- Extremes of high or low body mass index (BMI) which may adversely affect the ability to obtain accurate and precise measurements. Quantitative computed tomography (QCT) may be a desirable alternative in these individuals.
- Any condition that precludes proper positioning of the patient to be able to obtain accurate BMD values.
- Early model densitometers emitted substantial radiation that was not considered safe for evaluation during pregnancy. With the advent of fan-beam densitometers that emit low ionizing radiation, their use at the beginning of the second trimester of pregnancy became possible. However, DXA scans are not advised for women who are pregnant, and it is more appropriate to reschedule the exam after the delivery.

Who Should Have a DXA Measurement?

Most official groups recommend screening healthy women for osteoporosis at age 65 and testing higher-risk women earlier [17]. The International Society for Clinical Densitometry (ISCD) recommends screening men without risk factors for osteoporosis at age 70 and screening higher-risk men earlier. Risk factors include dementia, poor health, recent falls, prolonged immobilization, smoking, alcohol abuse, low body weight, history of fragility fracture in a first-degree relative, estrogen deficiency at an early age (<45 years), and steroid use for more than 3 months. Of course, BMD testing is an appropriate tool in the evaluation of patients who have diseases (e.g., hyperthyroidism, hyperparathyroidism, celiac disease, etc.) or use medications (e.g., glucocorticoids, GnRH agonists, aromatase inhibitors, etc.) that might cause bone loss. Another indication is radiographic evidence of "osteopenia" or a vertebral fracture.

Sites of Measurement of BMD

The ISCD recommends obtaining BMD measurements of the posteroanterior spine and hip [18]. The lateral spine and Ward's triangle region of the hip should not be used for diagnosis, because these sites overestimate osteoporosis and results can be false positive. Evidence suggests that the femur (neck or total hip) is the optimum site for predicting the risk of hip fracture and the spine is the optimum site for monitoring response to treatment. Thus, many authors recommend hip measure alone for the fracture risk assessment [19–24]. In very obese patients, those with primary hyperparathyroidism, or those in whom the hip or the spine, or both, cannot be measured or interpreted; BMD may be measured in the forearm, using a 33% radius on the non-dominant forearm.

Interpreting a DXA Scan

DXA scans should be critically assessed by the interpreting physician and densitometrist for abnormalities that may affect BMD measurements. In clinical practice, recognition of diverse artifacts and disease processes that may influence BMD results can be of major importance in the optimal interpretation of DXA scans [25]. Physicians not directly involved in the performance and interpretation of DXA should be familiar enough to detect common positioning and scanning problems, to know what should appear on a report, what questions to ask if the necessary information is not on the report, how to apply the results in patient management, and when to do and how to interpret a second measurement to monitor treatment [16].

The most important information to check are the correct identification of the patient, his date of birth, and also the gender and ethnicity which are mandatory to calculate T-scores. Gender is used by all manufacturers to calculate T-scores (i.e., T-scores for women are calculated using a female normative database, while T-scores for men are calculated using a male normative database). Although all manufacturers use race in calculating Z-scores, there is inconsistency in the way race is handled when calculating T-scores. Norland and Hologic are using race in calculating T-scores (i.e., T-scores for Caucasians are calculated using a Caucasian normative database, T-scores for Blacks are calculated using a normative database for Blacks); however, GE Lunar and recent Hologic machines use the database for young-normal Caucasians to calculate T-scores, regardless of the race of the subject. The ISCD recommends the latter approach for use in North America [26]. The reasons are that (1) it is not always possible to identify patient ethnicity, and reference data are not available for all ethnic groups; (2) there is insufficient evidence linking BMD to fracture risk in other ethnic groups; and (3) use of Caucasian reference data in African Americans results in a lower prevalence of "osteoporosis," which is in accordance with the lower rates of fracture among African Americans.

Positioning

The main purpose of the DXA scan image is to check if the patient is positioned correctly, something that the technologist should do before the patient leaves the testing center. It should also be double-checked by the clinician who interprets the test [25]. There are many available resources for BMD technologists and physicians training, such as ISCD or International Osteoporosis Foundation (IOF) courses.

Basic BMD measurement requires the patient to be "on the table" for about 2 minutes, undressed to light clothing, and with no metal piercings. Navel piercings can be a problem, because they cover the vertebra L4, which is a common site to scan. The maximum weight on a scanning table is 136 kg.

The spine is examined with patients lying on their backs and their knees flexed over a block at right angles to flatten out (partially) the normal lumbar lordosis. A scan with correct positioning of the spine is shown in Fig. 11.1a: the patient is straight on the table (spine is straight on the image), not rotated (spinous processes are centered), and centered in the field (roughly equal soft tissue fields on either side of the spine). Patients with scoliosis cannot be positioned with the spine straight on the table; moreover, with severe scoliosis, degenerative changes can occur that invalidate the spine measurement. The scan should extend up sufficiently far to include part of the lowest vertebra with ribs (which is usually T12) and low enough to show the pelvic brim (which is usually the level of the L4–L5 interspace).

For proper positioning of the hip, the patient should have the femur straight on the table (shaft parallel to the edge of the picture), with 15–25° of internal rotation, which can be achieved by the use of positioning devices. Internal rotation may be improved by having the patient flex the foot before doing the internal rotation and then relaxing the foot after the strap is in place. This amount of internal rotation presents the long axis of the femoral neck perpendicular to the X-ray beam, providing the greatest area and the lowest bone mineral content (and the lowest BMD), and is

confirmed on the scan by seeing little or none of the lesser trochanter (Fig. 11.1b) [4, 27]. If the desired amount of internal rotation cannot be achieved, as is often the case in patients with hip arthritis or short femoral necks, the technologist should place the patient comfortably in a position that is likely to be reproducible in a subsequent scan [5, 28].

DXA Scan Analysis

The software marks regions of interest in the spine and hip, but the technologist can and should adjust if needed. The spine region of interest consists of the L1 through L4 vertebrae (Fig. 11.1a). Correct placement of the top and bottom of the spine "box" is critical. The intervertebral lines can be moved or angled, if necessary. There must be sufficient soft tissue on both sides of the spine; otherwise BMD will be under estimated. The hip regions of interest include the femoral neck, trochanter, and total hip (Fig. 11.1b). Ward's region and the intertrochanteric region are not relevant (and can be deleted from the results reports). The default hip analysis includes a midline that must be placed correctly for the other sites to be identified correctly. The preferred position for the rectangular femoral neck box differs for the different manufacturers. For GE Lunar, the femoral neck box is located by the analysis program at the narrowest and lowest density section of the neck; typically, this will be about half way between the femoral head and the trochanter (Fig. 11.1b). For Hologic the box is on the distal part of the femoral neck (Fig. 11.1c). This induces a large difference among these two measurements, because of a gradient of BMD all along the femoral neck (the proximal being the highest, the distal being the lowest). Thus, careful checking of the femoral neck box is mandatory.

The image should be evaluated for artifacts (e.g., surgical clips, navel rings, barium sulfate, metal from zipper, coin, clip, or other metallic object) or local structural change (e.g., osteophytes, syndesmophytes, compression fractures, aortic calcification). Almost all artifacts and local structural change will spuriously elevate BMD [29]. This is especially true for spinal degenerative change, which can elevate spine BMD by 2, 3, or more T-score. In the spine, absent bone (laminectomy or spina bifida) or vertebral rotation (idiopathic scoliosis) will spuriously lower BMD. All evaluable vertebrae should be used, but vertebrae that are affected by local structural change should be deleted from the analysis. Most

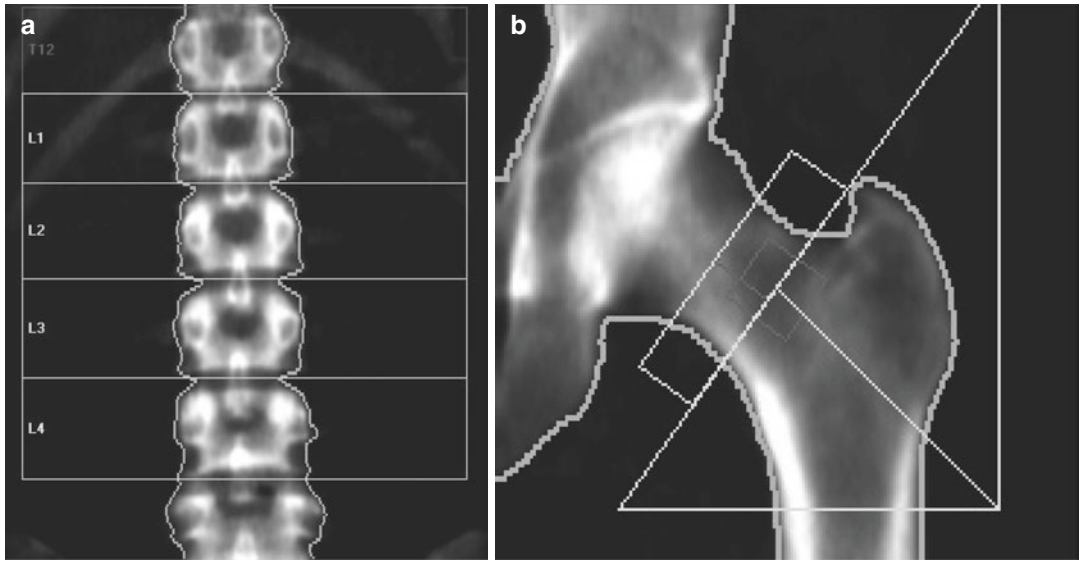

Fig. 11.1 Correct positioning and analysis of the L1–L4 spine (**a**) and the proximal femur (**b**)

agree that decisions can be based on two vertebrae; the use of a single vertebra is not recommended. If all vertebrae are affected, the spine should be reported as "invalid," with no BMD or T-score results given. Figures 11.2 and 11.3 show examples from common spine and hips scanning problems.

Concordance Between Measurement Sites

It is recommended to measure the lumbar spine and proximal femur and classifying the patient based on the lowest T-score from three sites (lumbar spine, femoral neck, and total hip). Although the BMDs at different anatomic regions are correlated, the agreement between sites is low when it comes to classifying individual subjects as osteoporotic or not. Thus, T-score discordance between the lumbar spine and hip testing sites is a commonly observed phenomenon in densitometry. T-score discordance is the observation that the T-score of an individual patient varies from one key measurement site to another.

Prevalence and Risk Factors of T-Score Discordance

Various studies have analyzed the prevalence and impact of T-score discordance on the management of osteoporosis [30–33]. Few studies focused on risk factors of this commonly observed discordance [30, 34, 35]. Five different causes for occurrence of discordance between the spine and the hip sites have been described [31].

1. Physiologic discordance is related to the skeleton's natural adaptive reaction to normal external and internal factors and forces. Mechanical strain especially related to weight bearing plays a key role in this kind of discordance. An example of this type of discordance is the difference observed between the dominant and non-dominant total hip [28, 36]. The explanation is that weight bearing can cause rise in bone density especially in the hip and femur regions. Moreover, the spine and hips usually start out with different T-scores (the spine is said to reach peak at least 5 years before the hip) [37]. And finally, bone loss observed with age in an individual may be more rapid and important in trabecular than cortical bone is another explanation [38]. Trabecular bones (typical of lumbar area) are known to have a more rapid rate of deprivation in early postmenopausal state in comparison to cortical bone (typical of proximal femur).
2. The second type of discordance described as pathophysiologic discordance is seen secondary to a disease. Common examples observed in the elderly include vertebral osteophytosis, vertebral end plate and facet sclerosis, osteochondrosis, and aortic calcification [39, 40]. Another important cause in younger patients is ankylosing spondylitis syndesmophytes [29, 41–44]. The abnormal calcium deposition within the field of the DXA region of interest (ROI) leads to the falsely elevated spine T-score. A second subtype is a true discordance resulting from a more decreased BMD in the lumbar spine than the hips. Indeed, most of the etiologies of the secondary osteoporosis (such as glucocorticoid excess, hyperthyroidism, malabsorption, liver disease, rheumatoid arthritis) first affect spinal column [45, 46]. This will lead to higher prevalence of lumbar osteoporosis.
3. Anatomic discordance is owing to differences in the composition of bone envelopes tested. An example is the difference in T-scores found for the posteroanterior lumbar spine and the supine lateral lumbar spine in the same patient.
4. Artifactual discordance occurs when dense synthetic manmade substances are within the field of ROI of the test: e.g., barium sulfate, metal from zipper, coin, clip, or other metallic object.
5. And finally, technical discordance occurs because of device errors, technician variability, patients' movements, and variation due to other unpredictable sources. With respect to positioning error, some studies showed that

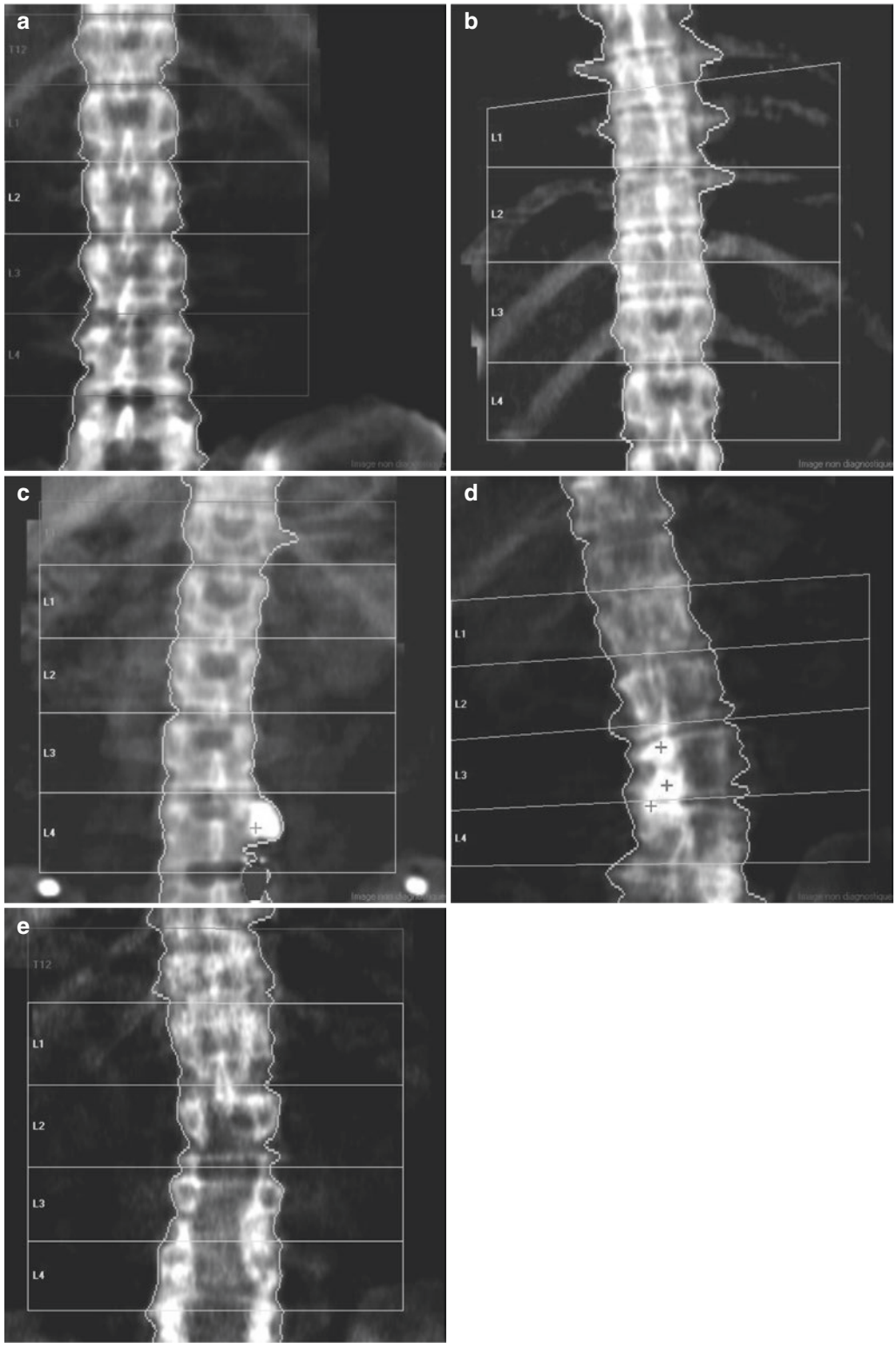

Fig. 11.2 Examples among some common spine scanning problems: (**a**) the spine is too close to the right side of the image; (**b**) vertebral levels are mis-identified; (**c**) metal button over L4; (**d**) scoliosis and osteophyte at L3–L4; (**e**) laminectomy

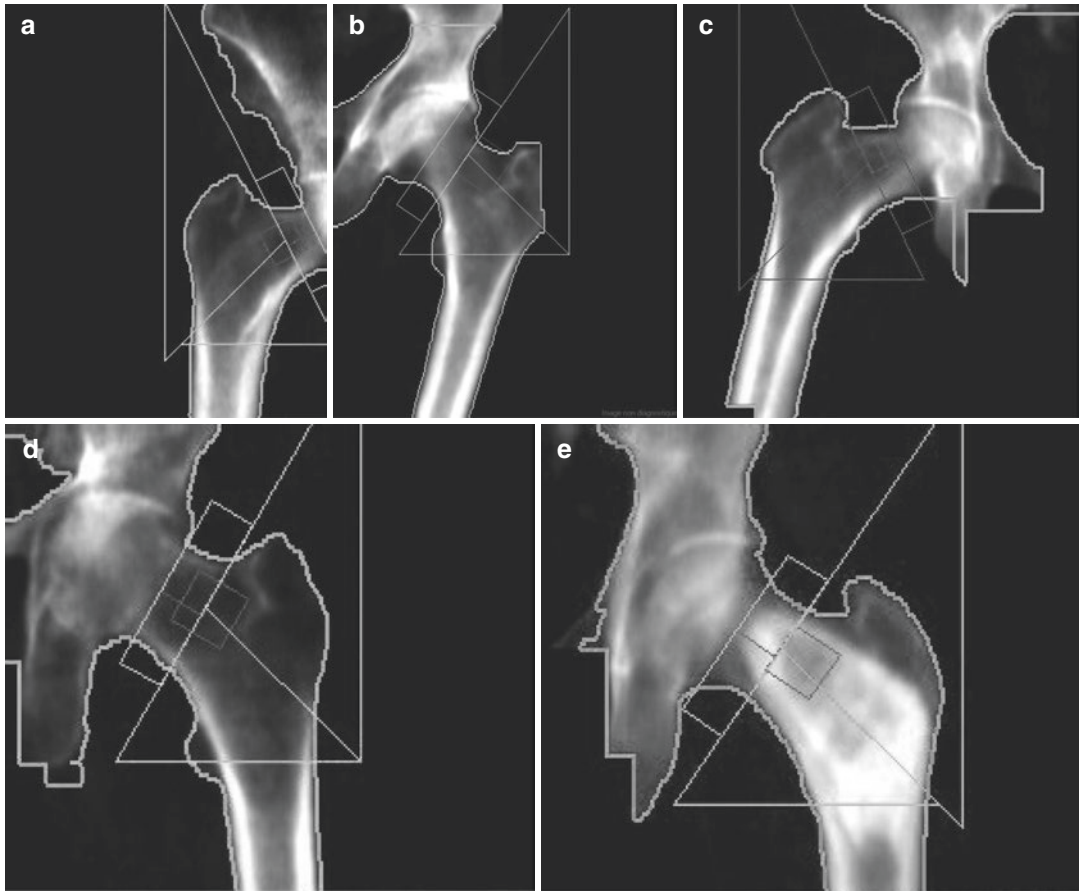

Fig. 11.3 Examples among some common hip scanning problems: (**a**) the scan did not go far enough laterally, and part of the femoral head is missing. (**b**) The femur is adducted. (**c**) The femur is abducted. (**d**) Suboptimal internal rotation (too much of the lesser trochanter is showing). (**e**) Abnormal bone (history of hip fracture and osteosynthesis)

either excessive internal or external rotation of the femur during test acquisition resulted in a BMD difference of as much as 10% compared with correct positioning. We demonstrated in a previous study that DXA in vivo reproducibility is twofold better in the hips than the spine especially when measuring both hips [41]. Finally, technical discordance can occur due to the normative reference data used by the device software to analyze the test [5, 47, 48]. This type of discordance occurs when the average BMD of the normative group used to calculate the T-score is significantly different from the average value found for the whole population.

Consequences of T-Score Discordance on Osteoporosis Management

The high prevalence of T-score discordance could induce some problems for the physicians in decision-making regarding these patients. In general, high prevalence of discordance between lumbar spine and hip T-scores suggests some defects in the cutoff values for definition of osteoporosis and osteopenia proposed with the WHO. The inconsistencies in the diagnostic classification of osteoporosis between skeletal sites lend credence to the notion that BMD should be used as only one of the factors in making therapeutic decisions when evaluat-

ing patients with osteoporosis. An international team convened by the WHO developed FRAX, a globally applicable measure of absolute fracture risk based upon multiple risk factors including BMD (http://www.shef.ac.uk/FRAX). Since its release in 2008, models have been made available for 64 countries in 34 languages, covering 80% of the world population [49].

Monitoring of DXA

It has become more and more common to perform a second DXA measurement to monitor BMD status or the effect of therapeutic intervention. When a second measurement is performed on a patient, the clinician needs to distinguish between a true change in BMD and a random fluctuation related to variability in the measurement procedure. The reproducibility of DXA measurements is claimed to be good. Such variability is due to multiple causes, such as device errors, technician variability, patients' movements, changing in the area of interest, and variation due to other unpredictable sources [50–54]. Under ideal conditions, the same technologist should perform DXA scans on the same densitometer and under similar circumstances [55].

The precision error is usually expressed as the coefficient of variation (CV), which is the ratio of the standard deviation (SD) to the mean of the measurements, although several other statistics to express reproducibility exist such as the smallest detectable difference (SDD) or the least significant change (LSC). The SDD represents a cutoff that can be measured in an individual and is usually considered more useful than the CV in clinical practice.

Methods of Bone Mineral Density Reproducibility Measurement

Precision errors are evaluated by performing repeated scans on a representative set of individuals to characterize the reproducibility of the technique [56]. Most published studies examine the short-term precision error, based on repeated measurements of each subject performed over a time period of no more than 2 weeks. Over such a short period, no true change in BMD is expected.

- *The Coefficient of Variation (CV)*

The CV, the most commonly presented measure for BMD variability, is the SD corrected for the mean of paired measurements. CV, expressed as a percentage, is calculated as $CV\ (\%) = (\sqrt{((\sum(a - b)^2)/2n))}/((Ma + Mb)/2) \times 100$ where a and b are the first and the second measurement, Ma and Mb are the mean values for the two groups, and n is the number of paired observations.

Reproducibility is far better for BMD measurement than for most laboratory tests. Reproducibility expressed by the CV is usually 1–2% at the spine on anteroposterior images and 2–3% at the proximal femur in individuals with normal BMD values; the difference between the two sites is ascribable to greater difficulties with repositioning and examining the femur, as compared to the spine. However, these data obtained under nearly experimental conditions may not apply to everyday clinical practice. Reproducibility depends heavily on quality assurance factors, including tests to control the quality and performance of the machine, as well as the experience of the operator. Assessment of machine performance requires daily scanning of a phantom (which may be anthropomorphic or not), followed by calculation of the in vitro coefficient of variation (CV), which serves to evaluate short-term and long-term performance and to detect drift in measurement accuracy. These in vitro data, however, do not necessarily reflect in vivo reproducibility, which should be evaluated at each measurement centre [57]. Measurements are obtained either three times in each of 15 patients or twice in each of 30 patients, and the CV (m/*r*) is calculated from the mean (m) and standard deviation *(r)* of these repeated measurements. The CV is expressed as a percentage and depends on mean BMD values. The standard

deviation reflects measurement error, which is a characteristic of machine performance and is independent from the value measured.

- *The Least Significant Change (LSC)*

For two-point measurements in time, a BMD change exceeding $2\sqrt{2}$ times the precision error (PE) of a technique is considered a significant change (with 95% confidence): the corresponding change criterion has been termed "least significant change" or LSC. LSC = 2.8 × PE, where PE is the largest precision error of the technique used (or more easily the CV expressed in percentage). This smallest change that is considered statistically significant is also expressed in percentage.

- *The Smallest Detectable Difference (SDD)*

The measurement error can be calculated using Bland and Altman's 95% limits of agreement method [58]. Precision expressed by this method gives an absolute and metric estimate of random measurement error, also called SDD. In this case, where there are two observations for each subject, the standard deviation of the differences (SD_{diff}) estimates the within variability of the measurements. Most disagreements between measurements are expected to be between limits called "limits of agreement" defined as $d \pm z_{(1-a/2)}\ SD_{diff}$ where d is the mean difference between the pairs of measurements and $z_{(1-a/2)}$ is the 100(1 − a/2)th centile of the normal distribution. The value d is an estimate of the mean systematic bias of measurement 1 to measurement 2. d is expected to be 0 because a true change in BMD is not assumed to occur during the interval between the two BMD measurements. Defining a to be 5%, the limits of agreement are $+1.96SD_{diff}$ and $-1.96SD_{diff}$. Thus, about twice the standard deviation (SD) of the difference scores gives the 95% limits of agreement for the two measurements by the machine. A test is considered to be capable of detecting a difference, in absolute units, of at least the magnitude of the limits of agreement.

Clinical Implications of Bone Mineral Density Reproducibility Measurement

In clinical practice, two absolute values (g/cm^2) have to be compared, rather than two percentages (T-scores). When serial measurements are obtained in a patient, only changes greater than the LSC (in %) or the SDD (in g/cm^2) can be ascribed to treatment effects. Smaller changes may be related to measurement error.

We studied the in vivo short-term variability of BMD measurement by DXA in three groups of subjects with a wide range of BMD values: healthy young volunteers, postmenopausal women, and patients with chronic rheumatic diseases (most of them taking corticosteroids). In all studied subjects, reproducibility expressed by different means was good and independent from clinical and BMD status. Thus, the clinician interpreting a repeated DXA scan of a subject should be aware that a BMD change exceeding the LSC is significant, in our center arising from a BMD change of at least 3.56% at the total hip and 5.60% at the spine. Expressed as SDD, a BMD change should exceed 0.02 g/cm^2 at the total hip and 0.04 g/cm^2 at the spine before it can be considered a significant change [41]. Indeed, it has become usual to perform repeated DXA measurement: in postmenopausal women to monitor efficacy of treatment and in patients with chronic rheumatic diseases where high prevalence of bone loss has been demonstrated especially when long-term corticosteroid therapy is used. It has been shown that reproducibility expressed using the SDD is independent of the BMD value, whereas reproducibility expressed using the CV or the derived LSC depends on the BMD value. Influence of age on BMD reproducibility is controversial. Previous studies have suggested that BMD measurement errors were independent of age even some studies suggested that SDD may vary in extreme ages (children and elderly) probably because of age-related factors other than BMD. However, a few data exist for reproducibility of DXA in women over 70. Ravaud et al. [59] data, as well as those of Fuleihan [53], show that the measurement error

is greater in older osteoporotic subjects. Several factors such as difficulties in repositioning could explain the increase of measurement error in this kind of patients. Therefore, the use of the SDD in the evaluation of an apparent BMD change gives a more conservative approach than the use of the CV at low BMD. Because of its independence from the BMD level and its expression in absolute units, the SDD is a preferable measure for use in daily clinical practice as compared with the CV and the derived LSC.

In contrast with all previous publications about DXA reproducibility, we found better results for the hip BMD variability than the lumbar spine. This is due to the fact that our study was the first to use the mean measure of the two femurs (dual femur). In this study, we showed in a group of young healthy volunteers that the SDD was ±0.0218 g/cm^2 when both femurs were measured, whereas it was ±0.0339 g/cm^2 when only one femur was measured. Thus, these results enhance to encourage the use of the measurement of both hips to improve the reproducibility of DXA at this site [41, 60].

In summary, reproducibility of BMD measurement by DXA expressed by different means is good at a group level. However, the clinician must remain aware that an apparent BMD change in an individual patient may represent a precision error. At each measurement center, the SDD should be calculated from in vivo reproducibility data. In clinical practice, the SDD should be used to estimate the significance of observed changes, in absolute values.

Other Factors Influencing DXA Monitoring

The first factor is the time interval between two measurements in the same patient which must be long enough to allow occurrence of a change greater than the SDD or the LSC. Therefore, it depends on the expected rate of change in BMD measurement (which varies according to whether the measurement site is composed predominantly of trabecular or of cortical bone) and the reproducibility of BMD measurement at that site. Thus, in clinical practice, a treatment-induced BMD increase can only be detected in general after 2 years [26]. However, in patients receiving long-term steroid therapy, the changes in BMD may be so important that they can be detected after 1 year. Thus, although the spine may not be the best site for the diagnosis of osteoporosis given the high prevalence of spinal degenerative disease, it is the most sensitive site for detecting changes over time.

The changes in BMD measurements are influenced by the ability of osteoporosis treatments to increase the BMD at the different skeletal sites [61]. In postmenopausal osteoporosis, treatment-induced increments in BMD with inhibitors of bone turnover are modest (typically 2% per year) in comparison to the precision error of repeat measurements (typically 1–2%) so that the time interval of repeat estimates must be sufficiently long in order to determine whether any change is real. Moreover, there is no proof that repeating BMD measurements improves compliance to treatment, as most patients discontinue antiresorptive medications after a few months because of administration constraints, side effects, cost of medications, or lack of interest [62]. Thus, in the absence of other clinical imperatives, a 3- to 5-year interval may be appropriate. For some treatments such as teriparatide, abaloparatide, and romosozumab, significant changes in spine BMD occur on time scales of 1–2 years in the majority of patients [63], so more frequent BMD tests may be considered.

The aim of all anti-osteoporotic treatments is to increase bone strength, in order to decrease the risk of fracture [49]. In untreated men and women, BMD is one of the major determinants of bone strength, and low BMD is an important predictor of fracture. However, whether the long-term anti-fracture efficacy of the drugs used to treat osteoporosis depends on the extent to which they can increase or maintain BMD is controversial. Meta-regressions, based on summary statistics, demonstrate a stronger correlation between the change in BMD and fracture risk reduction than results based on the individual patient data. This may partly be explained by the relatively modest changes in T-score observed to date with

most existing therapies (particularly in the hip), the small number of subjects from completed, long-term studies, and previous attempts to link fracture reductions with percentage change in BMD rather than the absolute BMD achieved while receiving different therapeutic agents. A recent meta-analysis [64] found that change in BMD across all published randomized trials is strongly predictive of hip and vertebral fracture reduction. In particular, BMD changes at the total hip or femoral neck are similarly predictive of both hip and vertebral fractures. In contrast, lumbar spine BMD changes were predictive only of vertebral fracture risk. Moreover, preclinical studies demonstrate normal or improved bone quality and biomechanical properties after treatment. Although these results cannot be directly applied to predict the treatment benefit in an individual patient, these studies suggest that drugs that can increase hip BMD substantially are able to decrease risk of hip and vertebral fractures.

The feasibility of treat-to-target (or goal-directed) strategies in the management of osteoporosis has been the subject of much debate [65]. While there is currently no consensus on which parameter would best define the treatment target, the T-score has been proposed as the likely choice (along with the goal of freedom from fracture) based on the 2017 ASBMR Task Force on Goal-Directed Therapy in Osteoporosis [66]. Specifically, a spine or hip T-score above −2.5 has been proposed for consideration by the task force, since achieving a T-score of −2.5 (for patients initiating treatment with a T-score <−2.5) would reflect the patient having a BMD above the intervention and diagnostic threshold for treatment initiation in many guidelines. Of note, the task force also suggests that therapy should be continued until a patient is fracture-free for 3–5 years and that a higher T-score goal (i.e., a T-score greater than −2.0) may be warranted in patients with a higher baseline risk, such as those over age 70 or with a recent vertebral fracture. A significant BMD decrease while taking a treatment indicates either a compliance problem or a lack of efficacy. The measurement of bone markers may be helpful in monitoring treatment besides BMD [56].

Vertebral Fracture Assessment (VFA)

The majority of vertebral fractures do not come to medical attention and thus remain undiagnosed. Moreover, moderate or severe vertebral fractures, even when asymptomatic, are strong risk factors for subsequent fracture at the spine and other skeletal sites. Thus, vertebral fracture assessment should be considered in high-risk individuals, using either lateral lumbar and thoracic spine radiographs or lateral spine DXA imaging. With the advent of high-resolution DXA systems, visual assessment of fractures became possible from DXA-based lateral spine images (Fig. 11.4). In this situation, the DXA system essentially functions as a digital X-ray imaging device. Visual assessment is performed from a computer monitor or high-resolution printout [67–69]. Using a DXA system for assessing vertebral fracture status has several advantages. The evaluation of spine fractures can be performed without a conventional lateral spine X-ray. This can be done at the same time and at the same place as the BMD measurement, with much less radiation than a conventional spine X-ray. Moreover, VFA is a technology for diagnosing vertebral fractures that may alter diagnostic classification, improve fracture risk stratification, and identify patients likely to benefit from pharmacological therapy who otherwise might not be treated [67, 70]. There are also some limitations that should be considered. Some skeletal radiologists have criticized the technique for being insensitive and inaccurate for detecting vertebral fractures in particular at the upper thoracic spine. A DXA image is of lower resolution than a conventional X-ray and might fail to identify other potential problems or diseases that would be apparent on a spine film. However, VFA allows ruling out vertebral fracture at levels where vertebral fracture is most common, i.e., the lumbar and the mid and lower thoracic levels, and the pencil beam mode of assessment eliminates parallax errors in viewing the vertebral body, which can sometimes make a normal vertebral body appear to have been compressed in a routine spine X-ray [69, 71–73].

The International Society for Clinical Densitometry (ISCD) has published indications

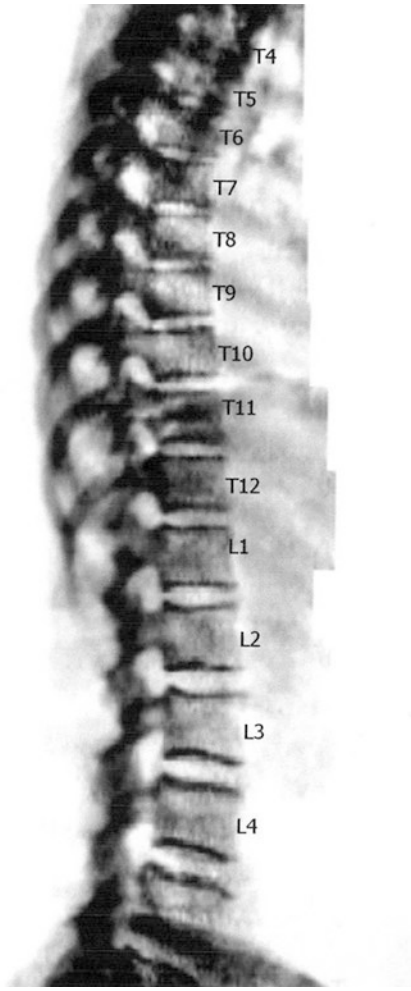

Fig. 11.4 Vertebral fracture assessment from a dual X-ray absorptiometry image of the spine

for performing VFA as part of bone densitometry [74]. Populations considered appropriate for VFA are those in whom the pre-test probability of one or more prevalent vertebral fractures being present exceeds 10% and for whom documentation of one or more vertebral fractures will alter patient management. Densitometric VFA is indicated when T-score is < -1.0 and of one or more of the following is present:

- Women age ≥ 70 years or men ≥ age 80 years
- Historical height loss >4 cm
- Self-reported but undocumented prior vertebral fracture
- Glucocorticoid therapy equivalent to ≥5 mg of prednisone or equivalent per day for ≥3 months

Fracture diagnosis should be based on visual evaluation and include assessment of grade/severity. Morphometry alone is not recommended because it is unreliable for diagnosis. The Genant visual semi-quantitative method is the current clinical technique of choice for diagnosing vertebral fracture with VFA. Severity of deformity may be confirmed by morphometric measurement if desired.

Patient positioning is particularly easy when using a densitometer with a rotating C-arm. In this instance, the patient is kept in the same position used to obtain AP lumbar spine bone density, supine with a bolster under the distal lower extremities such that the hips are flexed at 90 degrees, and arms held above the head. Without a rotating C-arm, lateral spine images for VFA are obtained in the lateral decubitus position. With this approach, proper positioning by the technologist produces VFA image quality comparable to supine lateral VFA images. The patient needs to be lying on the side without trunk rotation such that the coronal plane of the body is perpendicular to the plane of the densitometer table. If the body is rotated forwards or backwards from this position, the vertebral body outlines can be obscured. An indication that this has occurred is prominent appearance of the rib angles of one side of the rib cage posterior to the spinal column.

Parallelly to assessing vertebral fractures, it has been shown that abdominal aortic calcification may be adequately visualized on the VFA image. Aortic calcification is a well-established cardiovascular risk factor: many studies showed that it is significantly predictive of overall cardiovascular disease incidence and mortality, coronary heart disease, stroke, congestive heart failure, and peripheral vascular disease, independently of classical risk factors such as high blood pressure, high total and LDL cholesterol levels, smoking, obesity, and the presence of diabetes mellitus [75–78]. Several studies have also shown that aortic calcification is strongly associated to

low bone density and fragility fractures in men and women. Thus, identifying patients at risk for both cardiovascular events and osteoporotic fracture may help reduce morbidity and mortality associated with these highly common conditions.

Trabecular Bone Score (TBS)

TBS is a recently developed analytical tool that performs novel gray-level texture measurements on lumbar spine DXA images. It has been shown that it may capture information relating to trabecular microarchitecture. Low TBS is consistently associated with an increase in both prevalent and incident fractures that is partly independent of both clinical risk factors and areal BMD at the lumbar spine and proximal femur [79, 80]. It can thus be used as an adjunct to BMD measurements and is a software option for densitometers. Studies including a meta-analysis have shown an incremental improvement in fracture prediction when lumbar spine TBS is used in combination with FRAX variables.

Body Composition

Whereas whole body bone, fat, and lean mass can also be measured using DXA potentially contributing to the diagnosis of sarcopenia (a well-known risk factor for falls and fractures), these measurements are useful for research, but they do not assist in the routine diagnosis or assessment of osteoporosis.

Conclusions

Pitfalls in DXA are common, and errors can be categorized as patient positioning, data analysis, artifacts, and/or demographics. When DXA studies are performed incorrectly, it can lead to major mistakes in diagnosis and management. Measurement error must be considered when evaluating serial assessments. A clear understanding of the statistical principles impacting upon their interpretation is necessary to determine whether a change is real and not simply random fluctuation. Physicians interested in osteoporosis management, even if not directly involved in the performance and interpretation of DXA, should be familiar with the principles outlined here to minimize serious errors and allow proper use of bone densitometry.

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Osteopenia: Mind the Gap

12

Yasser El Miedany

Introduction

The terms "osteoporosis" and "osteopenia" were originally coined to convey the notion that an individual is susceptible to sustaining a fracture following minimal trauma because there is "not enough bone" [1–3]. In the absence of a true gold standard, the WHO proposed that the reference standard should be based on BMD measurement made at the femoral neck with dual-energy X-ray absorptiometry (DXA). This site has been the most extensively validated and provides a gradient of fracture risk as high as or higher than that of many other techniques [4]. The recommended reference range was the National Health and Nutrition Examination Survey (NHANES) III reference database for femoral neck measurements in Caucasian women aged 20–29 years [5]. This proposal has been endorsed by many international agencies including the International Osteoporosis Foundation (IOF), the International Society for Clinical Densitometry, and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). More controversially, a similar threshold value for femoral neck BMD that is used to define osteoporosis in women was proposed for the diagnosis of osteoporosis in men—namely, a value for BMD 2.5 SD or more below the average for young adult women [6].

Although it is well established that the risk of fracture is increased in women with the BMD levels in the osteoporosis range (i.e., BMD: T-score < −2.5), women with higher BMD levels, such as those in the osteopenia range (BMD: T-score < −1 to −2.49), have also been reported at increased risk for fracture. In a previous analysis of 200, 160 postmenopausal women in the National Osteoporosis Risk Assessment (NORA) study, women with osteoporosis had 2.74 times higher 1-year risk of fracture, and women with osteopenia had 1.73 times higher risk of fracture, compared with women with normal BMD, independent of demographic and clinical factors [7].

The BMD level appropriate for intervention with pharmacological treatment in postmenopausal women at increased fracture risk is a critical issue when assessing the potential for reducing the overall fracture rate in the population. Several medications have been shown to prevent bone loss or reduce the risk of fracture in postmenopausal women with low bone mass or osteoporosis [8–15]. However, there is no agreement on the ideal BMD measurement at which to initiate pharmacological therapy. The lack of consensus on treatment intervention thresholds reflects the trade-offs between the known potential benefits versus risks of these treatments, the willingness of patients to initiate and continue

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therapy, as well as the available resources to pay for medications.

Treatment threshold levels available for consideration in clinical practice emerge principally from two sources. The first is derived from reports developed by the World Health Organization (WHO), and the second is from the National Osteoporosis Foundation (NOF). The WHO provided an operational definition of osteopenia and osteoporosis in 1994 [16]. A postmenopausal woman with a BMD 2.5 SDs or more below the young adult mean (i.e., T-score ≤ -2.5) at any site (spine, hip, or mid radius) is considered to have osteoporosis, and a woman with a BMD between -2.49 and -1.0 is considered to have osteopenia. Although the WHO cutoff points were designed as diagnostic thresholds and were not developed to provide criteria for selecting patients in whom to initiate therapy, many clinicians and reimbursement sources use the WHO level for osteoporosis (T-score ≤ -2.5) as the treatment intervention threshold.

The NOF developed treatment thresholds by combining BMD measured at the hip with clinical risk factors for fracture (e.g., prior fracture as an adult, family history of fracture, BMI <18, cigarette smoking, excessive alcohol intake) [17, 18]. According to NOF recommendations, women with a T-score of -2.0 or less or -1.5 or less with at least one risk factor should be considered for treatment. The rationale for these particular threshold levels was evidence-based and influenced by cost-effectiveness considerations [19].

The observation that more than half (52%) of the NORA women experiencing an incident osteoporotic fracture within 1 year had a BMD T-score of -1.0 to -2.5 underscores the unmet need to identify those subjects who are most likely to fracture and might benefit from targeted pharmacological intervention. This chapter will discuss the evidence relating to fracture risk in the population who are classified in the osteopenia range. It will then expand to include current levels of case-finding and appropriate osteopenia management. Where available, analysis of published work describing models of care to implement best practice is presented. Finally, it will present an algorithm for osteopenia treatment-selected examples of clinical recommendations regarding pharmacotherapy.

From T-score to Bone Health

Trabecular bone loss and vertebral fractures are historical hallmarks of osteoporosis. However, 80% of the skeleton is cortical; 80% of all fractures are nonvertebral; and 30% of these are forearm fractures. Moreover, about 70% of all the appendicular bone lost during aging is cortical and results from intracortical remodeling which occurs throughout the cortex but is particularly vigorous in the cortico-trabecular junctional (transitional) zone where the cortical and trabecular compartments merge (Fig. 12.1) [20]. Remodeling during advancing age becomes unbalanced and removes more bone than it deposits leaving residual cortical porosity, which increases bone fragility exponentially and is a quantifiable "footprint" of bone loss [21–23].

Originally, the T-score concept was developed to assess for the probability of fragility fractures in postmenopausal white women in their mid to late 60s and older [21]. It has been useful because, in this age group, the disease prevalence is high. The T-score was endorsed as a surrogate marker for the histologic changes in aged bone that render it weak and susceptible to fractures from low loading forces: the lower the score, the worse the fracture risk. It followed intuitively that a low T-score determined the diagnosis of primary osteoporosis. Consequently, today's bone health specialists appreciate the importance of the T-score in diagnosing osteoporosis [24].

But the T-score has its problems when used outside this intended population. Practitioners have assumed that all patients with abnormally low scores have primary osteoporosis. However, this number alone is insufficient to accurately make such a diagnosis in patients outside the demographic group in which it was developed, simply because the low disease prevalence in younger groups makes the score less accurate as a predictive tool. Furthermore, it has long been

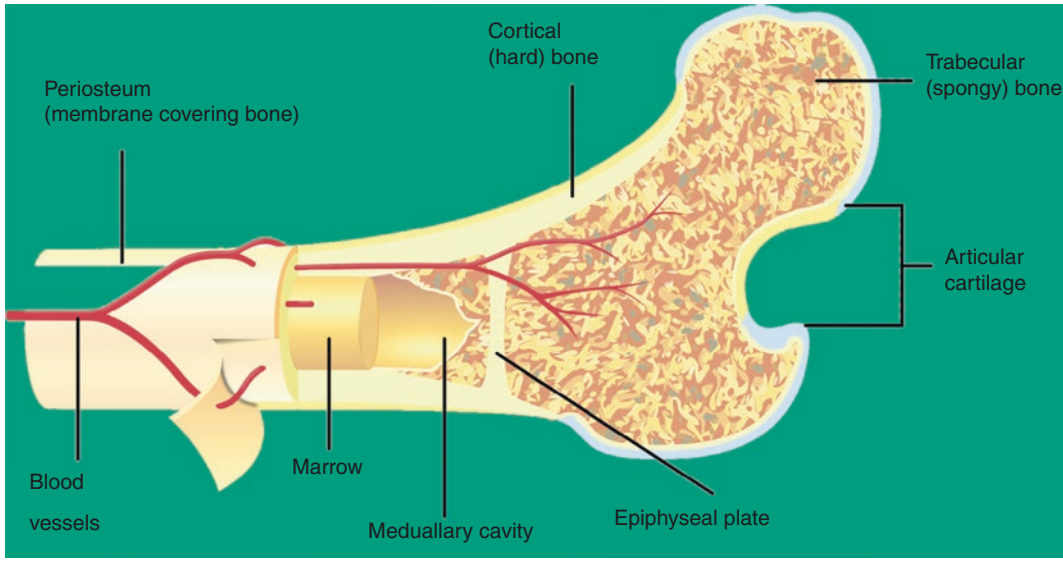

Fig. 12.1 Trabeculo-cortical junction

apparent that T-scores use is associated with issues, including different T-score values at various skeletal sites (lumbar spine, hip, distal 1/3 radius) [25].

Moreover, re-evaluation of data from pivotal clinical trials has brought into question the long-held idea that increases in bone density parallel increases in bone strength and reduction in fractures and that therapeutic improvement in bone density is the mark of success. Bone strength or resistance to fracture is more complex than density alone. Into this arena enters the concept of bone quality [26].

Bone Loss Is a Continuum, Not a T score

Another limitation of the term osteopenia is that there is a big distance under the curve from −1 to −2.49 standard deviations. Therefore, when it comes to risk assessment, it is important to remember that loss of bone mass is a continuum. And because the risk of fracture is directly related to bone mass, fracture risk is a continuum, too. For every standard deviation of bone mass lost, the relative risk of fracture doubles, but absolute fracture risk is highly age-dependent (Fig. 12.2). In younger women, the relative risk of fracture is quite low, and it remains low even when doubled. On the other hand, the absolute fracture risk of a 50-year-old with a T-score of −3 (a score most clinicians would be very concerned about) is exactly the same as the absolute fracture risk of an 80-year-old woman with a T-score of −1 (a score many clinicians might consider excellent for a woman that age). Thus, the T-score is only part of the story.

Bone mineral density (BMD) measures bone mass, which is simply one component of bone strength. BMD does not assess bone microarchitecture, although it can facilitate a diagnosis of osteopenia or osteoporosis using the WHO definitions. Similarly, BMD is used to monitor risk of fracture, much as blood pressure predicts the risk of cardiovascular disease. Many patients with high blood pressure never have a heart attack or stroke, and many patients with normal blood pressure do—but overall, rising blood pressure and rising risk of cardiovascular disease go together. In concordance, BMD is used to monitor response to treatment, but it is accurate only if the concept of least-specific change (LSC) is taken into account: LSC = 2.77 × the precision error of the machine. Thus, in a good center,

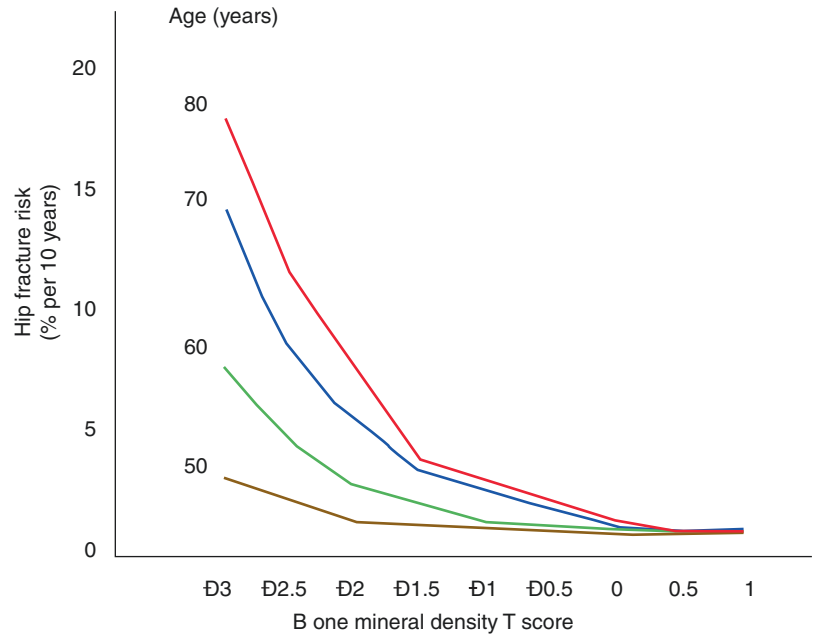

Fig. 12.2 Risk of fracture increases with advancing age and continuous loss of bone. (Adapted from Kanis et al. [118]. (Springer publisher/how to get the permission))

BMD measurement of the spine will be ±3%, and measurement of the hip will be ±5% [27].

In short, BMD measurement is used to reflect the bone remodeling continuum and degree of bone loss (Fig. 12.3). In turn, this would raise the question of which women should have their bone mass tested and who of them would require therapy? Various organizations have issued guidelines for measuring BMD in women to assess risk of fracture.

The Burden of Fragility Fractures

There is limited information concerning how many of all the fractures seen in postmenopausal women originate from the larger portion of the population with normal BMD or osteopenia. This information is important because it identifies the number of fractures that are likely to be averted by programs targeted at the whole community or only those with osteoporosis. In a study carried out to determine the age- and BMD-specific burden of fractures in the community and the cost-effectiveness of targeted drug therapy, 1224 women over 50 years of age sustaining fractures over 2 years' duration were assessed. Of the women sustaining fractures, 80% of 50–59 years olds did not have osteoporosis, 50% of 60–79 year old did not have osteoporosis, and even among those 80+ years old, 30% did not have osteoporosis [28].

Thus, referring to these fragility fractures as "osteoporotic" is misleading because it implies that the fractures come from a group of women identifiable by measurement of BMD. Although women with osteoporosis have an increased risk of fracture and the prevalence of osteoporosis in women with fractures is twice that observed in the population, most fractures in the population occur in women without osteoporosis. It is only in the oldest sectors of the population (80+ years) that a majority of fractures occur in women with osteoporosis.

These observations have important implications in deciding who, when, and how to treat. If a drug halves fracture risk, for each fracture averted, three times more women must be exposed to treatment when treatment is aimed at 50–59-year-olds than 80 + −year-olds. In addition, to identify osteoporosis in women over 50 years, a mass screening program would be required. This can be done by questionnaires to assess for fracture probability, e.g.,

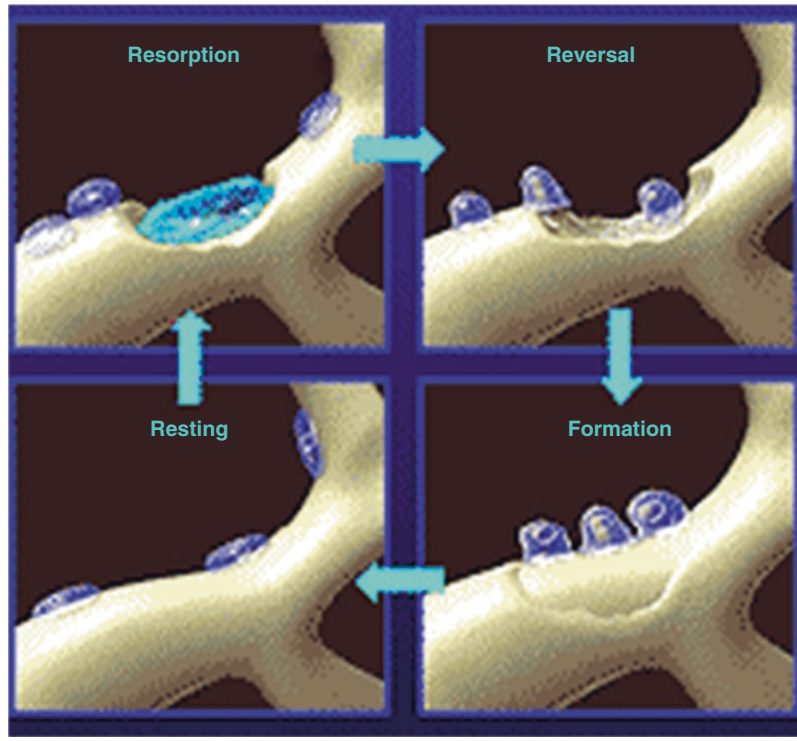

Fig. 12.3 The continuum of bone remodeling which in older adults pass into a phase of bone loss

FRAX. Adding other risk factors, such as bone remodeling status or prevalent fracture, may increase sensitivity and cost-effectiveness because it identifies the highest risk individuals who are most likely to benefit by actually averting the event they are likely to sustain.

These results as well as the outcomes of earlier studies such as the National Osteoporosis Risk Assessment (NORA) study [29]. This was a longitudinal observation study that included over 200,000 postemenopausal women who range in agre from 50 to 104 years and had baseline peripheral BMD measurements. The study assessed the frequency of low bone mass and its association with fracture in women 50–64 years of age in comparison to women ≥65 of age. NORA enrolled 200,160 postmenopausal women ≥50 years of age who had no prior diagnosis of osteoporosis. Baseline BMD was measured at the heel, forearm, or finger. A 1-year follow-up survey requesting incident fractures since baseline was completed by 163,935 women, 87,594 (53%) of whom were 50–64 years of age. Results revealed that more than half (52%) of the NORA women included in that work, who experienced an incident osteoporotic fracture, had a BMD T-score of −1.0 to −2.5.

Both results revealed a consistent pattern of a higher fracture incidence and lower peripheral BMD T-score in both the younger and the older women for all fracture sites, findings which support the suggestion that the definition of osteoporosis and the criteria for subsidized drug therapy would be better served by a gradient-of-risk model using a combination of several risk factors incorporating age and BMD with absolute fracture risk rather than being defined as a single BMD threshold [30–33].

The Problem of Osteopenia

The "Geoffrey Rose Prevention Paradox" applies to many chronic diseases, including osteopenia: "a large number of people at small risk give rise to more cases than the small number who are at high risk." In most countries less than half of women and men who sustain a fragility fracture

have osteoporosis as diagnosed by DEXA measurements of BMD. The majority have osteopenia. The outcomes of the NORA (Nordic Research on Aging) study were the first one to raise the attention to the "osteopenia challenge." Out of the 149,562 postmenopausal women aged 50–104 years (mean 64.5 years), only 6.4% of women had a BMD of <−2.5 SD (associated with 18% of all fractures and 26% of hip fractures), but 45.3% of women had a BMD of <−1.0 SD (associated with 70% of all fractures and 77% of hip fractures) [19, 29]. In the Rotterdam study of 4878 women who had DEXA measurements of the femoral neck and were followed up for a mean 6.8 years, the rate of self-reported nonvertebral fractures was 44% with osteoporosis, 43.3% with osteopenia, and 12.6% with normal BMD [34]. Similarly, in an Australian community study of 616 women who had DEXA measurements of the total femur, 124 women had one or more fractures. Of the women with fractures, only 26.9% had osteoporosis, 56.5% had osteopenia, and 16.6% had a normal BMD [35]. Most women and men who suffer from a fragility fracture do not have osteoporosis as defined by the WHO. Therefore, assessment of fracture risk and diagnosis and treatment should not be limited to those with osteoporosis but should include all patients with osteopenia and all patients with clinical risk factors for fracture.

Another work carried out by the Study of Osteoporotic Fractures Research Group in the USA has related the estimated time interval for 10% of women with different degrees of osteopenia to make the transition from osteopenia to osteoporosis. Normal BMD was defined as a T-score at the femoral neck and total hip of −1.00 or higher and osteopenia as a T-score of −1.01 to −2.49. Mild, moderate, and advanced osteopenia were defined as T-scores of −1.10 to −1.49, −1.50 to −1.99, and − 2.0 to −2.49, respectively. The intervals between baseline testing and development of osteoporosis in 4957 women aged 67 years and older (adjusted for BMI, current estrogen use and smoking, current or past use of oral glucocorticoids, and rheumatoid arthritis) in years with 95% confidence limits were normal BMD 16.8 (11.5–24.6), mild osteopenia 17.3 (13.9–21.5), moderate osteopenia 4.7 (4.2–5.2), and advanced osteopenia 1.1 (1.0–1.3). Accordingly, it is clear that the degree of osteopenia is a major factor in predicting the development of osteoporosis and of consequent fracture risk and the degree of osteopenia should be taken into account in arriving at all treatment decisions [36].

The Challenge of Case Finding: Mind the Gap

Among the large group of subjects with osteopenia, there exists a substantial subgroup with bone fragility contributing to the burden of fractures. If an aBMD measurement alone is used in an osteoporosis screening program, women with osteopenia will be excluded from further investigation and so will not be offered treatment [37–39]. Challenges of case finding of osteopenic patients are multifaceted (Table 12.1) including the healthcare professionals' awareness and interest in bone health, identifying specific subjects at high fracture risk as well as adopting appropriate management algorithms. One important approach to case finding—identifying those at risk for fracture in need of treatment, that is, applicable in standard clinical practice—is the use of the fracture risk assessment tool (FRAX) [38]. Another approach is to identify the structural basis of the bone fragility not captured by the aBMD measurement and thereby to quantify "microarchitectural deterioration of bone tissue," the descriptive component of the definition of "osteoporosis." Getting the right treatment to the right patient at the right time is of paramount importance if fracture rates are to be significantly reduced as the world's population ages and lifestyles change.

At the service setup, a good case can be made for the establishment of local groups, including generalists and specialists who are especially interested in osteoporosis, to agree on referral practices and treatment based on local resources. In large hospitals, an "osteoporosis clinic" including different disciplines may facilitate diagnosis and management. There is little doubt that the care of women and men with osteoporo-

Table 12.1 The challenge of case finding of osteopenia: possible causes and approaches to tackling

The challenge	Approach to case finding
Healthcare professionals	Patients with potential loss of bone mineral content (i.e., osteoporosis and osteopenia) are usually managed by general practitioners and specialists from various disciplines including orthopedics, rheumatology, gynecology, geriatrics, and endocrinology Few specialties receive training in osteoporosis for higher professional qualification Agree referral pathways Set up specialized bone health clinics
Fracture risk	Implement tools for assessment of absolute/probability of fracture risk in standard clinical practice Implement strategies in standard practice to identify patients with imminent fracture risk Quantify microarchitectural deterioration of bone tissue Adopting fracture liaison service
Appropriate management approach	Getting the right treatment to the right patient at the right time is vital to ensure prevention of fractures Adopting valid treatment algorithm for treatment of osteopenia

sis or osteopenia and those with fragility fractures, particularly the very elderly, can be enormously improved.

At the case finding level, strategies to ensure that individuals who are at high risk of sustaining fragility fractures in general, and hip fractures in particular, have been reliably identified by health systems and best practice guidance for treatment have been published [40].

Case Finding Strategies

While bone density remains one of the most valid and reliable measures of fracture risk, a better delineation of risk factors has led to renewed interest in absolute risk models such as FRAX. New imaging approaches, including vertebral morphometry, have been added to the diagnostic armamentarium and facilitate identification of fractures both early in the disease course (if properly identified) and with less radiation exposure to the patient. This is important because of the severe consequences of prevalent fractures in osteopenia as well as osteoporosis, not only of the hip but also of the much more common spine fractures.

Identification of Osteopenic Patients with High Fracture Risk

While BMD is used to reflect bone strength and, consequently, low BMD has been considered as a major risk factor for fractures, most patients presenting with a fracture do not have BMD-based osteoporosis, defined according to the World Health Organization (WHO) definition (T-score of −2.5 or below). The best example is hip fracture, where only half of the patients exhibit T-scores below −2.5 [41, 42]. In addition, and independent of bone-related risks, extra-skeletal risk factors such as falls contribute to fracture risk and are present in the majority of patients older than 50 years presenting with a clinical fracture, and falls are the dominant event leading to forearm and hip fracture [43]. Therefore, it is important to consider BMD screening for subjects who present with risk factors for bone loss as well as subjects older than 50 years old presenting with loss of balance and/or recurrent falls.

Identification of Patients with Prevalent Fractures

The primary risk factor for subsequent fracture is a prevalent low-energy fracture, irrespective of whether it is clinically apparent or not. Thus, most guidelines for treatment consider the presence of a low-energy fracture in an osteopenic patient a clear indication for specific osteoporosis therapy [44, 45]. A history of nonvertebral fracture is associated with a doubling of the risk of a subsequent fracture, and the subsequent fracture risk is even quadrupled after a vertebral fracture. The re-fracture risk is, however, not constant over time. It is highest (2–3X) in the years immediately after a first fracture, followed by a gradual

waning later on [46]. Forty to 50% of all subsequent fractures occur within 3–5 years after a first fracture, and the presence of such fractures demands rapid intervention with specific osteoporosis drugs to reduce the risk of a subsequent fracture. Prevalent hip, spine, and several other nonvertebral fractures are all associated with increased morbidity and mortality [15], which is higher immediately after fracture than later on. Hip, vertebral, and non-hip, nonvertebral fractures were each associated with approximately one-third of deaths. The major causes of death were related to cardiovascular and respiratory comorbidities [47].

Unfortunately subsequent follow-up of fracture patients after orthopedic fracture repair to identify patients in need of specific osteoporosis treatment is still very limited. Most studies show that only 10–15% of fracture patients treated at orthopedic departments are offered a DXA evaluation and even less patients are offered supplementation with vitamins D and Ca or specific osteoporosis treatment. Fortunately a lot of centers are recognizing this dilemma and have established initiatives for post-fracture care (e.g., fracture liaison service) [48]. Such interventions have the potential to reduce subsequent fractures, morbidity, mortality, and readmissions to hospital.

While hip and other nonvertebral fractures are clinically obvious, the detection of vertebral fractures constitutes a significant problem. Morphometric vertebral fractures are the most frequent fractures in women and men older than 50 years [49], and their presence is a strong predictor of future vertebral, nonvertebral, and hip fracture risk [50, 51]. Clinical vertebral fractures are characterized by back pain lasting for 2–3 months, depending on fracture severity, but they represent only a small subgroup of all vertebral fractures. In large-scale trials, symptomatic vertebral fractures constitute less than 10% of all morphometric fractures [52, 53]. Most morphometric vertebral fractures therefore remain undiagnosed, which results in many patients developing severe osteoporosis with multiple fractures and chronic pain, before effective treatment is initiated. Only when clinical suspicion, e.g., significant height loss, increasing kyphosis, protruding abdomen, rib-iliac crest distance of less than 2 cm, and acute or chronic back pain, is raised, a spine X-ray is performed. But even when lateral X-rays of the spine are available, vertebral fractures are often missed [54, 55].

Thus, detection of prevalent fractures is very important when making decisions on treatment in osteopenic women. This has been further facilitated by accessory software for DXA scanners yielding lateral X-rays of the spine, which permit assessment of vertebral fracture status. This procedure has been given many names: (vertebral morphometry, lateral vertebral assessment (LVA), vertebral fracture assessment (VFA)) (Fig. 12.4). The images are usually of good quality, albeit less detailed than conventional X-rays, and in most cases a good evaluation of compression fractures in the range Dorsal 4-Lumbar 4 is possible. Advantages are low radiation dose, the availability of semiautomatic image analysis tools to assist in measuring vertebral shapes of the individual vertebrae, its plan-parallel projection, and its high negative predictive value. The disadvantage is the inability to study upper thoracic vertebrae, but only a minority of fractures are found there.

If pathology outside this region of interest (ROI) is suspected, other imaging techniques will have to be used. The experience in most centers employing this methodology is, however, that such referrals are needed in less than 10% of cases. According to the International Society for Clinical Densitometry (ISCD), additional X-ray imaging is needed in cases of two or more mild (grade 1) deformities without any moderate or severe (grade 2 or 3) deformities, when lesions in vertebrae cannot be ascribed to benign causes, or when vertebral deformities are found in a patient with a known history of a relevant malignancy [54]. The methodology also permits assessment of spondylosis, and even arteriosclerosis of the abdominal aorta can be evaluated. Differential diagnosis of radiologic osteopenia is shown in Table 12.2.

The prevalence of previously unknown morphometric vertebral fractures has been studied in various at-risk populations. In a study of women

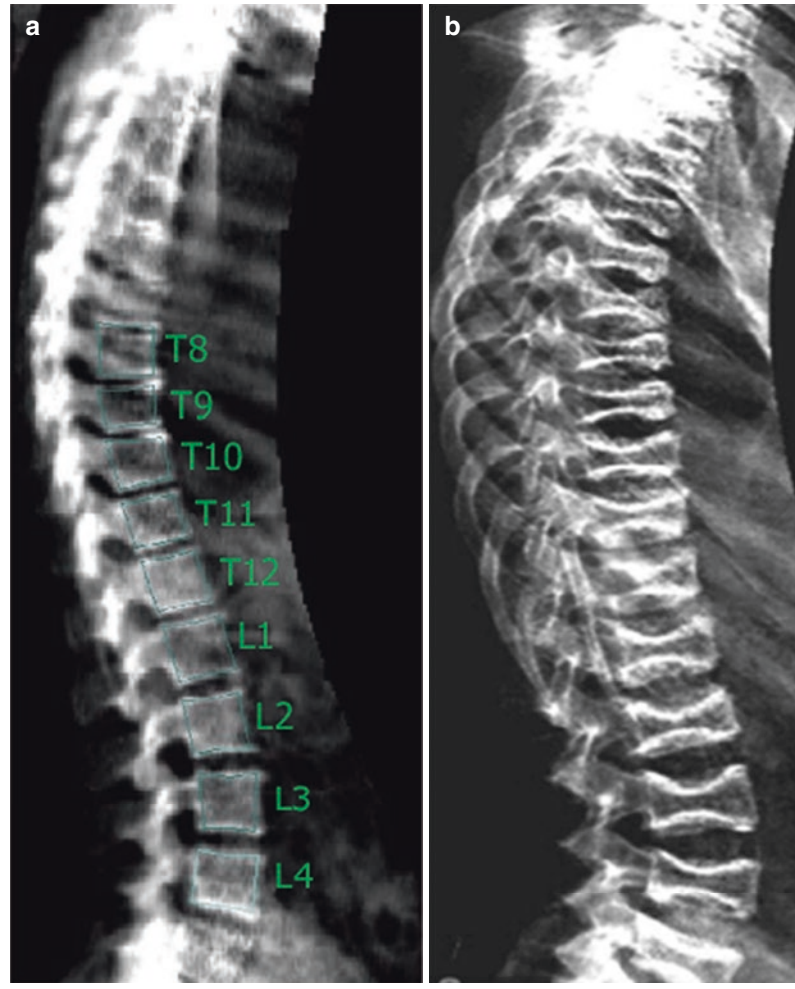

Fig. 12.4 Vertebral morphometry. (**a**) Normal spine. (**b**) Osteoporotic vertebral fractures

Table 12.2 Differential diagnosis of radiologic osteopenia

Disease	Specific radiographic clues
Hyperparathyroidism	Subperiosteal resorption
Osteomalacia	Looser zones
Disseminated multiple myeloma	Focal lytic lesions

and men presenting with a nonvertebral fracture, one out of four had a prevalent morphometric vertebral fracture on vertebral morphometry that was not recognized previously [56]. In another study, the prevalence of morphometric vertebral fractures was 21% in postmenopausal women with osteopenia [68/25].

In patients with BMD-diagnosed osteoporosis, a baseline vertebral fracture assessment (vertebral morphometry) is not necessary for treatment decisions but is helpful in detecting lack of treatment efficacy during follow-up. Fractures occurring in L1–L4 will increase apparent BMD and may be difficult to see on the standard AP image provided by a routine scan.

Identification of High-Risk Individuals Without History of Fracture

The vast majority of osteoporotic fractures take place in osteopenic patients without prevalent fractures. While on one hand many aspects of

osteoporosis and fracture risk are clinically recognizable (such as age, gender, and body weight), even before a first fracture has occurred, on the other hand, relative risk estimates are difficult to apply in daily clinical practice. This has been attributed to the finding that their clinical significance depends on the prevalence of fractures in the general population. In order to better delineate individuals at high risk of osteoporotic fracture, the WHO developed the Fracture Risk Assessment (FRAX) tool (www.shef.ac.uk./FRAX). FRAX is an internet-based clinical tool for calculation of fracture risk in the individual patient based on assessment of significant risk factors for osteoporotic fracture. The FRAX algorithm is based on large-scale prospective population-based studies which isolated the following risk factors as significant determinants of fracture risk: age, gender, body weight and body mass index, a history of fracture, hip fracture in parents, current smoking, excessive alcohol intake, rheumatoid arthritis, glucocorticoid use, and other forms of secondary osteoporosis (Table 12.3) [44].

The National Osteoporosis Foundation (NOF) in the USA and the National Osteoporosis Society (NOS) in the UK have integrated FRAX and BMD for case finding of individuals at high risk for fracture and for treatment decisions in their new guidelines. Treatment thresholds were put at 10-year fracture risk estimates from the FRAX algorithm, at which fracture prevention became cost-effective. Generally, FRAX-based 10-year fracture risk probability of 20% or higher for all osteoporotic fractures and 3% or higher for hip fracture are considered reasonable intervention thresholds [45].

Table 12.3 Causes of secondary osteoporosis as identified in FRAX tool

Causes of secondary osteoporosis as identified in FRAX tool for calculation of fracture probability
Untreated hypogonadism in men and women, anorexia nervosa, chemotherapy for breast and prostate cancer, and hypopituitarism
Inflammatory bowel disease and prolonged immobility (e.g., spinal cord injury, Parkinson's disease, stroke, muscular dystrophy, and ankylosing spondylitis)
Organ transplantation
Type I diabetes and thyroid disorders (e.g., untreated hyperthyroidism and overtreated hypothyroidism)

FRAX identifies patients at increased risk of osteoporotic fracture based on some of the dominant risk factors but cannot be used in isolation. However, several known determinant of fracture risk are not included in FRAX. The algorithm does not take into account well-known "dose effects" like glucocorticoid dose. Also, FRAX does not differentiate between having history of one or more osteoporotic fracture and when this fracture(s) has happened, hence miscalculation of the imminent fracture risk. Incorporation of BMD results is limited to results of BMD in the femoral neck. However, total hip BMD is a more precise measure and can be used interchangeably with femoral neck BMD in women, but not in men. Vitamin D deficiency, a well-established risk factor for falls and hip fracture, is not included. The same holds for bone markers, which have been shown to independently affect fracture risk. FRAX may also underestimate fracture risk in individuals with increased propensity for falls. More than 80% of women and men presenting with a clinical fracture to the emergency unit have one or more fall-related risks and exhibit a fourfold increased risk of falls in the year leading up to admission. In another study on 5- and 10-year absolute risks for fractures in patients using glucocorticoids, a history of falls had a greater impact on fracture risk than any other evaluated risk [57]. Finally, it is important to remember that FRAX is only applicable in untreated patients. It cannot be used as a helper in decision-making in patients, who already received specific osteoporosis treatment. However, recent studies revealed the applicability of FRAX in patients who received osteoporosis therapy [58, 59]. A recent study from Switzerland used FRAX to identify patient profiles with increased probability of fracture beyond currently accepted reimbursement thresholds for BMD and osteoporosis. The study found that in particular age, BMI, and parental history of fracture increased the risk for fracture substantially [60].

In patients with BMD-based osteoporosis or presenting with a clinical fracture or both, diag-

nostic evaluation is necessary to exclude secondary osteoporosis. Such evaluations should include hematologic parameters (Hb, WBC), serum 25-(OH)D3, calcium, creatinine, thyroid-stimulating hormone, parathyroid hormone (PTH), serum/urine electrophoresis, testosterone, and prolactin (in me). According to the clinical picture and suspicion, other serum measurements such as plasma cortisol, tests for celiac disease, and selected other evaluations looking for secondary causes are indicated [61]. It is generally considered that secondary causes of osteoporosis are more common in men than women. Among secondary causes, hypogonadism, which results from the treatment of breast cancer with aromatase inhibitors or the use of androgen deprivation therapies for prostate cancer is considered an emerging clinical challenge [76/29].

There is general consensus on the need for specific osteoporosis treatment in patients with spine or hip fractures and low BMD. For other nonvertebral fractures, different societies advocate different strategies. The NOS recommends drug treatment in all postmenopausal women with a history of any fragility fracture [12], while the NOF advocates performing a dual-energy X-ray absorptiometry (DXA) on patients after nonvertebral fractures to decide, whether specific osteoporotic therapy is indicated. Drug treatment should then be considered in patients having osteoporosis and in patients with osteopenia when FRAX indicates a 10-year fracture probability of at least 3% for hip or at least 20% for major fractures [41].

Thresholds for Intervention

Critically, none of the fracture risk assessment tools currently available directly yield an indication for treatment. Thus, the probability of fracture risk generated needs to be interpreted, and thresholds set, above which pharmaceutical intervention is judged to be warranted. The cost-effectiveness of a therapeutic approach is often a key consideration in threshold setting.

There are two major approaches to the health economic assessment in a particular condition [62, 63]. First, one can assess the cost-effectiveness of the intervention and set the threshold for intervention, for example, FRAX probability, accordingly. Alternatively, one can derive a clinically informed and appropriate intervention threshold and use cost-effectiveness analysis to validate a threshold. The 2017 National Institute for Health and Care Excellence (NICE) updated Multiple Technology Appraisal (MTA) on bisphosphonate use in osteoporosis [64] serves as an example of how, for a common disorder, the strict application of cost-effectiveness thresholds for relatively inexpensive drugs may lead to counterintuitive and potentially harmful guidance [62, 65]. The widespread availability of low-cost generic forms of the main oral and intravenous bisphosphonates resulted in oral treatments being deemed cost-effective above a 1% risk of major osteoporotic fracture. Unfortunately, these were initially interpreted by some payers as clinical intervention thresholds, but, in fact, NICE directs practitioners to the UK National Osteoporosis Guideline Group (NOGG) guidance, which provides an illustration of the alternative approach to threshold setting. NOGG developed its guidance on the basis of clinical appropriateness, setting the threshold at the age-specific 10-year FRAX probability of fracture equivalent to women having already sustained a fracture. This approach, which avoids inappropriate over-treatment of older individuals and under-treatment of younger individuals, has been shown to be cost-effective [44] and has been adopted in many countries [66].

The approach to threshold setting varies substantially across the world, with guidelines using either fixed or variable age-dependent threshold and, sometimes, combining a probability threshold with the requirement for BMD in the osteoporotic range [67]. Even between the USA and UK guidance, there is marked heterogeneity. The National Osteoporosis Foundation in the USA suggests BMD assessment in women and men aged $\geq$65 years or 70 years, respectively, or at younger ages if they have had a prior fracture, and treatment for those with either a history of vertebral or hip fracture, osteoporosis on BMD

assessment, or osteopenia and a 10-year FRAX-calculated probability of a hip fracture probability of ≥3% or major osteoporotic fracture probability of ≥20% [68]. Conversely, as mentioned above, the UK National Osteoporosis Guideline Group (NOGG) recommends the use of FRAX with or without BMD as the first step in risk assessment, with prior fragility fractures at older ages usually a sufficient basis for treatment regardless of other risk factors. Where a 10-year probability has been generated by FRAX, threshold graphs are subsequently used to guide appropriate intervention. The possible outcomes include patient reassurance with further risk calculation at a later date (low risk), BMD assessment (intermediate risk), or immediate treatment without the need for BMD assessment (high risk) [69]. Once BMD has been performed, the 10-year probability of fracture is plotted by age, either above or below a single treatment threshold, which is set at the 10-year fracture probability conferred by having had a previous fragility fracture, corresponding to older UK national guidance. The treatment threshold, thus, increases with age, but even so, the proportion of women potentially eligible for treatment rises from 20 to 40% across the age range assessed. A key message is that it should not be assumed that one size will fit all countries. For example, intervention in China at a threshold of 20% for FRAX major osteoporotic fracture, a threshold used in the USA, would lead to only a very tiny proportion of the population treated [67]. Accordingly, the International Osteoporosis Foundation has published guidance relating to osteoporosis and corticosteroid-induced osteoporosis, which can be readily modified to reflect national priorities and subsequent treatment thresholds [70–72].

Treatment Decisions

Criteria for diagnosis are not the same as those for treating osteoporosis and osteopenia. Treatment must be based on assessing future fracture risk and on the medical state/risk factors of each individual. Therefore, authorities agree that decisions about treatment must be individualized and based on good clinical judgment, taking into account patient preferences, comorbidities, previous drug use and risk factors not captured in FRAX, and possible under- or overestimation of fracture risk by FRAX [73, 74]. Treatment of osteopenia was reviewed in an article published by Erickson [40].

Lifestyle Changes General

Changes in lifestyle like smoking cessation, regular exercise, and optimization of nutrition should be implemented in all osteopenic patients. Patient compliance with these measures is, however, poor, and very few prospective data on the anti-fracture efficacy of such measures exist. Smoking has emerged as a significant risk factor for fracture in many epidemiological studies [75–77], albeit the influence of dose and duration is less well defined. The same holds for exercise [78, 79], but exercise can slow down bone loss after menopause and is important for muscular strength and coordination in the elderly [77]. The impact of poor nutrition on skeletal health is apparent in its most extreme form in anorexia nervosa, where significant improvement of skeletal mass is important without a reversal of caloric intake in these young women [80, 81].

Calcium and Vitamin Supplement Therapy

In recent years, vitamin D deficiency has emerged as a very important risk factor for osteoporotic fracture, especially at the hip. High turnover bone loss due to secondary hyperparathyroidism due to vitamin D deficiency is considered a major pathogenetic factor in senile osteoporosis [82]. Vitamin D deficiency is endemic worldwide [83], and patients with hip fracture generally have the lowest vitamin D levels among all patient groups studied [100, 101/39, 40]. Vitamin D deficiency does cause not only weaker bones due to osteomalacia but also severe myopathy with loss of muscle strength, selective loss of the rapid type 2 fibers,

dyscoordination, and consequently increased propensity for falls [84]. It is therefore not surprising that meta-analyses indicate that correction of vitamin D deficiency results in a decreased fall and fracture risk [85, 86], but the effects depend on the dose of vitamin D and the target population [87]. It is still a matter of debate which doses of vitamin D3 or D2 supplementation are necessary/optimal, taking into account baseline vitamin D status and the desired serum levels to be achieved by supplementation. Daily intake of 400 IU/day is not sufficient, while 800 IU/day reduce falls and fractures significantly [85, 86]. In their controlled clinical trial, Bischoff-Ferrari et al. demonstrated that in a population of post hip fracture patients maybe even higher doses are warranted. In this study, a dose of 2000 IU/day of D3 was superior to 800 IU/day in a cohort of 176 patients all undergoing moderate physiotherapy. Over a 1-year period, the dose of 2000 IU resulted in 25% less falls, 39% less readmissions to hospital, and a staggering 90% reduction in all cause infections, when compared to 800 IU per day [88].

Several reviews have emphasized the need of addition of calcium to vitamin D for fracture prevention, and a dose of 1000 to 1200 mg/day was advocated [89]. Whether the calcium dose can get too high is still a matter of debate, but studies from one center published in 2008 reported that supplements of 1000 mg calcium/day on top of a baseline intake of 800 mg/day increased the risk of vascular events including myocardial infarction in healthy postmenopausal women and men [108, 109/47, 48]. In this context, it is reassuring that, when intake of vitamin D3 is sufficient, the need for calcium intake is considered to be lower [90].

Prevention of Falls and Protection Against Fall Trauma

Over 90% of hip fractures and all Colles fractures are caused by falls, mostly in house. The role of physical exercise is still debated, but exercise interventions together with other measures such as removing loose carpets, reduce use of sleep medicine and other tranquilizers, correct visual impairment, etc. reduce the risk and rate of falls in older people living in the community [91], but no data that fall prevention decreases the risk of fracture are yet available. Similarly, as noted above, vitamin D supplements improve muscle function and decrease the risk of falls. The role of hip protectors remains controversial. They seem to work in nursing homes [92, 93], but less in community-dwelling elderly, mainly due to discomfort and practicality [94, 95].

Pharmacotherapy

Most clinical trials of specific therapies for osteoporosis and osteopenia have focused on patients with osteoporosis and/or the presence of hip or vertebral fracture. Few randomized controlled trials have been performed on patients with osteopenia, but some have included osteopenic patients allowing post hoc analyses.

Alendronate In the Fracture Intervention Trial (FIT) 1 and FIT 2 trials of patients with osteopenia of the femoral neck with and without vertebral fractures, alendronate decreased the risk of radiological fractures (relative risk (RR) 0.48, 95% confidence interval (CI) 0.41–0.81) and of clinical vertebral fractures (RR 0.41, 95% CI 0.19 - 0.76) [96]. The FOSIT study evaluated the safety and effects on bone mineral density (BMD) of alendronate 10 mg in postmenopausal women with lumbar spine BMD T-score of −2 or more. After 12 months the incidence of nonvertebral fractures was reduced significantly by 47% [97].

Risedronate Post hoc analysis of data available from four Phase III risedronate trials: BMD Multinational (BMD-MN) [98], BMD-North America (NA) [99], Vertebral Efficacy with Risedronate Therapy-Multinational (VERT-MN) [100], and Vertebral Efficacy with Risedronate Therapy-North America (VERT-NA) [101] (in which efficacy and safety of risedronate in the prevention and treatment of postmenopausal

osteoporosis have been demonstrated) were carried out. Using data only from osteopenic women included in these trials, the effect of risedronate in reducing the risk of fragility fractures in women with femoral neck T-scores in the osteopenic range and without prevalent vertebral fracture was evaluated. Six hundred and twenty postmenopausal women with osteopenia were included, receiving either placebo (=309) or risedronate 5 mg (=311). Risedronate reduced the risk of fragility fractures by 73% over 3 years versus placebo (=0.023); cumulative fragility fracture incidence was 6.9% in placebo-treated versus 2.2% in risedronate-treated patients. The magnitude of the effect was similar in the sensitivity analysis subset [102].

Zoledronate Zoledronate (also known as zoledronic acid) has characteristics that make it attractive for use in women who have osteopenia. It is administered by intravenous injection at intervals of 1 year or longer. Reid et al. [103] conducted a 6-year, double-blind trial involving 2000 women with osteopenia (defined by a T-score of −1.0 to −2.5 at either the total hip or the femoral neck on either side) who were 65 years of age or older. Participants were randomly assigned to receive four infusions of either zoledronate at a dose of 5 mg (zoledronate group) or normal saline (placebo group) at 18-month intervals. A dietary calcium intake of 1 g per day was advised, but calcium supplements were not provided. Participants who were not already taking vitamin D supplements received cholecalciferol before the trial began (a single dose of 2.5 mg) and during the trial (1.25 mg per month). The primary endpoint was the time to first occurrence of a nonvertebral or vertebral fragility fracture. Results revealed that women who received zoledronate had a lower risk of nonvertebral fragility fractures (hazard ratio, 0.66; P = 0.001), symptomatic fractures (hazard ratio, 0.73; P = 0.003), vertebral fractures (odds ratio, 0.45; P = 0.002), and height loss (P < 0.001). The study concluded that the risk of nonvertebral or vertebral fragility fractures was significantly lower in women with osteopenia who received zoledronate than in women who received placebo.

Strontium In the Spinal Osteoporosis Therapeutic Intervention (SOTI) and TReatment Of Postmenopausal OSteoporosis (TROPOS) trials [104] in women with osteopenia of the lumbar spine, strontium ranelate reduced the risk of vertebral fracture in women with no prevalent fractures (RR 0.41, 95% CI 0.17–0.99) and in women with prevalent fractures (RR 0.62, 95% CI 0.44–0.88).17 In women with osteopenia at both the lumbar spine and femoral neck, treatment with strontium ranelate reduced the risk of fracture (RR 0.48, 95% CI 0.24–0.96). Specific drug treatment appears to be effective and is justified to reduce the risk of further fractures in patients with osteopenia, particularly those with prevalent fractures.

Raloxifene Selective estrogen receptor modulators (SERMs) are nonsteroidal synthetic agents, which exert estrogen-like properties on the bone and cardiovascular systems but estrogen antagonistic actions in the breast and, in some cases, the endometrium. The first SERM developed both for breast cancer prevention and for osteoporosis, raloxifene, is now approved in many countries for the treatment of osteoporosis.

Multiple Outcomes of Raloxifene Evaluation (MORE) study [105] reported similar rates of vertebral fracture risk reduction in raloxifene-treated women with osteopenia—defined as a total hip T-score > −2.5 without a prevalent vertebral fracture—compared with those with osteoporosis at 3 years. The relative risk reduction for vertebral fractures with raloxifene compared with placebo was 0.53 (0.32–0.88, 95% CI) in osteopenic women; the relative risk for clinical vertebral fractures in osteopenic women was 0.25 (0.04–0.63). Information about reduction of nonvertebral fractures has not been provided raloxifene analyses.

Hormone Replacement Therapy (HRT) Conjugated equine estrogens significantly reduced the risk of clinical vertebral, hip, and total fractures in postmenopausal women in the Women's Health Initiative, the vast majority of whom did not have bone density testing but who were not selected based on having diagnosed osteoporosis [106].

Estrogen receptors have been demonstrated on both osteoblasts and osteoclasts [107, 108]. Estrogen replacement therapy (ERT) or combined estrogen/progestin therapy (HRT) reduces bone turnover by about 50% and improves bone balance at each individual BMU in postmenopausal women [109]. The Women's Health Initiative (WHI), a randomized study comprising over 16,000 postmenopausal women, demonstrated a significant 34% reduction of hip fractures after treatment with combined conjugated equine estrogen and [110] estrogen alone in those women who had undergone hysterectomy [111]. The study, however, also found a nearly 30% increased risk of coronary heart disease, 40% increased risk of stroke, increased risk of thromboembolic events, and 26–35% increased risk of breast cancer. These results led to less enthusiasm for long-term estrogen therapy worldwide. The decision to initiate ERT/HRT should be individualized and based on a balanced assessment of risk and benefits by the physician and patient. Current recommendations support restricting the use of estrogen in most women to 5 years in the perimenopausal period [40], with the aim mainly to reduce hot flushes and other postmenopausal symptoms, and regular mammography should be performed.

Androgen Replacement Therapy in Males

In hypogonadal males, low testosterone levels result in a high turnover state in bone leading to bone loss and increased risk of fracture. The main driver of this turnover increase is low circulating estrogen levels, just as in postmenopausal women [112]. The low estrogen arises from insufficient aromatase conversion from testosterone, either due to low testosterone levels or insufficient aromatase activity [113]. Testosterone replacement therapy in hypogonadism will increase circulating estradiol levels and thereby reduce bone turnover and increase BMD [114]. In hypogonadism, usually defined as total testosterone levels below 8 nmol/l and hypogonadal symptoms [115], testosterone replacement will lead to increases in bone mass similar to those seen after ERT/HRT [115, 116], but randomized controlled studies with fracture endpoints are still lacking. Due to the fear of inducing prostate cancer, clinicians have, however, been quite reluctant to institute testosterone replacement therapy. Recent data suggest, however, that prostate cancers occurring in hypogonadal males have a worse prognosis than cancers occurring in eugonadism [117]. Moreover, 16 population studies were unable to demonstrate any relation between testosterone levels and risk of prostate cancer [50]. Nevertheless, regular controls of prostate-specific antigen (PSA) and digital rectal exploration before and after institution of therapy are still warranted.

Management of Osteoporosis and Osteopenia in the Very Elderly

Very elderly women and men (aged 80 years and over) are the fastest-growing segment of the population. About 25–30% of the population burden of all fragility fractures is in women and men over 80, who are at high risk for fracture, particularly nonvertebral fracture, because of their high prevalence of osteoporosis and osteopenia and high incidence of falls. After a hip fracture, approximately 20% of patients do not survive more than a year, and 50% do not regain their previous level of independence. Vertebral fractures are associated with back pain, height loss, kyphosis, and functional disability. The prevalence of vertebral deformities increases from 5–10% in women in the 50s to 45–55% of those in the 80s. Only a proportion of older women and men with osteoporosis or osteopenia receive specific treatment. Some clinicians may consider

that patients over 80 years are too old or that it is too late to significantly alter the course of the disease. Based on pooled data of 1392 women aged 80 or over from the HIP, VERT-MN, and VERT-NA trials [10–13], risedronate resulted in a 44% reduction in vertebral fractures but not in nonvertebral fractures [102]. In 1488 women between 80 and 100 years of age from the SOTI and TROPOS trials [104] and followed up for 3 years, strontium ranelate reduced the risk of vertebral, nonvertebral, and clinical symptomatic fractures within the first year by 59% ($p = 0.002$), 41% ($p = 0.027$), and 37% ($p = 0.012$), respectively. At the end of 3 years, vertebral, nonvertebral, and symptomatic clinical fractures were reduced by 32% ($p = 0.013$), 31% ($p = 0.011$), and 22% ($p = 0.040$), respectively. Strontium ranelate was reported to be well tolerated and as safe as in younger patients. Women and men are therefore never too old for treatment, and it is never too late to treat those with osteoporosis or osteopenia, particularly when they have a fragility fracture.

Treatment Algorithm for Osteopenia

An ever-increasing array of effective treatments is available to protect patients with osteopenia against fractures. While there is general consensus on treating osteopenic individuals with prevalent low-energy fractures, the treatment of osteopenia without fracture is still debatable. However, current evidence indicates that specific pharmacotherapy should be instituted if an osteopenic patients has prevalent fractures or suffers new fractures, be it clinical or asymptomatic. Moreover, a significant accumulation of several significant risk factors, for example, as indicated by the FRAX tool may constitute an indication for pharmacotherapy. Patients without such risk factors should be counseled on a "bone-friendly" lifestyle with nutritional modifications, regular exercise, moderation in alcohol use, and if possible smoking cessation. In patients with low vitamin D levels, Ca and vitamin D supplementation may also be indicated (Fig. 12.5).

Bisphosphonates, taken orally or intravenously, remain the dominant treatment modalities for osteopenia. They reduce fracture risk in osteoporotic as well as osteopenic individuals. Questions exist about the very long-term safety of these drugs, but the best data available so far [72] suggest that 10 years with 90% suppression of bone turnover is safe. Denosumab constitutes a possible alternative to bisphosphonates. In younger postmenopausal women with osteopenia, estrogen or estrogen/progestin still has a place as a short-term (up to 5 years) treatment, especially in women with menopausal symptoms. Similarly, SERMs should be considered in younger postmenopausal women, especially those at increased risk of breast cancer. In males with low testosterone levels, testosterone substitution is indicated as it improves skeletal integrity. However, long-term controlled studies on this treatment are still required, but the risk of prostate cancer does not seem to be as big as previously anticipated. Teriparatide would currently rarely be considered in women or men with cheaper anabolics available; however, initial therapy with anabolics to bring osteopenic patients out of the risk zone followed by an antiresorptive would probably be the ideal treatment [40].

In conclusion, osteopenia is not a disease but is a marker for risk of fractures. Older persons are at risk of having unrecognized osteoporosis, which may be discovered only after a fracture (such as a broken hip). The need to establish treatment efficacy in osteopenia has become more pressing, given the clinical trend to base intervention decisions on absolute fracture risk. Many patients at high risk for fracture do not have T-scores of less than −2.5 but rather have osteopenia in combination with other risk factors, such as age. Intervention in such patients currently lacks an adequate evidence base, though several therapeutic options are available. A treatment algorithm has been suggested based on bone mineral density and the fracture risk probability. If the bone density is already abnormal, lifestyle changes can help slow progression of bone loss and reduce the occurrence of fractures. Pharmacotherapy is

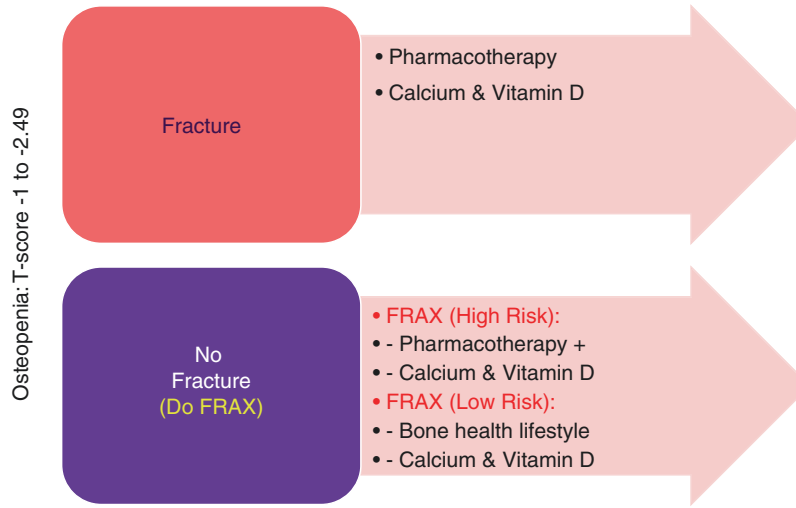

Fig. 12.5 Algorithm for osteopenia treatment: intervention thresholds based on the occurrence of fracture and the 10-year risk probability of major osteoporotic fracture/hip fracture calculated by FRAX tool. High fracture risk: major osteoporosis fracture risk >20%/hip fracture risk >3%. Low fracture risk: major osteoporosis fracture risk <20%, hip fracture risk <3%

indicated in patients with osteopenia and low-trauma fractures or at high risk of sustaining a fracture.

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Part III

Prevention: Recent Advances

Imminent Fracture Risk

13

Yasser El Miedany

Introduction

Fragility fractures due to osteoporosis are common. More than nine million fragility fractures have been estimated worldwide based on the year 2000 [1], and in Europe, 3.5 million fragility fractures were reported to occur annually [2]. In a study of patient records in Malmö, Sweden, for women aged 50 years, the lifetime probability of a fragility fracture was 23% for hip fracture and 15% for clinical vertebral fracture [3]. Moreover, the number of fragility fractures is expected to rise as the population ages, and in Europe, a 28% increase in the number of fragility fractures has been estimated by 2025 [4].

Fragility fractures cause substantial individual burden related to the significant reduction in a patient's mobility, functional ability, and quality of life [5, 6]. Premature mortality following fracture is also well recognized, particularly for hip and vertebral fractures [7–10], and there is accumulating evidence of increased mortality risk following other types of osteoporotic fractures [8–14], although increased mortality following minor fractures, such as those of the forearm, has not been demonstrated in all studies [9, 15]. In concordance, earlier studies revealed increase in morbidities associated with fragility fractures which was found to be greater than those attributed to aging alone and represents a major clinical problem [16–19]. Consequently, an understanding of the variables leading to fracture is an important area of research, to enable treatment strategies to focus on those most at risk and effectively reduce the clinical burden of disease.

Multiple factors are known to increase the risk of sustaining a fragility fracture [20–22]. Among them, prior fragility fracture is a well-documented major risk factor for future fragility fracture [23–26]. The risk of a subsequent fracture changes over time, and the time elapsed since sustaining a prior fracture is now recognized as an important factor influencing subsequent fracture risk (Fig. 13.1). The concept of "imminent risk" for fracture, defined as a markedly elevated risk of fracture within the next 12–24 months, has been emphasized over the past few years, with calls for implementing it into standard clinical practice [27–30]. This chapter will discuss the concept of imminent fracture risk, its importance, and the challenge of identifying the long-term risks of fractures. It will expand to answer the question whether imminent risk is observed whatever the location of the previous fracture and present an approach to predict imminent risk for fracture. The chapter will also discuss the patients' perception about osteoporotic fractures and the possibility of extending the imminent risk concept to patients with osteoporosis but (not yet) fracture. Lastly the chapter will present how the imminent

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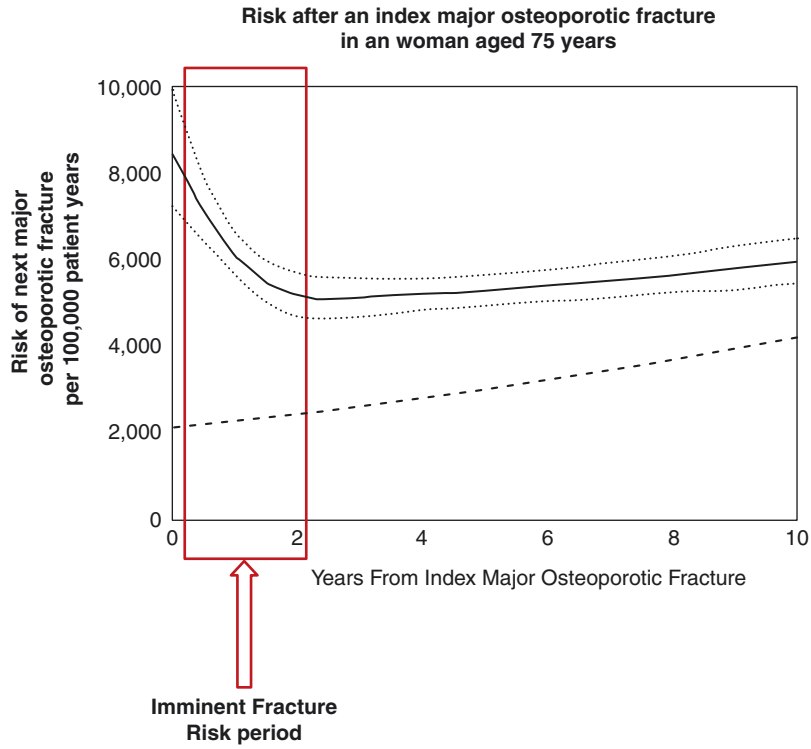

Fig. 13.1 Time dependency of re-fracture after index fracture adapted from Johansson et al. [36]. Solid line, risk per 100,000; dotted lines, 95%CI; dashed line, risk of first major osteoporotic fracture in population (Springer Publisher/how to get permission)

risk of subsequent fracture after the first fracture creates a window of opportunity to prevent new fractures and how this can be the rationale for adopting the fracture liaison services.

Imminent Fracture Risk

Fractures due to fragility are the strongest risk or indicator of future fractures. Several studies documented this relation and revealed that patients who have had a fracture at any site present approximately twice the risk of having a fracture in the future, in comparison with individuals who have never had such injuries. Johnell et al. [31] reported that patients with fractures due to low-energy trauma to the wrist, hip, proximal humerus, or ankle present a risk of future fractures that is almost four times greater. Also, patients with a vertebral fracture will have new vertebral fractures within the next 3 years, and many will have them within the first of these years [31]. Other studies revealed that patients with vertebral fractures present a risk of having similar injuries in the future that is almost five times higher and a risk of having hip fractures and other nonvertebral fractures that is twice as high. Patients who suffer wrist fractures present a relative risk of having hip fractures in the future that is almost twice as high. Secondary fractures occur rapidly after the first fracture, and the risk of subsequent fractures seems to be higher especially in the first year [32, 33].

In a large community-dwelling population, 41 and 52% of subsequent fractures in women and men, respectively, occurred within 2 years after initial fracture [34]. Subsequent fractures cluster in time after the first fracture [35]. This has been shown in a population-based study of 4140 postmenopausal women aged between 50 and 90 years; 22% had a first fracture and 26% had a subsequent one; 23% of all subsequent fractures occurred within 1 year (and 54% within 5 years) [35]. Thus, the relative risk is not constant overtime: it reaches "5.3" 1 year after the fracture and declines thereafter: 2.8 within 2–5 years and 1.4 within the 6–10 years. The 1-year absolute risk for subsequent fracture was 6.1%. Analyzing in

details the time-dependent effect showed that there is a 65% higher risk of subsequent fracture in women with a recent one as compared to patients with a prior fracture more than 5 years before. Such results were confirmed in a large population-based cohort of 18,872 men and women: 1 year after the first major osteoporotic fracture, the risk of a second one was 2.7 (2.4–3.0)-fold higher than the population risk [36]. Consequently, there is a high need for prioritizing patients who sustained a fracture for assessment and starting treatments, so as to avoid other secondary fractures [37–39]. Contrary to what might be imagined, these patients can benefit greatly from treatment [40, 41].

Therefore, initiatives for avoiding secondary (subsequent) fractures should be offered to all men and women over the age of 50 years who have had fractures due to fragility, since these fractures may precede hip fractures in a cycle in which one fracture leads to another, in a "cascade" of fractures [42–44]. An initial fracture due to fragility is sufficient for requesting an evaluation that includes measurement of bone mineral density, with evaluation of the risk of fractures, and for starting the treatment if there is no formal contraindication [45, 46]. Studies with the highest level of evidence have shown that osteoporosis can be treated, thus diminishing the likelihood of fractures in the future [46]. Around 50% of all cases of hip fracture are concentrated in 16% of the postmenopausal female population, with histories of fractures. Therefore, secondary prevention presents an opportunity for intervention in around half of all hip fracture patients [47–49].

The Challenge of Identifying the Long-Term Risks of Fractures

The difficulty in assessing the long-term risk of an outcome such as re-fracture stems from its dependency upon survival. The most widely used method to analyze time-to-event outcomes is the Kaplan-Meier method. This method was initially designed to analyze the time to a single event. With this method, any other outcome, such as death, which may prevent the outcome of interest, such as re-fracture, is censored. This is not a problem if the other events are independent of the event of interest, e.g., loss to follow-up. However, if a competing event is related to the event of interest and particularly if it is a high-frequency event, censoring of the competing risk can lead to an overestimate of the event of interest. This is exactly the case following fracture, when both re-fracture and associated mortality are high and re-fracture is itself associated with increased mortality. Moreover, it is axiomatic that in the event of a patient dying, there is no possibility of a subsequent fracture [50].

The use of a competing risk model, in which both these outcomes are considered as separate time-to-event occurrences, and which does not make any assumptions about dependency, overcomes the shortcomings of the Kaplan-Meier analysis. Although competing risk or cumulative incidence competing risk (CICR) analyses have been mainly used in the cancer literature, they are now also appearing in other medical fields.

In order to present a realistic picture of all the outcomes of interest following an event such as fracture, the most accurate way of describing the separate incidences of these outcomes is to use a competing risk model. In such a design, all separate outcomes are modeled, and censoring is reserved for those whose time of follow-up is limited by their time of entry into the study or by their loss from the study. Importantly, a competing risk analysis in this situation should simultaneously describe all the possible outcomes following fracture, including re-fracture, mortality, and mortality following re-fracture. The simpler competing risk model in which re-fracture is considered as an endpoint itself, without following up its consequences, will underestimate the overall mortality.

Knowing the true risk of re-fracture, mortality following fracture, and mortality following re-fracture is important from a clinical point of view for a number of reasons. First, it is well established that, at least for those with osteoporosis and a low bone density, up to 50% of re-fractures can be prevented with treatment. Second, there is increasing evidence that premature mortality is related to fracture. Third, there has been recent

evidence that treatment may reduce post-fracture mortality risk. Thus, accurate reporting of all fracture outcomes is essential [51–55].

Imminent Risk and the Location of the Previous Fracture

Central Versus Peripheral Sited Fractures

The predominant sites of fractures vary with age, and proposed explanations include changes in fall tendency, fall mechanism, and differential loss of cortical and trabecular bone at different stages of aging [56, 57]. In clinical assessment after a fragility fracture, the site of fracture adds important information on future fracture risk. In general, while a fragility fracture doubles the risk of any subsequent fracture [44], a hip fracture triples the risk of another hip fracture, whereas a vertebral fracture increases the risk of subsequent vertebral fracture four to seven times [44, 58]. The imminent risk of subsequent fracture is highest in the first year after a major osteoporotic fracture (vertebral, hip, distal forearm, proximal humerus) and is more marked in advanced age [27, 59].

These differences in fracture incidence and re-fracture risk occurring at sites can be attributed to the variation of the amount and distribution of cortical and trabecular bone. Earlier data revealed that patients with fractures at central sites, with abundant trabecular bone (vertebral, hip, proximal humerus, and pelvis), seem to be older and exhibit more pathological features on bone mineral density (BMD), trabecular bone score (TBS), and vertebral fracture assessment (VFA) than patients with fractures at peripheral sites with relatively more cortical bone (forearm, ankle, and other peripheral fractures). Such stratification into central and peripheral fractures diverges from established classifications of fractures such as axial (vertebral, chest, and pelvic) versus appendicular (upper and lower limb) fractures and hip or vertebral versus non-hip/nonvertebral fractures. Such differences observed between central and peripheral fractures can be of significance, as it can help to select patients with higher imminent risk of a subsequent fracture first and patients at lower risk second in the standard model of care [27].

Over the past years, the differences between central and peripheral fractures and whether the location of osteoporotic fragility fractures may add information to post-fracture risk estimation have attracted the attention of bone health researchers. A recent cross-sectional study that included 495 women and 119 men ≥50 years with fragility fractures was carried out to explore potential differences between central and peripheral fractures. Results revealed that those with centrally and axially located fractures exhibited lower BMD and lower trabecular bone score (TBS) and exhibited more vertebral fractures than those with peripheral and appendicular fractures. These differences remained significant after adjustment for sex, age, BMI, and femoral neck BMD, which supports the notion that intrinsic skeletal properties and localization of fractures are connected [60].

Such stratification of fragility fractures into central versus peripheral fractures is supported by the clinical observation of similarities in patients with these types of fractures, which also is in accordance with the relative proportions of trabecular and cortical bone at these sites. The group of central fractures includes both axial and hip/vertebral fractures, in addition to proximal humeral fractures. The group of peripheral fractures consists of mainly forearm and ankle fractures, but also other fractures of the limbs from the diaphysis and distally of the humerus and femur. Patients with central fractures exhibited lower BMD including femoral neck, lower trabecular bone score (TBS), and a higher prevalence of vertebral fractures, all associated with increased fracture risk [61, 62], than did patients with peripheral fractures. Anatomically, the axial and proximal appendicular part of the skeleton encompasses a large proportion of trabecular bone, in most areas exceeding 50%. The patients with central fractures also exhibited lower femoral neck BMD than those with peripheral fractures. Femoral neck BMD can be considered as a proxy of cortical bone strength, because 75% of

the bone volume at this site is cortical [57]. Hence, in patients with central fractures, both trabecular and cortical bone strength are reduced compared to those with peripheral fractures. Cortical bone architecture is important for fracture propensity, as shown in an earlier work "the Tromsø study" [63]. A thinner cortex and increased cortical porosity at the proximal femur were associated with increased risk of fractures [64]. The importance of coexisting cortical and trabecular deterioration for fracture propensity was supported by another study which assessed distal forearm bones in women using CT [65, 66]. Results of these studies revealed that cortical porosity was associated with fractures in the presence of deteriorated trabecular density (OR 2.30; 95% CI, 1.30 to 4.05; $p = 0.004$), but not if trabecular deterioration was absent (OR 0.96; 95% CI, 0.50 to 1.86; $p = 0.91$). Likewise, trabecular density was associated with fractures in the presence of high cortical porosity (OR 3.35; 95% CI, 1.85 to 6.07; $p < 0.0001$), but not in its absence (OR 1.60; 95% CI, 0.78 to 3.28; $p = 0.20$). Therefore, it was suggested that the disease of bone fragility is best captured by cortical and trabecular deterioration and that a measurement of coexisting cortical and trabecular deterioration is likely to identify women at risk for fracture more robustly than absolute values of cortical porosity, trabecular density, or BMD [65].

Predicting Imminent Risk for Fracture

Understanding the factors that might increase the likelihood of sustaining a short-term fracture is important for identifying patients at imminent risk of fracture, as they merit prompt evaluation and treatment for osteoporosis/fracture prevention. Furthermore, in older postmenopausal women and in women with a recent fracture, ascertainment of risk factors for imminent fracture may have greater clinical relevance than identification of risk factors that have long-term prognostic importance but poorer predictive accuracy over the short run.

Despite endorsements of FRAX by both NOF (National Osteoporosis Foundation, USA) and WHO, it has a number of limitations: (1) the general nature of some of the items (e.g., fracture history does not take into account the timing or number of fractures); (2) the exclusion of falls information [67, 68]; (3) a relatively low area under the curve (AUC) in validation studies (only about 60% for major osteoporosis-related fracture); and (4) application only to persons who are untreated for osteoporosis [69, 70]. The importance of some of the items in FRAX also may be questionable. One study, for example, reported that there was no significant difference in predictive accuracy as measured by AUC between FRAX and simple models based only on BMD and age [71]. Finally, 10-year fracture risk is not necessarily indicative of short-term fracture risk because the annual incidence of fracture increases substantively with age; thus, the risk in the first year of a given 10-year interval is undoubtedly lower than that in year "10." Moreover, the relative risk of fracture for those with (versus without) a history of fracture is highest in the period soon after the event (i.e., within the 1- to 2-year period) and declines thereafter [72]. Identifying these patients can reinvigorate the treatment discussions in this undertreated population.

For older women with established osteoporosis, short-term risk prediction may be much more important than 10-year risk, especially within the context of decisions regarding the use of new, high-cost bone anabolic agents. Moreover, the importance of age, BMD, and other risk factors may be different in the prediction of short-term fracture risk among older women with established osteoporosis compared with the prediction of long-term fracture risk among the general population of postmenopausal women. Identification of women with high risk of fracture may be especially important in elderly women with osteoporosis or osteopenia. Therefore, it is vital to understand the risk factors for imminent fracture (i.e., within 1–2 years) in this population [73].

Several recent studies have also examined the risk of imminent fracture and reported similar factors derived from claim databases and clinical studies. Two studies [72, 74] on the 1- and 2-year

risk, from the Medicare 20% sample and the Truven Commercial and Medicare Claims Dataset, supported the importance of several risk factors including older age, history of other adult fracture, prior recent falls, poorer health status, diagnosis of osteoporosis, and comorbidities that trigger more frequent falls (Alzheimer's disease, CNS diseases), as well as medications and equipment that linked to poorer cognition, physical function, and motor skills (use of wheelchair, walker, cane, narcotics, centrally sedating anticholinergic medications, and sedative hypnotic medications). Other research from observational cohorts (Study of Osteoporotic Fractures, Canadian Multicentre Osteoporosis Study, Kaiser, Swedish Register Data) have demonstrated similar findings with older age, BMD T-score, prior fracture, falls, and fall-related risk factors (comorbidities, medications) being the dominant predictors [73]. These results support many of the fracture risk prediction tools that focus on longer term risk prediction (5–10 years) with the exception that falls and fall-related factors (diseases and medications) are also quite important. Currently, only tools such as Q-fracture capture these important risk factors, whereas FRAX and others do not consider them. Previous research has reported that falls represent at least 30% of the risk of fracture, which would be accurate for these risk factors to factor so consistently and prominently into defining the imminent risk fracture patient across data source and type [67]. Imminent (1–2 year) risk of fracture appears to be an important time frame, yet relatively understudied, that may be relevant to stimulate more patient interest in therapeutics aimed at fracture prevention [74].

There is a strong inverse relationship between bone density and risk of fracture, with a two- to threefold increased risk per standard deviation decline in BMD. Nonetheless, at any given level of BMD, fracture risk increases with advancing age, highlighting the fact that factors other than bone density are independently related to risk of fracture. Although some of these factors affect skeletal integrity (e.g., bone turnover, trabecular architecture), non-skeletal factors may also play an important role to the extent that they increase the risk of falls, which are the precipitating factor in the vast majority of osteoporotic fractures [73].

Not surprisingly, falls are one of the main predictors of imminent fracture risk despite data on falls occurrence being somewhat limited in scope (self-reported yes/no, different assessment tools available that vary among themselves to some extent). A 2016 case-control study of short-term fracture risk using US claims data reported higher imminent fracture risk for older adults with falls, poor health, specific comorbidities, psychoactive medication use, and mobility impairment [72]. A 2017 cohort study of women in the Study of Osteoporotic Fractures (SOF) also found prior falls as well as prior fracture, walking speed, Parkinson's disease, smoking, and stroke to be predictive factors [75–77]. The claims data study examined class of medications rather than specific medications but reported similar findings for variable medications including antidepressants [72, 76]. Attributing risk to medication prescribing may suffer from bias by indication, making it quite difficult to discern the disease from the medication used to treat the disease, as the causal risk factor. Falls and other variables (Table 13.1) were most predictive of short-term fracture risk in the 1-year time frame. Consequently, understanding the factors that elevate short-term fracture risk is important for identifying patients at

Table 13.1 Predictors of imminent risk for fracture

Age
Gender:
Previous fracture
Previous fracture within the last 2 years
Fracture site: vertebral, hip, proximal humerus, and pelvis
BMD assessment result:
Falls risk
Medical disorders (e.g., central nervous system disease, inflammatory arthritis, Alzheimer's disease, parkinsonism, psychosis)
Relevant medications (e.g., narcotics, centrally sedating anticholinergic medications, and sedative hypnotic medications)
Evidence of sarcopenia
Steroid therapy
Poor functional ability (HAQ <1)

imminent risk of fracture, as they merit prompt evaluation and treatment for osteoporosis.

Imminent Fracture Risk: Patient Perception

Most of the patients perceive their own fracture risk as low, even if they have been diagnosed as having osteoporosis, even if they have suffered from loss of balance, and even if they receive an anti-osteoporotic treatment [78]. Fractures are perceived as random events, and patients believe that high risk has little relevance to their personal circumstances [79]. In patients' mind, the fractures are related to hazard in environment, accidental falls, or unsafe behavior, and not to the underlying osteoporosis, with the perception that careful attention against falls is enough to prevent fractures and thus that taking a drug for years is unnecessary [80]. Moreover, the level of risk at which a treatment is necessary differs dramatically for patients in contrast to their physicians [81]. Finally, the 10-year risk is a misnomer for some patients as they consider that other health problems, which they perceive as more important than osteoporosis, can occur within this long period of time. Indeed, awareness of complications of other chronic diseases is dramatically higher than awareness about the devastating consequences of osteoporosis [80]. Nevertheless, physicians' perception for some patients is that not only the risk of sustaining a fracture is high but also that this event may occur soon [82].

The patients' role extends beyond the occurrence of the first fracture to share, whether directly or indirectly, in sustaining another fracture. Following the first fracture, the imminent risk of re-fracture can be linked to different factors. By itself, the treatment of the fracture and post-fracture care can, paradoxically, increase the risk, through an increasing risk of falls during rehabilitation, attributed to the use of walking aids, plastering, and/or impaired coordination. The patients are usually afraid of sustaining another fall again and, hence, prefer bed rest rather than active movement [81]. In turn, the immobility may increase cortical and trabecular bone loss as well as muscle wasting and consequently trunk and extremity weakness. Furthermore, the perioperative period can increase the frailty of some patients, with acute changes of cognitive functions. Moreover, the underlying conditions may not be appropriately managed; for example, in a study that included a total of 168,133 patients with a fragility fracture, mean age 80 years, roughly 70% of patients were exposed to at least one drug associated with increased fracture risk, and this proportion was unchanged at the time of discharge [83]. Thus, the fracture and its impact on the patient were a missed opportunity for secondary prevention.

On another front, one of the major challenges in fracture prevention is the possibility of extending this imminent risk concept to patients with osteoporosis but (not yet) fracture. There are no data suggesting that bone parameters only can predict a short-term risk, at least with current bone density measurements. Combination of quantitative and microarchitecture parameters should be included in the assessment with this objective. In daily practice, the perception of the patients on the role of falls must be recognized and could be used as a motivation for appropriate care [80]. A study, using US commercial and Medicare supplemental insured data for women and men without recent fracture, analyzed more than 60 patients characteristics and potential risk factors for fracture. These patients were selected with the diagnosis of osteoporosis in the database, but the T-score and bone mineral density data were not available. Of 163,186 subjects, 32,094 had a fracture; the most important 12-month pre index predictor was falls (OR 6.67 (6.03–7.37)).

Advancing age, central nervous system (CNS) diseases, concomitant medications (targeting the CNS), and factors decreasing mobility were also significant predictors with odds ratio ranging between 1 and 2 [27]. In individuals with a history of frequent falls, this highly relevant risk factor should be incorporated in algorithms of short-term fracture risk assessment [84].

Medication Adherence

With osteoporosis proven to be associated with mortality due to fragility fractures [7, 8, 85], several medications have been made available to treat osteoporosis and improve the patients' physical health by significantly reducing the risk of fracture [86]. However, the efficacy of osteoporosis medications informed via clinical trials may not reflect real-world practice. Real-world treatment patterns and/or patient behaviors are different when compared with those within a controlled clinical trial environment. Medication compliance and adherence have proved to be limiting factors in predicting overall real-world effectiveness of osteoporosis medications [87–90]. As such, compliance among osteoporosis patients has been relatively poor and has therefore contributed to increased fracture risk—by as much as 50%—and associated hospitalizations [89, 91].

Some major reasons for poor compliance include medication side effects, patients' perception of medication effectiveness, medication safety profile, and out-of-pocket medication cost [92]. Other reported factors associated with low compliance include treatment administration frequency, patients' ability to follow a treatment regimen over the long term, and the health consequences of osteoporosis [93]. Overall, poor medication compliance has contributed significantly to morbidity and medical costs [94].

Low adherence has been shown to decrease bone mineral density (BMD), leading to more severe types of osteoporotic fracture and higher osteoporosis-associated healthcare spending [95, 96]. Few studies have explored the relationship of osteoporosis treatment adherence to subsequent fractures. A recent study [97] was carried out by Keshishian and colleagues, with the aim to examine the association of osteoporosis medication adherence and the risk of subsequent fractures among women with a previous fragility fracture. Patients were required to have continuous medical and pharmacy enrollment 12 months pre- and post-fracture date. In addition, patients were required to have an osteoporosis medication prescription for a bisphosphonate (alendronate, risedronate, pamidronate, etidronate, zoledronate, and tiludronate), calcitonin, denosumab, raloxifene, or teriparatide during the follow-up period. Adherence was calculated using cumulative medication possession ratio (MPR) from the treatment initiation date in 30-day increments. MPR was stratified into high adherence (MPR $\geq$ 80%), moderate adherence (50% $\leq$ MPR > 80%), and low adherence (MPR < 50%). Outcomes included first subsequent fracture after treatment initiation; patients were censored at treatment discontinuation or end of the 12-month period post-treatment initiation. Covariates included demographics, comorbidities, osteoporosis medications, medications associated with falls, and healthcare utilization. Results revealed that a total of 103,852 women aged ≥65 years with a fragility fracture were identified. Overall, 27,736 (26.7%) patients were treated with osteoporosis medication within 12 months of the fragility fracture (mean time to treatment initiation was 85.0 ± 84.6 days). Over half of the patients were highly adherent (MPR ≥ 80%) to osteoporosis medications during the follow-up (n = 14,112; 50.9%). Almost a third of the patients had low adherence (MPR < 50%; n = 9022, 32.5%), followed by patients with moderate adherence (50% ≤ MPR > 80%; n = 4602, 16.6%). After adjusting for demographics and clinical characteristics, patients with low and moderate adherence to osteoporosis medications were 33% (hazard ratio [HR] = 1.33; 95% CI = 1.17–1.50, P < 0.001) and 19% (HR = 1.19; 95% CI = 1.02–1.38, P = 0.026) more likely to have a subsequent fracture, respectively, compared with patients with high adherence. Low adherence patients had a 32% and 34% increased risk for a hip/pelvis/femur fracture (HR = 1.32; 95% CI = 1.09–1.59, P = 0.005) and a clinical vertebral fracture (HR = 1.34; 95% CI = 1.09–1.63, P = 0.005), respectively, compared with high adherence patients. These outcomes highlight the importance of improving osteoporosis medication adherence among women presenting with a low-trauma fragility fracture [97].

Imminent Fracture Risk Assessments and Fracture Liaison Service (FLS) Setting

In view of the fact that a fragility fracture is per se a major risk factor for further fractures, healthcare systems started to acknowledge the benefits of secondary fracture prevention [98]. Despite this, less than 50% of patients receive effective secondary fracture prevention after a fragility fracture [99]. This has led to international initiatives to improve clinical services by implementing fracture liaison services (FLSs) [100–106]. Successful funding of a new FLS is usually influenced by the number of fractures expected to be prevented in the first few years after an index fracture. The expected number of fractures prevented is in turn determined by the baseline risk of subsequent fracture, the number of patients at high fracture risk, enough to warrant anti-osteoporosis medication, and the degree of fracture risk reduction by osteoporosis therapy. Underestimating fracture risk in the post-fracture period will lead to fewer expected fractures prevented and lower perceived benefit of the FLS by payers and importantly also by patients, families, healthcare providers, and payers. Tools are available to determine the long-term risk of fracture based on patient factors, including previous fracture [107–110]. Of these, FRAX and recency of fracture is one of several determinants of imminent fracture risk. Whereas FRAX and similar models include previous fracture history, the focus of these algorithms has been on use in primary care. However, the recency and site of fracture have not been considered, both of which significantly influence imminent risk. Linear interpolation of FRAX risk, for example, by dividing the 10-year probability by 5 to estimate the 2-year probability ("interpolated FRAX"), unfortunately underestimates shorter-term risk immediately following a fracture [111]. This is particularly relevant to the FLS population given that by definition all cases have had a recent fracture [112].

Estimating the imminent fracture risk within an FLS population is feasible. From observational cohort studies, the rate of subsequent fragility fracture within 2 years in women varies from 7.6% to 23.2% [34, 113, 114, 2823]. Important determinants of the absolute imminent fracture risk include age, gender, fracture site, bone mineral density, and specific comorbidities [34, 113–116, 2823]. Furthermore, for imminent fracture risk to be relevant in the FLS setting, consideration should be also given to the therapeutic modalities that can rapidly reduce fracture risk well within the 2 years after an index fracture. For fracture liaison services, the expected number of fractures prevented is directly related to the expected fracture rate in the imminent fracture risk period and the risk reduction through the use of quicker acting potent osteoporosis treatment. While imminent fracture risk has clear implications for the planning and justification of FLS services, it also leads to the equally clear message that potent osteoporosis management should be considered promptly following a fragility fracture. The use of potent osteoporosis therapy in an imminent fracture risk approach to risk assessment is in line with treat-to-target strategies recommending potent osteoporosis medication used first followed by maintenance therapy with bisphosphonates afterwards [117–121]. However, the route to the implementing imminent fracture risk into standard clinical pathways, as opposed to its use in service planning, remains a challenge. A recent study [122] gave an example of how to include fracture risk assessment into the standard hospital setting through using a specific screening model (tick boxes) developed based on the identified predicting factors of imminent fracture risk, in addition to the FRAX model and falls risk assessment for patients attending the fracture clinic/accident and emergency department. Also, the imminent fracture risk screening tool has been included the DXA request form. Results revealed that it is feasible to identify those patients with imminent fracture risk in standard practice. This was also helpful to classify and risk stratify those patients most in need of immediate and appropriate treatment to decrease fracture risk. However, since imminent fracture risk is not included in the FRAX 10-year fracture probability, a threshold

based on a modified form of this metric might offer a further way forwards.

There are many apparent challenges of integrating imminent fracture risk approach into FLSs. For it to be effective, eligible patients need to be identified, investigated, initiated, and adhered to osteoporosis therapy soon after the index fracture. Results from the 2017 UK national audit of FLSs demonstrated that 41% of patients were monitored within 16 weeks of index fracture and 31% had initiated therapy [100]. Improving detection of silent vertebral fractures is likely to require integration with radiology systems [121]; reducing the time to treatment is likely to need integration of FLS directly into existing orthopedic pathways, minimizing additional clinical workup [123]. While the benefits of potent osteoporosis therapy in the setting of a recent fracture have not been formally tested, subgroup analyses from studies stratified by recency of fracture have been encouraging [124].

The benefits need to be weighed against costs, potential side effects, and the ability of the health systems to rapidly identify, investigate, and initiate therapy in the real-world setting. From a payer perspective, work is urgently needed to simulate the impacts of incorporating an imminent fracture risk approach into secondary fracture prevention on the clinical and cost-effectiveness of the intervention in a real-world FLS population, considering differences in age, gender, fracture site, and type of osteoporosis therapy administered. This is particularly relevant for FLSs, whose current benefits are usually calculated based on a uniform interpolation of fracture risk using 10-year values and generic alendronate. Consideration of prior fracture location and recency in future versions of FRAX may thus offer a further opportunity to assess these impacts, especially given the global priority for establishing the benefits for sustainable resourcing of effective FLSs [125].

Gaps in Treatment

Despite substantial evidence that previous occurrence of a fracture results in increased risk of a subsequent fracture, fewer than 30% of postmenopausal women and fewer than 10% of men with previous fractures are treated [126, 127]. Independent of the availability of medications that reduce the risk of repeated fractures by 25–70%, the majority of patients with incidental osteoporotic fractures are neither investigated nor treated [128, 129]. Current practices have the result that 80% of patients with fractures due to fragility are neither evaluated nor treated for osteoporosis or for prevention of falls so as to reduce the future incidence of fractures. The consequence of this gap in treatments is that very many fractures occur but could have been avoided. These are an affliction among elderly people and cost millions of dollars around the world [130, 131].

Therapeutic Window of Opportunity

Early initiation of osteoporosis therapy, following a primary fracture, was reported to diminish recurrent fracture rates by between 30% and 60% [132, 133]. In concordance, commencing osteoporosis treatment shortly after surgical management of a hip fracture, caused by low impact trauma, has been correlated with a reduced rate of new clinical fractures and with lower mortality and longer survival [41, 55, 134, 135]. Studies revealed that patients who have sustained hip fractures are the group at highest risk of subsequent fractures [135]. Consequently, priority needs to be given to starting their treatment as early as possible, in order to avoid secondary fractures. Contrary to common assumptions, these patients may benefit greatly from this treatment [49].

The best approach, therefore, would be through stratifying patients into high-risk and low-risk groups and to identify and prioritize the patients at highest risk first for post-fracture assessment in this large volume of patients. The imminent risk of subsequent fracture is highest in the first year after a major osteoporotic fracture (vertebral, hip, distal forearm, proximal humerus) and is more marked in advanced age [136]. This constitutes a window of opportunity where anti-osteoporotic treatment should be targeted promptly towards patients at highest risk [137].

Worldwide, fracture liaison service (FLS) has been reported to be the most effective tool to make imminent fracture risk amenable to therapeutic intervention. The FLS is a service dedicated to prevent new fractures and to treat patients prone to sustain fragility fractures, following their first fracture experience. This is perhaps the best effective means for achieving a change in the current panorama. This approach creates a continuum of care and makes it possible to overcome the gaps in investigation and management. A non-randomized study showed that, as compared to patients receiving standard procedures, those followed in a FLS had a reduction of 35 and 56% in mortality and risk of subsequent nonvertebral fracture over 2 years of follow-up [138]. This was the result of both pharmacological and non-pharmacological approaches.

Unfortunately, none of the clinical trials assessing the anti-fracture effect of different osteoporosis medications give the information on the recency of fractures before inclusion. Only one observational study is available in this matter [139]; this study which included 31,069 subjects, 50 years and older who sustained a fragility fracture, suggests a 40% decrease in the 3-year risk of subsequent fracture; however, only 10% of patients were treated with anti-osteoporotic therapy; the rates of fracture were 7.5 and 9.7% in trxients, respectively. In most of the clinical trials, the incidences of fractures over 1 or 2 years are very low, as patients were selected on the basis of underlying low bone mineral density, and prevalent vertebral fractures for most of them, but of unknown timing. These studies were not designed and powered to assess the short-term benefit of the treatment, yet the absolute decreases in fracture incidence are significantly low over 1 or 2 years. Regardless of the levels of statistical significance, divergence of the curves of fracture incidence in treated and placebo groups occurs at month 12 for clinical fractures in most of the studies. The early effect of treatments is mainly driven by the effect on vertebral fractures. In the subset of women in Fracture Intervention Trial (FIT) who had osteoporosis at baseline, alendronate reduces the risk of clinical vertebral fracture by month 12 and of nonvertebral fracture by month 24; the risk was actually decreased as early as 6 months after initiation of the treatment [140]. A significant reduction in morphometric vertebral fractures has been shown with risedronate after 12 months [141] and with denosumab for new vertebral fractures at 1 year [142]. In a post hoc analysis of the study of zoledronic acid in patients after hip fracture, significant divergence in the fracture-free survival curves between treated and placebo groups for all clinical fractures was seen as early as 12 months [143]. Anabolic agent teriparatide and abaloparatide decrease vertebral and nonvertebral risk over 21 months [144] and 18 months [145], respectively, and less vertebral fractures were observed over 1 year in patients treated with romosozumab as compared to placebo-treated patients [146].

Data from FLS have shown that patients at higher risk of short-term recurrence of fractures are those having both bone and falls risk factors. Among 834 consecutive patients included in a FLS with a recent nonvertebral fracture, 57 (6.8%) had a subsequent nonvertebral fracture over 2 years: the risk of sustaining a subsequent fracture was twofold higher in patients having both bone and fall-related risk factors as compared to other patients (but this does not reach significance after adjusting for age and baseline fracture location) [147].

Risk factors for falls are well known, and several of them are present and interact in most individuals. Prevention of falls is mandatory in frail patients, and data suggest that some structured physical activity and rehabilitation programs may help in this matter [148, 149]. However, the contribution of risk factors is different for each fracture site; past falls are important for all fractures except spine [150], whereas vertebral fractures represent the paradigm for anti-osteoporotic drug's efficacy. To what extent adherence to a program of fall prevention will improve adherence to an anti-osteoporotic treatment is unknown.

In conclusion, older adults presenting with their first fracture usually either attend an accident and emergency service or go to an orthopedic fracture unit who offers the expertise and skills to manage the acute condition and repair the fracture. However, there is an additional dimension: knowing that the fracture occurred in

an individual with low bone resistance identifies this person as presenting higher risk of future fractures, i.e., patients with imminent risk of fracture. In identifying these patients as high priority, properly assess and manage them and provide the first step of making this first fracture the last. Fracture liaison service provides the best model to adopt such approach in standard clinical practice. Combining epidemiological data and time of onset of effectiveness of pharmacological treatments on vertebral fractures, it has been suggested to consider the 2-year post-fracture as the highest risk period. Patients with an imminent fracture risk include osteoporotic patients initiating high dose of corticosteroids, postmenopausal women with a recent major osteoporotic fractures, and frail elderly patients with history of frequent falls. Patient education should extend the "imminent fracture risk" concept to patients with osteoporosis but "not yet" fractured. In daily practice, physicians and patients will easily reach agreement on the decision to decrease such an imminent fracture risk.

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Fracture Liaison Service

14

Yasser El Miedany

Introduction

Osteoporosis is characterized by a reduction in bone mass and strength, predisposing patients to an increased risk of fragility fractures [1]. The condition is asymptomatic, and therefore its first clinical manifestation is often a low-trauma (fragility) fracture. Fragility fractures cause significant morbidity and mortality and therefore are a considerable public health burden (Fig. 14.1) [2]. The National Osteoporosis Foundation estimated that one in two women and one in five men will experience an osteoporotic-related fracture during their lifetime [3]. Furthermore, a previous low-trauma fracture, at any site, increases the risk of a subsequent fracture by approximately twofold in women and men (Fig. 14.2) [4, 5].

Fracture liaison services (FLS) are considered the coordinator-based model of secondary fracture prevention services with a broad remit. FLS have been designed to identify patients who are at increased risk of secondary fractures, carry out comprehensive assessment, and ensure that the appropriate treatment is initiated through improved care coordination and communication [6–8]. Several organization bodies including the International Osteoporosis Foundation (IOF), the American Society for Bone and Mineral Research (ASBMR) [9], and European League Against Rheumatism(EULAR)/European Federation of National Associations of Orthopaedics and Traumatology (EFORT) have endorsed the provision of FLS services in standard practice for the prophylaxis of secondary bone fractures [10]. Meta-analysis studies confirmed the positive role of FLS and its impact on rates of BMD assessment as well as osteoporosis treatment initiation [11, 12].

However, it is acknowledged that treatment gaps remain [11] and pharmacological prevention remains suboptimal. In 2013, the International Osteoporosis Foundation (IOF) initiated the promotion of FLS programs, continually being implemented worldwide; however, so far, their outcomes show wide variability in the literature. This chapter will discuss the concept of fracture liaison service, its different models and components, and outcomes. It will expand to discuss the cost-effectiveness of fracture liaison services and its impact on bone mineral density testing, initiation, as well as adherence to therapy. It will conclude by presenting the best practice published by the International Osteoporosis Foundation for fracture liaison services.

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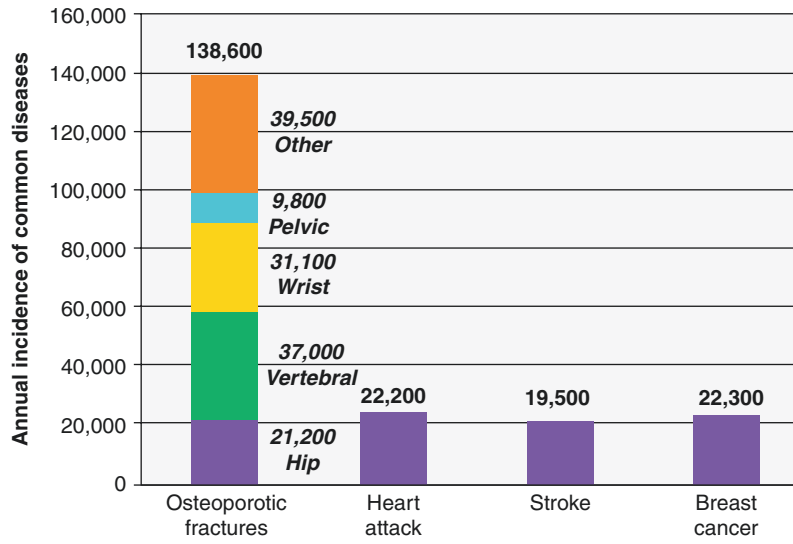

Fig. 14.1 Incidence of osteoporotic fracture, heart attack, stroke, and breast cancer in Canadian women. References for the figure: Leslie et al. [102], Burge et al. [103], Public Health Agency of Canada [104], Canadian Cancer Society/National Cancer Institute of Canada [105]

Fig. 14.2 Fracture Liaison service: approach to prevent secondary fractures

Fracture Liaison Service: The Concept

Given the global problems leading to and caused by osteoporosis, fracture liaison services came about to help diagnose and begin long-term management in these patients who sustain a fragility fracture as their initial presentation of osteoporosis. The World Health Organization (WHO) has identified fragility fracture as one which occurs due to forces equivalent to a fall from a standing height or less and are not attributed to high-energy traumas like motor vehicle accidents or

high velocity mechanism of injuries [13]. In a healthy individual, the result of such a fall may be bruised skin and a bruised ego. In patients with osteoporosis, such a fall may result in fractures [14]. The most common initial fracture in younger adults tends to be distal, e.g., distal forearm. In older adults, the most common fragility fractures occur at the hip, wrist, spine, humerus, or pelvis. Fracture liaison services seek to seamlessly transition these patients from surgical care of the fracture to long-term management of the disease in order to treat the disease process and prevent future fracture.

A fracture liaison service (FLS) systematically identifies, treats, and refers to appropriate services for all eligible patients aged 50 and older within a local population who have suffered fragility fractures, with the aim of reducing their risk of subsequent fractures.

An FLS is an essential component of a comprehensive and integrated approach to preventing falls and fractures among people over the age of 50 years. Assessment within an FLS should be part of the pathway for all patients with a fragility fracture. An FLS comprises a dedicated coordinator (often a nurse specialist) who works to preagreed protocols to case-find and then assess patients who have had a fracture. The service may be based in hospital or in the community and requires support from a medically qualified practitioner (typically a hospital doctor or GP with special expertise in bone health and fragility fracture prevention).

Fracture Liaison Service Models

Fracture liaison services (FLSs) are effective models for prevention of osteoporotic fractures. Marsh et al. [15] described 12 different models that have been described in scientific literature to deliver secondary fracture prevention. These ranged from programs aimed at increasing awareness of osteoporosis through to intensive programs that identify, investigate, and initiate treatment (Fig. 14.3). Some programs are completely delivered within the FLS model, and some involve the general practitioner (GP) in

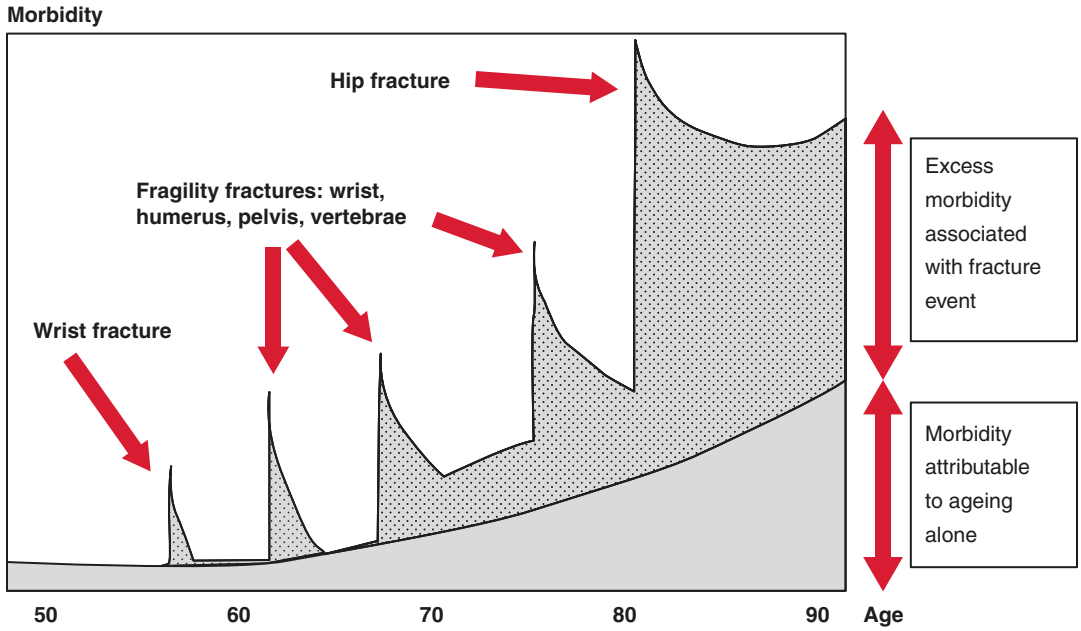

Fig. 14.3 Osteoporosis and fragility fractures throughout the life course. Capture the fracture; each and every fracture was a missed opportunity to diagnose and treat osteoporosis to prevent the subsequent fractures. (Quoted from: British Orthopaedic Association, British Geriatrics Society. The care of patients with fragility fracture 2007. https://www.bgs.org.uk/sites/default/files/content/attachment/2018-05-02/Blue%20Book%20on%20fragility%20fracture%20care.pdf)

primary care. Ganda et al. [16] conducted a similar review and grouped all published programs in scientific literature into four "types" of FLS models, referring to them as types A to D.

- Type A: defined as a service that identifies, investigates, and initiates treatment.
- Type B: services identify and investigate patients but then refer back to the primary care physician for treatment initiation.
- Type C: services identify patients at risk and inform them and their primary care physician. However, they do not undertake any assessment or treatment of the patients.
- Type D: services identify at-risk patients and inform and educate them but take no further part in communicating their findings to other stakeholders in the patient's care.

In the era of artificial intelligence (AI), recent FLS models have been established by smart healthcare systems which can assist clinicians and case managers to identify, investigate, and initiate treatments and improve adherence efficiently. The role of AI will become increasingly important assisted by an efficiently working intelligent healthcare information system. The AI system can automatically analyze reports of X-ray and DXA examinations and identify patients with hip fractures and vertebral compression fractures, osteoporosis, low bone mass, as well as high fracture risk. Moreover, the system's data analysis can not only reduce the rate of missed patients but can also reach a 93.6% rate of 1-year medication adherence [17]. Therefore, the smart healthcare case management system can be a novel model to achieve better outcomes in the fragility fracture prevention program of FLSs. Table 14.1 shows the most common FLS models.

Components of Fracture Liaison Service

FLSs include mainly evaluation of all people aged 50 years or older who have sustained a new fracture or radiological fragility fracture at any skeletal site, though exceptions are justified for fractures of skull, facial, digit, and scaphoid bones that are typically caused by a traumatic injury. A pragmatic approach to the definition of a fragility fracture which is vital to initiate the process with exclusions might only be made in the case of a road traffic collision (or other clearly significant trauma) or where a fall has clearly been from above standing height. Table 14.2 shows a summary of the main components of the fracture liaison service, which include:

Identify

The FLS identifies people aged 50 years or older who sustain a new fragility fracture. This includes:

- Newly identified vertebral fracture.
- Newly identified low trauma fracture.
- A new fracture occurring while a patient is taking an osteoporosis drug therapy.

Identifying people aged 50 years or older with a new clinical fracture is in the core of the FLS process and is a main responsibility of the service. Ideally, this is carried out by an "FLS coordinator" who is a dedicated nurse specialist, although this role may also be undertaken by allied health professionals (AHPs) or nonclinical personnel. Identification of new clinical fracture presentations is achieved according to the approach the patient has been handled by the hospital:

Table 14.1 Examples of fracture liaison service models

3 "I"	4 "I"	5 "I"Q	5 "I"
Identify	Identify	Identify	Identify
Investigate	Investigate	Investigate	Investigate
Initiate	Inform	Inform	Initiate
	Initiate	Initiate	Improving adherence
		Integrate	Intelligence (Artificial intelligence)
		+ Quality	

Table 14.2 Main components of the fracture liaison service

Component		Description
1	Identify	People aged 50 years and over with a fragility fracture are systematically identified
2	Investigate	Investigations to assess risk of fragility fractures and falls and possible underlying secondary causes for osteoporosis are offered to people identified by the FLS
3	Inform	Information and support are offered to people (and where relevant their carers) using the FLS
4	Intervene (initiate)	Interventions to reduce the risk of fragility fractures are offered to people as required
5	Integrate	The FLS will integrate with the wider healthcare system to facilitate an inclusive patient pathway, ensuring effective case-finding, onward referrals, and long-term management of osteoporosis
6	Improving adherence	Improving patients' adherence to therapy and adopt a system to monitor the patient's response to management and adherence to therapy as well as to remind physicians and case managers about non-adherent patients
7	Intelligence	Implementing artificial intelligence takes the FLS into the smart healthcare era. The AI system can analyze reports of X-ray and DXA examinations and identify patients with hip fractures and vertebral compression fractures, osteoporosis, and low bone mass. It can also help professionals to provide adequate control on pharmaceutical treatment to the patients
Q	Quality	The FLS demonstrates clinical accountability, ongoing quality improvement, effective governance, and funded access to continuing professional development

Inpatient Fractures

People who need to stay in hospital after their fracture are not only at highest future fracture risk [18, 19] but also are among the most straightforward to identify. Identification of this group can be carried out either through orthogeriatric inpatients service, setting up a notification system with orthopaedics team, trauma nurse, or using IT/informatics systems. Coordination with the local orthopedics and trauma teams is essential in order to agree roles and responsibilities for identifying people aged 50 or older who have had a fragility fracture and to grant the FLS staff access to the patients under the care of Orthopaedic or Accident and Emergency Departments. Similarly, falls which occur during hospital admission that result in a fracture should be also assessed by the FLS. These can be identified via DATIX (or similar incident reporting systems), seen in fracture clinic or transferred to orthopedics.

Outpatient Fractures

People who are managed in outpatient fractures clinics could be considered as easier identifiable cohort. These can be recognized by reviewing accident and emergency department lists, screening fracture clinic notes, leaving questionnaires with the receptionists to be handed over to the patients to complete while attending the clinics, reviewing primary care records, and linking with virtual fracture clinics.

Silent Vertebral Fractures

Vertebral fractures are among the most common osteoporosis-associated fractures and very important in predicting future osteoporotic fractures. Unfortunately, they are often missed, and studies reveal that they account for less than 5% of clinical fracture presentations to FLS [20]. Best approaches to identify this cohort is through liaising with radiology to agree a notification system highlighting any vertebral fractures identified in X-rays which can be incidental findings on plain X-rays, CT, and MRI scans images, also to carry out vertebral fracture assessment (VFA) [20, 21]. Liaising with physiotherapy-led musculoskeletal back pain services or other interface might also be helpful to identify any case lost from the record.

Organization bodies recommend that radiologists should (1) review the spine in all images of the chest, abdomen, and pelvis; (2) report

vertebral fractures clearly using the term "vertebral fracture"; and (3) recommend further assessment and management to reduce fracture risk. This would help using electronic software that are able to search or the word "fracture" or "vertebral fracture" and generate an automatic electronic letter to the FLS.

Referrals

Referrals to the FLS from other services, such as GPs, pain clinics, interface services, and falls services, should also be encouraged. Referral pathways should be set up to ensure all the patients receive appropriate bone healthcare provided by the FLS.

Out of the Hospital FLS Setup

An out-of-hospital FLS requires another setup that relies mainly on reporting from fracture clinic accident and emergency department as well as radiology departments. This mandates close liaison with local secondary care center(s) to enable seamless, continuous capture of all relevant cases. Similar approach should be followed regarding in-patients where coordination with orthopedic department, orthogeriatrics, as well as radiology department should be implemented to identify patients who may get admitted with fractures or sustain a fracture during their hospital admission.

It is, however, improbable that any single approach will identify all patients with a new fracture and the FLS coordinator will customize screening methods as per local systems. Therefore, it is recommended that multiple strategies are used for identification to maximize the yield.

Investigate

A comprehensive multifactorial assessment should be carried out targeting the group of people who need it. Prompt assessment and intervention is highly required as the risk of having a subsequent fracture is high particularly in the first year following an index fracture. Therefore, investigations should start as soon as feasible after the fracture so that interventions are not delayed. These include:

Fracture Risk Assessment

There are several fracture risk assessment tools. The commonest in use is FRAX which is endorsed by the International Osteoporosis Foundation and National Osteoporosis Foundation. Q-fracture has been recommended for use mainly in the UK. Guidelines and treatment recommendations regarding how to implement FRAX or Q-fracture in fracture risk assessment should be followed to develop local protocols. However, users need to be aware of key limitations of these risk tools to understand how to handle the calculated fracture risk scores. These limitations include differences in one fracture risk by differences in fracture site, number of fractures and recency of fracture, as well as prevalence of other medical conditions such as diabetes mellitus or drug therapies such as androgen deprivation therapy.

DXA Scans

BMD measurement is an important part of clinical decision-making. It quantifies 16 the severity of osteoporosis, serves as a means to quantify fracture risk, is an important part of clinical as well as therapeutic decision-making, and also establishes a baseline for future evaluation of treatment performance. Therefore, it is recommended to have a BMD measurement before commencing osteoporosis drug therapy wherever feasible.

Vertebral Fracture Assessment (VFA)

In addition to BMD measurement, DXA can be used to assess for prevalent vertebral fractures. Quick and cheap to perform and with minimal additional X-ray exposure, VFA not only precludes the substantially higher cost and radiation exposure of conventional plain spine radiology but

also can reliably identify the presence of vertebral fractures and semi-quantitatively assess the degree of the vertebral fracture. Guidelines produced by the International Society for Clinical Densitometry [20] can be used to develop local protocols.

Trabecular Bone Score (TBS)

The trabecular bone score is a measure of bone texture correlated with bone microarchitecture and a marker for the risk of osteoporosis. Introduced in 2008 [22], its main projected use is alongside measures of bone density in better predicting fracture risk in people with metabolic bone problems. The trabecular bone score is a textural parameter that can be applied to DEXA, which quantifies the local variations in gray level. TBS is derived from the evaluation of the experimental variogram, obtained from the grayscale DEXA.

It was reported that TBS is a reflection of the structural condition of the bone microarchitecture. TBS is strongly correlated with the number of trabeculae and their connectivity and negatively with the space between trabeculae [23, 24]. That is to say that a high TBS value means that microarchitecture bone is dense, well connected with little spaces between trabeculae. Conversely, a low TBS value means that the microarchitecture of bone is incomplete and poorly connected with wide spaces between trabeculae [25]. FRAX scores can be adjusted for TBS. An algorithm derived from WHO FRAX calculation tool (available online https://www.sheffield.ac.uk/TBS/) has been developed to adjust: probability of fracture from clinical risk factors and BMD to account for TBS. The calculated probabilities of fracture have been shown to be more accurate when computed including TBS.

Falls Risk Assessment

All people aged 65 years and older checked be checked for whether they have fallen in the past year and about the frequency, context, and characteristics of their fall/s. Older people reporting a fall or considered at risk of falling should be observed for balance and gait deficits and considered for their ability to benefit from interventions to improve strength and balance. This may also be appropriate in people aged 50–64 seen by the FLS who have risk factors for falls. FLS coordinators will need adequate training and expertise in these initial assessment techniques.

An FLS will engage closely with local falls services, to determine access to appropriate pathways to ensure early falls risk assessment and intervention post-fracture. Several tools to assess for falls risk are available which can be implemented in standard practice [26–30]. While the responsibility for any subsequent multifactorial falls assessment and targeted intervention will lie primarily with local falls services, measures to protect the patients from sustaining another fracture should be tackled by the FLS team. Therefore, there must be clear and timely linkage to the necessary intervention pathways.

Other Investigations

Patients believed to be at increased risk of fracture should be also medically assessed for:

(a) Osteosarcopenia as this makes the subject prone to falling over and sustain low-trauma fractures.
(b) Underlying secondary causes of osteoporosis/high fracture risk including exclusion of diseases that can present with osteoporosis and vertebral fracture (such as multiple myeloma or malignancies/metastasis).

Laboratory tests should be carried out to guide treatment selection and ensure treatment safety. Blood tests for bone profile and kidney functions should be carried out from point of view of safe prescribing, whenever a bisphosphonate treatment is advised. Vitamin D assessment would help in the assessment of osteosarcopenia.

Other procedures may be appropriate for individual patients depending on the clinical presentation and local protocols. These may include [31]:

- Full blood count (FBC).
- Erythrocyte sedimentation rate (ESR).

- C-reactive protein.
- Liver function tests (LFTs).
- Thyroid function tests (TFTs).
- Serum protein immunoelectrophoresis, serum free light chains, and urinary Bence-Jones protein.
- Plasma parathyroid hormone particularly in patients with hypercalcemia.
- Serum prolactin.
- Serum testosterone, sex hormone-binding globulin, follicle stimulating hormone, luteinizing hormone (in males).
- 24-hour urinary free cortisol/overnight dexamethasone suppression test
- Endomysial and/or tissue transglutaminase antibodies.
- Biomarkers of bone turnover.
- Urinary calcium excretion.

Inform

Patient education is an important component of an FLS. By adopting the patient-centered care of management style, this will ensure giving sufficient time within the patients' appointment to encourage them to raise their queries, discuss their management options and available medications, provide information about other services they may be referred to (such as falls prevention, physiotherapy, pain clinics, orthopedic surgery, etc.), and explain the next steps in their care. The priorities are to cover simple key points and back this up with information resources in appropriate formats. Information should cover:

- Osteoporosis and risk factors for fracture.
- Lifestyle interventions aimed at reducing fracture risk including nutrition and exercise.
- Coping with pain and any disability associated with their fracture.
- Drug treatment options for osteoporosis management—including information on benefits and possible side effects.
- Reducing falls risk.
- Next steps in their care plan and follow-up appointments.
- People may feel overwhelmed when they are given a diagnosis. Feeling concerned and worried about themselves may make them not able to absorb or understand all the information given to them in the standard clinic setting. Information leaflets summarizing the key information in an appropriate format can give them extra information outside the clinic setting after their FLS appointment. Ways to contact the FLS staff or through an information helpline by organization bodies such as Royal Osteoporosis Society in the UK should be provided. Patients groups also are helpful in spreading the word and sharing experiences. All written communications and materials need to be in layman's terms and easily understood by the person who has had a fracture. It is good practice to ensure the person receives a copy of reports and clinic letters from the FLS appointments to facilitate their ongoing care.

Intervention

Intervention following FLS assessment will comprise a package of care tailored to the individual patient's needs. This should address all the modifiable fracture risk factors that have been identified for the individual person. In general treatment strategy should handle three main pillars:

- People at high risk of fragility fracture should start an appropriate osteoporosis therapy.
- People at high risk of falling should be referred to falls prevention services and offered interventions such as balance exercise and measures to improve sarcopenia to keep them strong, steady, and independent.
- People who are start interventions to reduce risk of fracture should be monitored by the FLS team.

Osteoporosis Therapy

There are a range of effective drug treatments for osteoporosis [32, 33]. Treatment decisions should adopt shared decision-making approach taking into account the patient's medical status, the

patient's preference, and an analysis of benefit versus risk (side effects). An optimal treatment choice should be supported by a strong evidence base and should have demonstrated benefits in terms of reducing vertebral and nonvertebral (including hip) fracture risk [31].

Falls Management

Many fragility fractures occur as a result of a fall, and many of the falls contributing risk factors are modifiable with appropriate interventions. Though clinical trials of falls interventions have not to date demonstrated an effect upon fracture risk reduction, common sense should be adopted in promoting these proven interventions to reduce future falls risk [34, 35]. Exercise can also reduce fear of falling and improve confidence [29]. It may help to promote bone strength as well as help with the symptoms caused by vertebral fractures especially postural changes and back pain [36].

In most cases, the development of an individualized multifactorial intervention will be undertaken by the falls prevention service which may comprise:

- Strength and balance training.
- Home hazard assessment and intervention.
- Vision assessment and referral.
- Medication review with modification/withdrawal.

Regular balance exercises are recommended for anyone who is unsteady or older 48 than 65 years and not doing regular active leisure or sports [37].

Improving Adherence

Commonly reported barriers to osteoporosis treatment adherence include actual and perceived side effects, dosing complexity, medication costs, lack of perceived need for therapy, poor perceptions regarding treatment effectiveness, poor patient-provider relationship, little patient involvement in treatment decision-making, and lack of treatment follow-up [38–42]. Evidence suggests that patients regularly reassess their perceived need for treatment against barriers to continued therapy [42, 43]. Strategies that enhance patient-provider communication and treatment follow-up may thus help to improve treatment adherence [44].

First, patients who feel comfortable with their physicians are more likely to trust the diagnosis, accept a prescribed treatment, and return to their doctor to discuss medication problems [40, 44]. Healthcare providers play a key role in shaping perceptions of fracture risk and osteoporosis drug effectiveness [40, 45, 46]. However, many patients fail to associate fracture with a diagnosis of osteoporosis [45, 46], and patients underestimate the extent of bone loss identified by bone mineral density testing [47]. Improved patient understanding of bone quality and need for pharmacotherapy is therefore critical [39, 41, 43]. Second, early treatment follow-up facilitates adherence by addressing adverse drug effects and problems with dosing complexity [40]. In fact, drug switching, between drugs or drug regimens, improves compliance to osteoporosis pharmacotherapy [48, 49].

Potential strategies to improve adherence to osteoporosis pharmacotherapy include improving patient-provider relationships and increased treatment monitoring through regular follow-up, clinical testing, and reminder systems [50, 51]. Providing patients with educational material alone does not improve treatment adherence [50, 52]. Instead, multifaceted and individualized approaches with regular follow-up are needed [44, 51]. An intensive intervention involving patient education and ten scheduled motivational interviews over a 12-month period has shown promising outcomes with positive impact on treatment adherence [53].

Integrate

An FLS can be based in hospital or in the community. Regardless, in order to be effective, the FLS will be integrated with other services and the wider fracture prevention care pathway. This

enables an FLS to maximize case-finding, refer to appropriate services to meet a patient's needs, and ensure transfer of care to facilitate long-term management of osteoporosis. Osteoporosis drug treatments need to be taken correctly for long periods in order to gain maximum benefit. Ensuring good communication among health professionals delivering fracture preventative care enables long-term support for patients to maximize treatment adherence and benefits.

Management Plan

Long-term treatment of osteoporosis will be managed by the GP. Clear management plans from the FLS will outline the recommendations for treatment and review timescales. The FLS report will support transfer of care and long-term management of osteoporosis by the patient's primary care team. A report template will be created with input from GPs and patients, and feedback should be invited to ensure the report meets their needs. Inclusion of the following information is recommended:

- Patient demographics and unique identifier.
- Details of fragility fracture(s).
- Current osteoporosis treatment.
- Results of assessments including fracture risk assessment, BMD results, and laboratory tests.
- Management recommendations including treatment changes, recommended review dates, and circumstances for re-referral.
- Appropriate primary care codes including the fracture site and type of fracture (e.g., osteoporotic).

FLS should carry out initial follow-up contact by 16 weeks and at 52 weeks, to follow up regarding the individual patient's management. Later further annual reviews should be completed outside of the FLS. In day-to-day practice, this can be set up subject to the local capability and capacity. Examples include via a GP or another member of the primary care team or a community pharmacist.

A reassessment of fracture risk should be carried out by the GP at 3 years (for intravenous zoledronic acid) or 5 years (for oral bisphosphonate) to determine whether it is appropriate to continue drug treatment or take a "drug holiday." Denosumab treatment should only be discontinued after advice from a specialist in bone metabolism [ROS report].

Quality

Leadership, governance, professional accountability, and staff development are essential to providing an efficient, coordinated, and consistent service that meets the needs and expectations of its patients. In order to deliver high-quality care, staff will demonstrate the necessary professional competencies and will participate in CPD to maintain their knowledge.

Service improvement involves individual staff, work teams, and organizations looking at how making changes to the way they work can help improve patient care by making services better. Auditing and peer support help to share experience and learn from each other challenges.

Clear lines of responsibility ensure that complex healthcare systems work most effectively for the benefit of patients. Within the FLS, there are some criteria that help to keep the service provided to the optimum. These include:

- A designated lead clinician accountable for all components of the service.
- The FLS is developed in line with a local fracture prevention strategy.
- Core clinical data from people identified by the FLS is recorded on an operational database. – A quality assurance framework is in place which includes:
  (a) An ongoing program of service/quality improvement including regular audit.
  (b) Participation in national audits.
  (c) Peer review.
  (d) Patient and carer experience measures.
- Staff are active participants in a regional clinical or professional network.

FLS Outcomes

Future Fracture Risk Reduction

The golden outcome of FLS is to reduce the risk of developing a subsequent fracture. Most of the studies carried out to assess for the outcomes of FLSs were studies evaluating FLS models. These research works proactively identified at-risk patients and initiated bone health assessments on them according to specific FLS protocols. Comparing the results of these studies to either primary care follow-up or a comparable hospital without an FLS program revealed a significant reduction in subsequent fractures over 2–4 years following the index fracture in the FLS group [16, 54–65].

In one of the studies carried out at the Concord facility in Sydney, Australia, patients who were followed up in the primary care by their GP had a markedly increased risk of subsequent fracture (hazard ratio [HR] 5.63, 95% confidence interval [95% CI] 2.73–11.6, P 0.01) after adjustments for other predictive factors, i.e., age and weight, compared to those assessed by their Type A FLS over 2–4 years follow-up [59]. In another study based in Newcastle, Australia, patients who were managed by their Type A FLS had a lower rate of re-fracture, 5.1%, compared to those not included in their assessment group, 16.4% ($P < 0.001$) after 2 years [60]. This same service was then compared with a comparable cohort from another hospital that does not have an FLS. It demonstrated that over 3 years there was a 30–40% reduction in re-fracture rate among FLS patients (all fractures: HR 0.67, 95% CI 0.47–0.95, $P = 0.025$; major fractures – hip, spine, femur, pelvis, humerus: HR 0.59, 95% CI 0.39–0.90, $P = 0.013$) [65]. Similarly, in the Netherlands, when a hospital with an FLS program was compared against one without, the FLS center had a reduced re-fracture rate, in a time-dependent fashion: after 1 year of follow-up, there was a non-significant 16% reduction (HR 0.84, 95% CI 0.64–1.10), but after 2 years of follow-up, there was a significant 56% reduction (HR 0.44, 95% CI 0.25–0.79) [66].

The Kaiser Permanente Southern California Healthy Bones Program, adopting a Type A service, the FLS reported itself to be very successful and has been highly commended by the International Osteoporosis Foundation (IOF) Capture the Fracture initiative [67]. They have published their outcomes from their collection of 11 medical centers, with an average reduction in re-fracture rate of 37.2% (range 23.1–60.7%) over the first 4 years [63, 64]. Subsequent analysis revealed a 38.1% reduction in expected hip fractures [54]. A cohort study conducted in Sweden analyzing patients in the year before and after the implementation of a Type B FLS program demonstrated a reduction in re-fracture rate of 42% in the FLS group (HR 0.58, 95% CI 0.40–0.87) after 6 years [67].

Less intense models focusing on improving patient and physician knowledge of bone health have not demonstrated any improvement on re-fracture rates. A randomized trial that allocated at-risk patients to four different arms, physician education, patient education, patient and physician education, and standard care, demonstrated no significant difference in re-fracture rates [68].

Vertebral Fragility Fractures

Big percentage of the FLS studies focus on the patients who sustained hip fractures, as these are generally associated with the greatest morbidity and mortality, and appendicular fractures, as these fractures seek medical attention allowing a good capture rate. In contrast, in standard practice, there is another important cohort of osteoporotic fragility fractures who are usually missed. These are those who develop vertebral fractures. Most vertebral fractures are asymptomatic, and only one-third present to medical attention. Symptomatic and asymptomatic vertebral fractures are associated with significant frailty, morbidity, and mortality [70–73]. In hospital, rate of vertebral fractures detection is poor and, even when detected, generally does not lead to initiation of any bone health assessment or treatment

[74]. A key area for improvement is how the secondary prevention care is delivered. The FLS program pays full attention as it has been specifically developed to identify such silent vertebral fragility fractures as well as those admitted to hospital. Earlier study revealed a threefold increase in the referral rate for BMD assessment for patients with silent vertebral fractures [75].

Mortality

Few studies have been published discussing mortality as an outcome associated with FLS programs. In the study carried out by Huntjens and colleagues, adopting a Type A FLS, the patients were followed up for 2-years duration. Outcomes revealed a 35% reduction in mortality following a fragility fracture compared with a comparable cohort not assessed by FLS (HR 0.65, 95% CI 0.53–0.79) [66]. In another large cohort study carried out in the UK by Hawley et al., using hospital admission data from 11 hospitals also reported a reduction in 30-day mortality by 20% (HR 0.80, 95% CI 0.71–0.91) and 1-year mortality by 16% (HR 0.84, 95% CI 0.77–0.93) in patients admitted to hospital after a hip fracture [76]. This data set included hospitals with a newly implemented orthogeriatric service and an FLS program.

Bone Health and Bone Mineral Density Assessment

There is overwhelming evidence that FLS is associated with an increased number of patients referred for DXA scanning. Compared to either usual care or a specified period pre-FLS, there was almost a 2- to 18-fold increase in DXA referrals. Comparison of the different FLS models revealed that a more involved FLS program, such as a Type A model, was more likely to lead to higher referral rates compared to a less intensive model (Table 14.3).

A Scottish study compared two hospitals, one with a Type A FLS and one with usual care, and found that rates of offering DXA scans were significantly higher at the FLS center (85% vs 6% for humeral fractures, 20% vs 9.7% for hip fractures) [77]. Another study based in Edmonton, Canada, which randomly assigned patients with hip fracture to either an FLS or usual care, also reported a significant increase in BMD testing in the FLS group (80% vs 29%, adjusted odds ratio [OR] 11.6, 95% CI 5.8–23.5, P 0.01) [78]. The same department subsequently evaluated this same model in patients with wrist fractures, and

Table 14.3 FLS models of care and their impact on the patients' management in terms of BMD testing as well as receiving osteoporosis treatment

Model	Description	% receiving BMD testing	% receiving osteoporosis treatment
Status quo	Manitoba statistics for major osteoporotic fractures (2007/2008)	13%	8%
Type D (zero model)	Only provides osteoporosis education to the fracture patient. Primary care provider (PCP) is not alerted or educated	No study on BMD testing	8%
Type C (1 "I" model)	1. Identification the PCP is alerted that a fracture has occurred and further assessment is needed. Leaves the investigation and initiation of treatment to the PCP	43%	23%
Type B (2 "I" model)	1. Identification 2. Investigation leaves the initiation of treatment for fragility fracture patients to the PCP	60%	41%
Type A (3 "I" model)	1. Identification 2. Investigation 3. Initiation of osteoporosis treatment where appropriate	79%	46%

it also showed increased BMD testing in the FLS group (52% vs 18%, relative risk [RR] 2.8, 95% CI 1.9–4.2, $P < 0.01$) [79]. Even in studies where the comparison was made with a period pre-FLS, a significant increase in DXA referral was noted. An Italian study reported that their Type A inpatient FLS model of patients over 65 years with a proximal femoral fracture increased BMD testing by over threefold, from 14.5% to 47.6% ($P < 0.01$) [80]. A similar finding was reported in another study based in America where the initiation of an FLS during hip fracture rehabilitation increased BMD testing from 35% to 65% [57]. The Kaiser Permanente FLS have published multiple reports addressing the issue of osteoporosis investigation since their establishment in 2002. They reported a 247% increase in total annual DXA scans over the first 4 years [63] and a 263% increase over the first 6 years [54]. In concordance, visual data showed further increase in annual DXA scans in their seventh and eighth years [64].

On the other hand, findings from less intensive services have not been as robust. An education-based Type C service reported that patients followed up 3 months after their index fracture via a phone call were more likely to have been recommended a DXA scan (OR 5.22, $P < 0.01$) compared to a control group that received no contact [81]. Yet, it was not reported how many of these recommendations translated into referrals. Another study employing an educational program (Types C and D) reported no significant difference in BMD assessment between the different groups, suggesting that the less intensive services may be less effective [68]. Hence, being able to initiate bone health assessment as part of an FLS program appears crucial in ensuring that a BMD assessment is done. This was demonstrated when a Type D service (education in the form of a letter) was compared with the same service with an additional offer for a free BMD assessment. The group offered the BMD assessment showed a significantly higher rate of investigation for osteoporosis (38% vs 7%, $P < 0.01$) [82]. The same department later compared an outpatient Type B service with the aforementioned Type D service, showing more BMD testing with the more involved Type B intervention (83% vs 26%) [58]. Again, this reaffirms that a more intensive model is more efficient in initiating bone health assessment.

Referring a patient for BMD assessment with DXA is not a thorough assessment of fracture risk. Besides BMD measurement, a comprehensive bone health assessment includes assessment of other risks for future fractures. A two-center comparison study (Type B vs standard service), comparing the practices in postmenopausal women with hip fractures, found much improved investigative work in terms of documentation of osteoporosis risk factors at the FLS center (83% vs 7%) [83]. A Type A FLS from Sydney, Australia, reported that a total of 84% of patients identified by their service had a comprehensive assessment that also included a DXA scan [84].

Overall, referrals for DXA from an FLS program range from 67.4% to 73.4% in Scotland [13] and 83.0% to 99.6% in the Netherlands [85]. Using an automated referral system has been reported to increase referral to 100% [86]. However, as many as 45% of those referred would either decline or not attend [13, 87].

Osteoporosis Treatment Initiation and Adherence

As an outcome of BMD assessment and considering the other risk factors, once the diagnosis of osteoporosis or high fracture risk probability is made, this would mandate starting osteoporosis therapy. This is supported by the results of earlier studies in which osteoporosis treatment was shown to be effective in reducing subsequent fracture risk. Oral bisphosphonates are the most prescribed pharmacological agent. However, adherence to oral bisphosphonate has been reported to be poor with only a third continues taking the medication at 1 year [88]. Therefore, osteoporosis treatment outcomes can be splitted into the rate of initiation of therapy and the level of adherence to therapy treatment at later point of time.

There is overwhelming evidence that FLS increases initiation of osteoporosis treatment.

The Type A services reported treatment initiation by an RR 1.50–4 [89], with data gathered up to 2 years after joining an FLS program [55, 60, 77, 78, 80, 90]. The Edmonton series described treatment as an outcome measure in their trials. Results of the study revealed that comparing the FLS cohort outcome to the standard service revealed higher number of bisphosphonates prescription in the FLS group at 6 months after hip fracture (51% vs 22%, adjusted OR 4.7, 95% CI 2.4–8.9, $P < 0.01$) and wrist fracture (22% vs 7%, adjusted RR 2.6, 95% CI 1.3–5.1, $P = 0.008$) [78, 79]. They also described more patients receiving "appropriate care," i.e., their overall treatment was concordant with guidelines, in the FLS group [78, 79]. The comparative study of the Fracture Prevention Clinic in Newcastle, Australia (Type A FLS vs standard service), also demonstrated increased treatment rates in the FLS group after an average of 2 years of follow-up (81.3% vs 54.1%, $P < 0.01$) [60].

Even when recommendations for osteoporosis therapy were made by the FLS but initiated in the primary care by the GP, there was an increase in treatment rate after fracture from 12.6% to 31.8%, after 1 year of follow-up in the study carried out by Axelsson and co-authors [91]. Another study that looked at a cohort of older women with hip fractures showed that more patients for who the FLS had recommended osteoporosis treatment were prescribed treatment compared to standard care (90.5% vs 60.9%, P 0.01) [83]. However, when no treatment recommendations were made (Type C or D model – educational programs), it made no difference to treatment initiation rates [68].

Analysis of the adherence to osteoporosis treatment revealed that there was wide variation, particularly for bisphosphonates, both in reported adherence and also when adherence was measured. Overall, adherence at 1 year has been reported to range from 44% to 80% [80, 91–93]. The Geisinger Medical Center High-Risk Osteoporosis Clinic (HiROC), Pennsylvania, USA, which includes monitoring osteoporosis patients at 3 months (via phone) and a follow-up visit at 1 year, reported that adherence to oral bisphosphonates was 80.7% at 3 months and 67.7% at 12 months. In another study, although adherence at 1 year improved since the start of a dedicated hip fracture FLS program compared to a pre-FLS period (44.07% vs 14.04%, $P < 0.01$), it demonstrated a significantly low proportion of patients on treatment [80]. A Spanish study which included patient education and telephone follow-up at 3, 6, 12, and 24 months recorded adherence rates to treatment of 72% at 1 year and 73% at 2 years, with significantly better adherence among women and those who had previously been treated with a similar drug [92]. Among patients initiated treatment in a French hospital, adherence was recorded as 80% after 1 year and 67.7% at final follow-up (mean 27.4 [11.7] months) [93].

Cost-Effectiveness of an FLS

In addition to clinical effectiveness, commissioning of an FLS needs to also weigh up the cost-effectiveness of such an intervention. A number of FLSs have conducted formal cost analysis of their existing FLSs, most of them using decision analysis models. Analyses conducted alongside a randomized trial of an FLS for hip fracture and wrist fracture patients with usual care reported that for every 100 patients managed, they would prevent 6 fractures (4 hips) and 3 fractures (1 hip), respectively [8]. This would result in a saving of over US$250,000 to the healthcare system and up to 4 quality-adjusted life years (QALY) gained [94, 95]. Analysis from another Canadian center, the Osteoporosis Exemplary Care Program in Toronto, showed that assessing 500 patients per year would prevent three hip fractures, saving CA$48,950 per year [96]. They also calculated that the employment of an FLS coordinator would still be a cost-effective measure even if they managed as few as 350 patients per year [97]. In the USA, a model based on a Type A FLS in Boston calculated that for every 10,000 patients managed, 153 fractures (109 hip) would be prevented, which equated to an overall saving of US$66,879, and there would be an increase in quality-adjusted life expectancy (QALE) of 37.4 years [98]. The Glasgow, UK, FLS devel-

oped a cost-effectiveness and budget-impact model, based on their internal data. They calculated that for 1000 patients managed in their FLS program, which identifies, investigates, and initiates treatment costing £290,000, they prevented 18 fractures (11 hips), leading to an overall saving of £21,000 [99].

In a separate study also based in Ontario, Canada, cost-effectiveness was compared between a less intense Type C model and a Type A model. For the Ontario Fracture Clinic Screening Program (Type C FLS), 4.3 quality-adjusted life years (QALYs) were gained, and an extra CA$83,000 was spent per 1000 patients, equating to a cost of CA$19,132 per QALY gained. Their subsequent enhanced FLS called the Bone Mineral Density Fast Track program (Type A FLS) was reported to be even more cost-effective at CA$5720 per QALY gained [100]. Hence, this almost fourfold difference in cost-effectiveness suggests that a more intense model may deliver better outcomes.

These studies demonstrate that FLSs are not only cost-effective but also cost-saving. Investment in FLS will reduce future fractures, which ultimately translates into lower overall healthcare cost. However, the cost-effectiveness of each FLS very much depends on the structure of each individual FLS in the context of the healthcare model of that respective geographical region.

Best Practice Framework for Fracture Liaison Services

The IOF released a landmark document entitled Capture the Fracture in 20,127 and went on to publish their Best Practice Framework (BPF) (https://www.capturethefracture.org/), in order to provide guidance for institutions in the process of implementing an FLS and to allow evaluation of services using pre-determined outcome measures. It included 13 key domains—patient identification, patient evaluation, post-fracture assessment timing, identifying vertebral fragility fractures, adherence to local/regional/national guidelines, evaluating secondary cause of osteoporosis, access to falls prevention services, lifestyle risk assessment, initiation of treatment, review of treatment, communication between primary and secondary care, plan for long-term management (>12 months), and all fragility fractures being recorded on a database [101].

Similarly, the UK Royal Osteoporosis Society (ROS) have also published their FLS clinical standards (https://theros.org.uk/healthcare-professionals/tools-and-resources/clinical-guidance/documents/clinical-standards-for-fracture-liaison-services/) based on a 5IQ process of identifying those at risk, investigating bone health and falls risk, informing patients about their condition and management plan, intervening with bone protection and falls intervention, integrating patient care between primary and secondary care, and maintaining quality of the service via database collection, audit, and professional development.

Recently, the International Osteoporosis Foundation launched a new FLS program "Getting to Gold." This new initiative provides effective long-term support for FLS that were established with the help of the Capture the Fracture mentorship program (FLS workshops and onsite trainings). Getting to Gold helps to ensure that a developed FLS can improve and sustain itself in the long run. While the standard FLS workshops and onsite trainings focus more on the early stages of development and building business cases, Getting to Gold focuses on making sure FLS grow in number and quality and are sustainable locally. The first step of the program is the development of a team of key national FLS mentors. The local mentors will be trained through a series of online and in-person sessions. Once evaluated and certified by the IOF, they will support local service development as well as help local FLSs become efficient, sustainable, and able to offer a good patient experience.

In conclusion, the fracture liaison service model appears to address many of the historic shortcomings in traditional management of fragility fractures. It has proven to improve diagnosis and long-term treatment and to decrease morbidity in these patients. It also takes away

ambiguity regarding which specialty manages the disease and allows for efficient communication between multiple specialties and reduces the chance a patient may get lost while navigating the current healthcare system. As the population continues to age, managing and preventing life-altering fractures will become an increasingly important issue. Given that the sentinel sign of osteoporosis is fracture, and the increasing interest in several organization bodies as well as the documented cost-effectiveness of the project, the role played by FLS is expected to grow over time in a trial to comply with the initiative of "Capture the Fracture" launched by the International Osteoporosis Foundation.

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15 Unmet Needs and Challenges in Osteoporosis

Yasser El Miedany

Introduction

Osteoporosis is always a hot topic that is discussed on yearly basis at all the international conferences dealing with the topic of bone health, reflecting the importance of the disease. In fact osteoporosis is a major health issue, affecting around 200 million women worldwide. Moreover, although osteoporosis is typically linked to women, it is also diagnosed in men, however, to less extent. While one in three women over age 50 will experience osteoporotic fractures, one in five men aged over 50 will sustain the disease [1, 2]. Worldwide, osteoporosis accounts for a greater disability burden than cancer, with the exception of lung cancer [3]. This is supported by the reports showing that the incidence of osteoporosis is increasing [2]. In contrast, osteoporosis treatment remains a challenge, with 50–70% of the patients discontinuing their osteoporosis medications within the first year of initiation [4]. Therefore, there is an urgent need for improved management of osteoporosis and its consequences.

Over the past decade, several guidelines have been published for the pharmacological management of osteoporosis in postmenopausal women, which highlight the need for earlier, more widespread screening, and treatment are published [5]. However, a US observational study of women experiencing a first hip fracture between 2008 and 2013 showed that only 17% and 23% had evidence of osteoporosis assessment and/or treatment within 6 or 12 months of their fractures, respectively [6]. Furthermore, the Healthcare Effectiveness Data and Information Set (HEDIS), which is a tool used by more than 90% of America's health plans to measure performance on important dimensions of care and service for a number of disease areas [7], assessed the number of women aged 65–85 years who suffered a fracture and who had either a bone mineral density (BMD) test or prescription for a drug to treat osteoporosis in the 6 months after their fracture with the intent to reduce the risk of fractures resulting from osteoporosis in older women. Testing/treatment rate in women who sustained a fracture in the USA reached 49.6% in 2018 [8]. Results from a recently published survey of untreated postmenopausal women with osteoporosis and their physicians reported that patients themselves decided against pharmacological treatment in at least half of the cases of nontreatment. The most frequent reasons for this patient decision were concerns regarding side effects, alternative nonprescription options (including behavioral modification), and questioning medication benefits [6, 9].

Such inconsistency in management, together with underdiagnosis and undertreatment of peo-

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Table 15.1 Unmet needs and challenges in the field of osteoporosis

Optimizing peak bone mass in young adults
Definition of high-risk patients
Inclusion of imminent fracture risk in the FRAX calculation of osteoporosis fracture risk
Optimizing the diagnostic approach of the patients with clinical risk factors for osteoporosis
Inclusion of bone strength as measurable parameter
Closing the treatment gap and the introduction of new drugs with new mechanisms of action
Introduction of critical thinking into share decision making tools
Clear definition of treat-to-target and drug holiday

ple who are at high risk for fracture, represents the unmet need in the diagnosis and management of osteoporosis. It is, therefore, vital to identify and address these factors which may contribute to such challenge. Table 15.1 summarizes the unmet needs and challenges in the field of osteoporosis. This chapter will discuss the unmet needs and challenges of diagnosing and management of osteoporosis and the limitations of currently available tools.

Challenge 1: Fracture Risk Score and Absolute Risk of Fracture

The National Institutes of Health Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy defines osteoporosis as a skeletal disorder characterized by low bone strength and increased risk of fracture [10]. This definition of osteoporosis reflects the changing perspective on this disease, i.e., osteoporosis is no longer considered a disorder of low bone mineral density alone. Epidemiologic studies have been performed to examine the risk factors that are associated with low bone mineral density and fragility fractures [11, 12]. Consequently, assessments of clinical risk factors that are independent of BMD have been identified as important prognosticators for fracture prediction. Namely, in addition to BMD, advancing age, prior history of fragility fracture, chronic glucocorticoid use, low body mass index (BMI), parental history of hip fracture, cigarette smoking, and excess alcohol intake are the risk factors that have been demonstrated to be most predictive of fracture.

Expression of fracture risk: Absolute risk (AR) is the probability of fracture, usually expressed as a percentage, over a specified period of time. Relative risk (RR) is the ratio of absolute risks of two populations [13]. RR tends to overestimate fracture risk in some populations and underestimate it in others [14]. As an example, a 50-year-old and an 80-year-old woman with a hip T-score of −2.5 each have the same RR for hip fracture compared with an age-matched population with normal BMD [13], while the 10-year probability of hip fracture is much higher in the 80-year-old woman. Both are measures of risk, but estimation of an individual's fracture risk requires knowledge of absolute risk when relative risk estimates are used. Therefore, absolute risk is a measure easily explainable to both the physician [15] and the patient.

Several fracture risk assessment tool have been developed; however, the most popular and commonly used out of them is the developed, in 2008, by the University of Sheffield (FRAX) that estimates the 10-year probability of hip fracture and major osteoporotic fracture (hip, clinical spine, proximal humerus, or forearm) for untreated patients between ages 40 and 90 years using easily obtainable clinical risk factors for fracture and femoral neck BMD (g/cm^2, using dual-energy X-ray absorptiometry [DXA]), when available [16, 17]. As well as the FRAX tool, other fracture risk calculators are available online which include the Garvan fracture risk calculator (www.garvan.org.au) and QFracture (www.qfracture.org) .

There are several important limitations that need to be considered when FRAX is used as a calculation tool. The relationships between risk factors and fracture risk incorporated within the FRAX model have been constructed from the primary data of nine population-based cohorts around the world [18–20]. Databases from most of the countries incorporated into FRAX provided accurate rates of hip fractures because all patients with a hip fracture are admitted to a hospital. However, patients with a wrist or proximal humeral fracture are usually treated as outpa-

tients, leading to an underestimation of the incidence of these types of fractures [21]. Assessing the rate of clinical vertebral fracture is also challenging since it is difficult to distinguish between patients with a clinical vertebral fracture and patients who have back pain with an incidental vertebral compression fracture. Therefore, the reported rates of major osteoporotic fractures at sites other than the hip may not be accurate. Kanis et al. [19] studied the use of clinical risk factors to predict osteoporotic fractures on the basis of baseline and follow-up data from nine population-based cohorts. They found that models for predicting hip fractures were substantially better than those for predicting osteoporotic fractures at other sites, regardless of whether the models included bone mineral density alone, clinical risk factors alone, or a combination of both [22]. For these reasons, the prediction of the risks of three other major osteoporotic fractures (proximal humeral, wrist, and clinical vertebral fractures) may not be as accurate as the prediction of the risk of hip fracture.

There is also a question of the generalizability of data obtained from the population-based cohorts. For example, the US FRAX model was formulated from data from the Rochester cohort, which was recruited from two random population samples in Olmsted County, Minnesota. This community is predominantly White and is better educated than the White population of the USA as a whole [23]. In addition, recent data have shown that the incidence of hip fracture among Olmsted County residents is declining [24]. Therefore, the incidence and mortality data in the US FRAX model may not reflect current incidence and mortality rates.

The use of FRAX sometimes results in 10-year fracture probabilities that lead to treatment recommendations that contradict those of the National Osteoporosis Foundation. For example, a 50-year-old postmenopausal woman with a body mass index of 24.1 kg/m^2, no clinical risk factors, and a T-score of −2.5 meets the threshold for pharmacological therapy on the basis of the T-score; however, the fracture probabilities calculated with the FRAX tool (8.7% for a major osteoporotic fracture and 2.5% for a hip fracture) are below the treatment threshold. Conversely, an 80-year-old postmenopausal woman with the same body mass index, a parental history of hip fracture, and a T-score of −1.0 has 10-year risks of 26% and 9.9%, respectively, for a major osteoporotic fracture and for a hip fracture—a level of risk at which treatment should be considered [25]. Yet, there is no strong evidence to support treatment of patients with this level of bone mineral density. In addition, FRAX may not accurately predict fracture risk across all age groups [22]. Furthermore, fracture risk probabilities calculated with FRAX are not valid for patients who have already received pharmacological treatment for osteoporosis such as bisphosphonates.

The magnitude by which FRAX may over- or underestimate fracture risk has been studied using large population databases, and procedures for adjusting FRAX probability have been proposed [26, 27]. As an example, an analysis of the Canadian Manitoba BMD database shows that when there is discordance between lumbar spine and femoral neck BMD, the FRAX estimate for major osteoporotic fracture may be increased or decreased by one-tenth for each rounded T-score difference or offset between lumbar spine and femoral neck (e.g., when the lumbar spine T-score is 1.0 less than the femoral neck T-score, the 10-year probability of major osteoporotic fracture can be increased by one-tenth) [26]. Another analysis using the UK General Practice Research Database showed that for patients exposed to high-dose glucocorticoids (prednisolone >7.5 mg/day or equivalent), the 10-year probability of major osteoporotic fracture may be increased by 15 percent and the 10-year probability of hip increased by 20 percent [27]. The increase in fracture risk associated with type II diabetes mellitus may be captured by entering "yes" for rheumatoid arthritis in the FRAX algorithm [28]. With modifications such as these, the FRAX probability of fracture can be refined [29]. However, these correction factors have not been computed for the majority of countries represented by FRAX, including the USA. Thus, they should be applied to US populations with caution.

Other important risk factors for fractures are not included in this calculation tool. These include

the serum level of 25-hydroxyvitamin D, physical activity, risk of falls, and biochemical bone markers. Therefore, the calculated risk may be less than the actual risk. In addition, FRAX does not take into account bone mineral density at the spine or the substantially higher risk of spine fracture among those with a history of vertebral compression fractures. A cohort study of 6459 women 55 years of age or older with low bone mineral density, of whom 31% (2027) had a radiographically detected vertebral fracture at baseline, demonstrated that a combination of a vertebral fracture on a baseline radiograph, femoral neck bone mineral density, and age predicted incident radiographically evident vertebral fractures significantly better than did use of FRAX and bone mineral density at the femoral neck ($p = 0.0017$) [30]. Nevertheless, FRAX remains an important tool that represents an advance in the care of osteoporosis. The current FRAX model provides an aid to enhance patient assessment by the integration of clinical risk factors alone and/or in combination with bone mineral density. It is anticipated that the limitations described above will be addressed in future FRAX versions.

Challenge 2: Implementation of Health Economics into Clinical Guidelines

The use of health economic thresholds incorporating QALYs (quality-adjusted life year) led to some difficulties with some of the initial guidelines developed [31, 32], as the costs of treatments meant that patients with osteoporosis confirmed by dual-energy X-ray absorptiometry (DXA) would not have access to drugs, since estimated health costs exceeded £20,000/QALY [7]. In response, the National Osteoporosis Guideline Group (NOGG) in the UK developed evidence-based guidelines with alternative treatment thresholds, which were not set using health economic considerations but the clinical fracture risk after a first low-trauma fracture [33]. On the other hand, the National Osteoporosis Foundation osteoporosis treatment recommendations were based on the 10-year fracture probability model, whereas, in Scotland, "SIGN" (Scottish Intercollegiate Guideline Network) guidelines took an alternative approach, interpreting clinical trial-based evidence to support drug treatment for those who have had a vertebral fracture and hip fracture or with a bone mineral density (BMD) T-score less than −2.5 [34]. The most recent recommendations from NICE [35] are a radical change, with no health economic argument against oral or parenteral therapy down to a 10-year fracture risk of 1%. However, it recently has been suggested that "Unthinking assimilation of the NICE multiple technology appraisal risks a generation of older individuals taking a bisphosphonate regardless of the individual benefit-to-risk ratio" [36]. There are now a number of guidelines on osteoporosis across Europe and North America, with country- and comorbidity-specific recommendations. Each takes a slightly different approach, resulting in inconsistent recommendations (Table 15.1). Consequently, clinicians are faced with an overwhelming amount of guidance on the management of osteoporosis and bone health from international, national, and local governing bodies. No wonder, such global inconsistency would reflect on the patients' management particularly at the primary care level.

In addition, there is a low reimbursement for DXA investigations in the USA. It is possible that pharmaceutical industries also play a role, as during the first years after introduction of osteoporotic drugs, an increase of bisphosphonate use was observed (in 2007 ~ 15% of postmenopausal women used bisphosphonates) [37]. Currently, there is a growing market share of generics drugs and increased withdrawal of large pharmaceutical industries, which might be related to a decrease in bisphosphonate use. This emphasizes the certain unmet need for new drugs with an even better efficacy/safety profile.

Challenge 3: Treatment Thresholds

After the advent of absolute fracture risk calculators, guidelines for the management of osteoporosis have been published. These have been updated

several times over the past decade. However, there were disparity between different guidelines and the treatment thresholds advised which represent a challenge to osteoporosis specialists trying to manage their patients, according to these guidelines. Best examples are the guidelines released by the US-based National Osteoporosis Foundation (NOF) and the UK-based National Osteoporosis Guidelines Group (NOGG) which differ markedly in their approaches to treatment recommendations.

The National Osteoporosis Foundation recommendations for pharmacological treatment of osteoporosis [38] are based in part on the US adaptations of the World Health Organization 10-year fracture probability model and algorithms for determining treatment thresholds [39]. These recommendations are based on cost-effectiveness in populations of patients and should be used together with other considerations when making treatment decisions for individual patients. According to the National Osteoporosis Foundation recommendations, treatment of osteoporosis should be considered for (1) patients with a history of hip or vertebral fracture, (2) patients with a T-score of −2.5 or lower at the femoral neck or spine, and (3) patients who have a T-score of between −1.0 and − 2.5 at the femoral neck or spine and a 10-year hip fracture risk of ≥3% or a 10-year risk of a major osteoporosis-related fracture of ≥20% as assessed with the FRAX. The advantages of this new recommendation as compared with the earlier published National Osteoporosis Foundation recommendations include better allocation of limited healthcare resources to patients who are at higher risk for fracture and most likely to benefit from therapy. In addition, these new guidelines take into consideration different ethnicities in the USA and include the male population.

Similar to the National Osteoporosis Foundation, the UK developed by the National Osteoporosis Guidelines Group (NOGG) [39] incorporated FRAX-derived risk calculations. However, the approaches taken to recommendations for intervention by these guidelines differ markedly, as summarized in Fig. 15.1. The NOF intervention thresholds are based upon economic

NOGG guidelines	NOF guidelines
1. Treat if previous fragility fracture. 2. If clinical risk factors present, estimate 10 yr probability of major osteoporotic fracture using FRAX without BMD. If probability > intervention threshold: treat. If probability < assessment threshold: reasure. If probability falls between threshold: measure BMD. 3. If BMD measurement, re-estimate 10 yr probability of major osteoporotic fracture using FRAX with BMD. If probability > intervention threshold: treat. If probability < assessment threshold: reasure.	1. Treat if previous hip or vertebral fracture. 2. For women age 65 and older, measure BMD. 3. Trat if osteoporosis (BMD T-score -2.5 at proximal femur or lumbar spine). 4. Trat if osteoporosis (BMD T-score -1 to -2.5 at proximal femur or lumbar spine). AND FRAX-estimated 10yr probability of hip fracture ≥ 3% or major osteoporotic fracture ≥ 20%

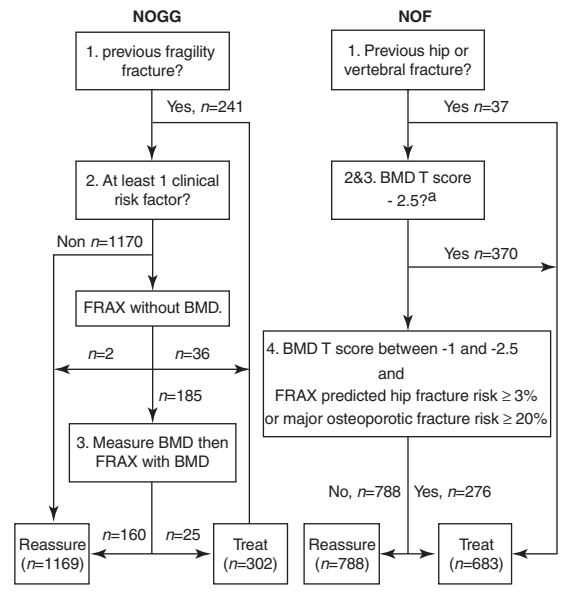

Fig. 15.1 Summaries of the NOGG and NOF guidelines for management of osteoporosis (left), with their application to a cohort of 1471 healthy older women (right). a, Nineteen women in the cohort were younger than 65 yr. at baseline. The NOF guidelines recommend BMD measurement in women younger than 65 yr. if there are concerns based on the risk factor profile. For the purposes of this analysis, we assumed that all these 19 women had a measurement of BMD for this reason. (Unless provided in the caption above, the following copyright applies to the content of this slide: Copyright © 2010 by The Endocrine Society)

cost-effectiveness analyses [40–44], whereas the NOGG guidelines recommend intervention if the probability of fracture exceeds that of a person of the same age who has suffered a previous osteoporotic fracture [45]. Thus, the NOGG intervention and assessment thresholds vary by age and gender, such that reassurance is recommended for older individuals at high risk of fracture, whereas intervention is recommended for younger individuals at lower risk of fracture.

Potentially, the differing approaches between guidelines might lead to different treatment recommendations and fracture outcomes. In the study done by Mark and Grey [46], two illustrative clinical cases were presented to symbolize the difference between the two treatment recommendations. Patient (1) is a female, aged 80 years old, in good health, with BMI of 23.8 kg/m^2, no personal or parental history of fracture, and a femoral neck BMD T-score of −3. Her estimated 10-year risk of major osteoporotic fracture using FRAX with BMD is 21% and of hip fracture is 9%. Applying the NOGG guidelines leads to a recommendation to reassure, whereas the NOF guidelines recommend treatment. Patient (2) is a female, aged 65 years old, in good health, and also has a BMI of 23.8 kg/m^2, no personal or parental history of fracture, and a femoral neck BMD T-score of −3. Her estimated 10-year risk of major osteoporotic fracture is 16% and of hip fracture is 5%. Both the NOGG and NOF guidelines recommend treatment. This paved the way for the most recent osteoporosis treatment recommendations published by NOGG in 2017, in which NOGG has released its update in which the intervention thresholds have been based on FRAX probability and so cannot be used with fracture risk derived from QFracture or other calculators [4]. NOGG recommended also that diagnostic assessment should include not only the assessment of BMD where indicated but also the exclusion of diseases that mimic osteoporosis, elucidation of the cause of the osteoporosis, and the management of any associated morbidity. In addition, recommendations for the routine investigation of patients with osteoporosis have been advised and are summarized in Tables 15.2 and 15.3.

Challenge 4: DXA

Appropriate and accurate use of densitometric techniques is of great importance: bone mineral measurements provide not only diagnostic criteria but also prognostic information on fracture risk probability, and they are also used to monitor treated or untreated patient [47]. For this reason, several guidelines have been developed in the last years with a number of recommendations that include indications for BMD testing, which skeletal site to measure and how to interpret and report BMD results, and proper timing for follow-up [48–51]. These guidelines, typically issued by relevant medical societies or specialized working groups, play an important role in clinical practice: they provide valuable suggestions based on the highest level of evidence, which is usually achieved through a critical evaluation of systematically searched primary studies [52, 53].

The distribution of bone density across a population is dependent on race, age, and gender. For example, African-Americans have lower rates of fracture compared to US Caucasians and Asians, and this parallels the population distribution differences among races [54]. In one study, the age-adjusted mean for femoral neck BMD was 0.686 g/cm^2 in US Caucasians and 0.841 g/cm^2 in African Americans [55]. Because of such racial and ethnic differences, the significance of T-scores must be considered based on the fracture risk of ethnic and racially matched persons. A similar rationale can be applied to men who have larger skeletal structures compared to women. To control for racial differences, DXA calculates T-scores using normative databases based on NHANES III data that include non-Hispanic White, Black, Hispanic, and Asian individuals [56]. A pediatric normative base is also available. However, while bone size is directly related to strength, DXA does not account for bone size in assessing fracture risk. Attempts to correct bone size for height and weight have been reported [57]. Some DXA manufacturers allow for weight correction in the calculation of Z-scores to adjust for an expected decrease in fracture risk as weight increases. Height correc-

Table 15.2 Comparative analysis of the most popular osteoporosis guidelines, their targeted subjects, as well as thresholds of treatment

Guideline (year)	country	Targeted people	Drugs included	Thresholds of treatment	Comments	Reference
NOF (2014)	The USA	Men and women over 50 years	FDA-approved medications: alendronate, ibandronate, risedronate, zoledronate, calcitonin, raloxifene, bazedoxifene, teriparatide, denosumab	Treatment should be considered for: Hip or vertebral fracture T-score ≤ −2.5 at hip or spine on DXA T-score between −1.0 and − 2.5 with a 10-year risk ≥20% for major fracture or ≥ 3% for hip fracture	Just recommends the use of an FDA-approved medication Does not give an order for first-line or second-line agents	37
NOGG (2009 and updated 2017)	The UK	Men and women over 50 years	Alendronate, risedronate, zoledronate, HRT, raloxifene, strontium, denosumab and teriparatide	10-year fracture risk used Men and women aged 70+ years With a fracture or On long-term prednisolone over 7.5 mg daily should be considered for bone protection	FRAX used without BMD to determine fracture risk (high, low, or medium), then refine into high or low risk Calculate risk to age 70+ years; thereafter fixed risk of 20% for major and 5% for hip fracture used Oral bisphosphonate first line No alteration to threshold for use of alternative agents High cost of teriparatide restricts use for those at very high risk of vertebral fractures Incorporates guidance on investigation and management of osteoporosis including vitamin D and falls	38
ESCEO and IOF (2008 updated 2013),	Europe	Postmenopausal women	Alendronate, ibandronate, risedronate, zoledronate, HRT PTH therapies, raloxifene, calcitonin, denosumab, strontium ranelate	10-year fracture risk using FRAX Country-specific thresholds for treatment If prior fracture, consider treatment without further risk assessment	Does not specify order of use of medications Note that cost alone would suggest alendronate as first line DXA depends on country, e.g., very good access in Belgium but very difficult in others such as Bulgaria Offers advice on investigation, vitamin D, management, and fall prevention	39

(continued)

Table 15.2 (continued)

Guideline (year)	country	Targeted people	Drugs included	Thresholds of treatment	Comments	Reference
AACE/ACE (2016)	The USA	Postmenopausal women	Alendronate, ibandronate, risedronate, zoledronate, raloxifene, teriparatide, denosumab	T-score ≤ −2.5 at femoral neck, total hip or lumbar spine or A history of fragility fracture or FRAX probability of ≥20% for a major fracture or hip fracture ≥3%	FDA-approved medications considered Different choices of first or second line depending on situation No previous fracture then first line would be alendronate, risedronate, zoledronate, or denosumab Second-line ibandronate or raloxifene switch to injectables if problems with oral bisphosphonate or to teriparatide Prior fractures first-line denosumab, zoledronate, or teriparatide alternatives alendronate/risedronate or switch to teriparatide	40
Scientific advisory Council of Osteoporosis Canada	Canada	Men and women over 50	Alendronate, ibandronate, risedronate, zoledronate, raloxifene, teriparatide, denosumab	Based on FRAX or CAROC fracture risk calculation 10-year major osteoporotic fracture risk ≥20% Aged over 50 years with a hip, vertebral or multiple fractures are high-risk T-score ≤ −2.5 moderate risk and moderate risk needs combining with additional risk factors and patient preference	Includes information on investigation and management as well as falls risk Vitamin D checked and targeted ≥75 nmol/L in those requiring treatment First-line treatment Women: alendronate, risedronate, zoledronate, and denosumab Men: alendronate, risedronate, zoledronate, and testosterone	41
SIGN (2015)	Scotland	Men and women Over 50 years	Alendronate, risedronate, ibandronate, etidronate, zoledronate, denosumab, HRT, tibolone, raloxifene, strontium ranelate, teriparatide	Primary prevention FRAX risk ≥10% for major fracture and T-score ≤ −2.5 Secondary prevention at least one fragility fracture and a T-score ≤ −2.5 Hip fracture Vertebral fracture	Once over threshold any treatment may be used but First-line alendronate and risedronate Teriparatide if severe spinal osteoporosis Second-line zoledronate or denosumab Third-line ibandronate, etidronate, HRT, tibolone, raloxifene, and strontium Treatment can be initiated without BMD measurements in	34

NICE TA464 (2017),	England and Wales	Men and women	Alendronate, ibandronate, risedronate, zoledronate	Oral BP IV BP if 10-year fracture risk is ≥10% or ≥1% and oral bisphosphonates intolerant, contraindicated, or failed	Replaces TA-160 and TA-161 recommendations on bisphosphonates Denosumab guidance awaited Uses FRAX or QFracture to estimate fracture risk Analysis shows that medications are cost-effective down to low levels of risk because of their low cost. However, these are not treatment thresholds and NOGG guidance highlighted as a possible clinical guideline to treatment	35

Table 15.3 proposed approach to investigations for a case of osteoporosis

Basic bone profile	Advanced bone profile assessment
History and physical examination Blood cell count, sedimentation rate or C-reactive protein. Serum calcium, albumin, creatinine, phosphate, alkaline phosphatase, and liver transaminases Thyroid function tests Bone densitometry (DXA)	Lateral radiographs of lumbar and thoracic spine or DXA-based lateral vertebral imaging Serum protein immunoelectrophoresis and urinary Bence Jones proteins Serum 25-hydroxyvitamin D Plasma parathyroid hormone Serum testosterone, sex hormone-binding globulin, follicle-stimulating hormone, luteinizing hormone Serum prolactin 24-hour urinary-free cortisol/overnight dexamethasone suppression test Endomysial and/or tissue transglutaminase antibodies Isotope bone scan Markers of bone turnover Urinary calcium excretion
Other investigations, for example, bone biopsy and genetic testing for osteogenesis imperfecta, are largely restricted to specialist centers	

tion is especially important in assessing fracture risk in children affected by short stature or growth delay [58].

DXA images are a two-dimensional (vertical and horizontal) condensation of a three-dimensional structure. As such, bone thickness is not measured in this scan. The BMC measured reflects the amount of cortical and trabecular tissue present within a structure that acts to attenuate the X-ray signal; bones with more tissue attenuate the signal to a greater degree resulting in a higher gray value and BMC measure. Bone area is a measure of the size of the region of interest "ROI." For the hip, the ROI width is fixed, and thus variation in bone area reflects differences in external bone size. The ratio of these two variables provides a measure of the mass density but not a measure of morphology or material properties. Further, BMD does not differentiate whether the variation in BMD arises from differences in cortical mass, trabecular mass, or external bone size [59].

Conventional wisdom is that women uniformly lose endosteal and trabecular bone in a similar pattern. Recent data however suggest that the pattern of bone loss with aging in women is not uniform [60]. Bone shape and size at the menopause transition may in fact have a critical role in determining long-term bone loss with aging. Women with narrower femoral necks experienced modest decreases in BMC compared to those with wider femoral necks (Fig. 15.3). But, women with narrow femoral necks also had larger increases in femoral neck area compared to women with wider femoral necks. BMD is the quotient of the BMC divided by the area. Because the larger increase in the denominator (area) in women with narrow femoral necks is similarly matched by the larger decrease in the numerator (BMC) in women with wide femoral necks, the result is that both groups have similar losses in BMD over time but for very different reasons. The impact of these structural and mass changes on strength is currently under investigation. In addition to the previous discussion regarding how most fragility fractures occur in persons with T-scores > -2.5, this example illustrates another limitation of DXA scanning to accurately predict bone strength and fracture risk.

Diagnosis of Osteoporosis: More Than Dual-Energy X-Ray Absorptiometry Alone

It could be argued that performing a VFA (vertebral fracture assessment) in all patients for whom a DXA is indicated and performed would be beneficial [61]. With this technique, (asymptomatic) vertebral deformities can be detected. For example, it was recently documented in a cross-sectional study that vertebral fractures were found in 13% of rheumatoid arthritis (RA) patients [62]. Vertebral fractures are clinically relevant: although only one-third of the vertebral deformities are associated with clinical signs and

symptoms of an acute vertebral fracture, they are a good predictor of subsequent vertebral and hip fractures and may have impact on quality of life [63]. Moreover, assessment of vertebral fractures in addition to BMD enhances fracture risk prediction [64]. Thus, the finding of one or more moderate or severe vertebral deformities in patients with osteopenia may make the difference between starting treatment with anti-osteoporotic medication or not.

The European League Against Rheumatism (EULAR)/ European Federation of National Associations of Orthopaedics and Traumatology (EFORT) recommendations advocate that in all patients 50 years and over with a recent fracture in addition to DXA/VFA, fall risk evaluation and screening for secondary causes of osteoporosis need to be performed [65]. In patients with an elevated fall risk, it is clinically relevant to establish whether modifiable risk factors can be identified; the same is true for potentially treatable causes of secondary osteoporosis and other metabolic bone disorders. Obviously, both high fall rate and untreated secondary osteoporosis may limit the effect of both nonmedical and drug treatment. There are hardly any data on the implementation of these four crucial diagnostic steps in daily practice. However, considering the access to DXA which is suboptimal and the poor implementation of the other four steps (VFA incorporation in DXA, fall risk assessment, fracture risk assessment, and active screening for secondary causes of osteoporosis), this emphasizes that there is an urgent need for better diagnostic procedures in patients at risk for fractures [66].

Challenge 5: Measuring Bone Strength

Although the DXA device is an easy-to-use tool for diagnosing osteoporosis, a limitation is that the DXA device measures only one aspect of bone strength, that is, bone density, which can be considered as the amount of hydroxyapatite (Ca10(PO4)6(OH)2) per bone area. Therefore, the BMD value measured by DXA is influenced by degenerative changes, atherosclerosis (aortic calcifications), and fractured lumbar vertebrae, as these conditions are characterized by calcifications potentially increasing BMD values [67, 68].

Another limitation of DXA is that it creates a two-dimensional image of bone structures, and therefore details cannot be identified. A large proportion of fractures occur in individuals not identified by a low augmented BMD (aBMD) (Fig. 15.2). For these reasons, new and more advanced techniques such as trabecular bone score (TBS), high-resolution peripheral quantitative computed tomography (HR-pQCT), ultrasound, finite element analysis (FEA), and magnetic resonance imaging (MRI) are under development.

TBS is a surrogate marker for bone microarchitecture and has been associated with prevalent and incident fractures [69]. Although TBS changes during treatment, TBS is less sensitive to change than aBMD. Although TBS may have a role in predicting future fracture risk in specific disorders like hyperparathyroidism and diabetes, its precise role in osteoporotic care remains to be elucidated.

HR-pQCT is probably a more promising technique: one of the biggest advantages of HR-pQCT is that it constructs a three-dimensional image of the bone and it has the additional value of measuring the microarchitecture of bone, that is, both cortical and trabecular aspects of bone. Previous studies showed that several HR-pQCT-derived bone parameters, with or without FEA, are associated with previous fractures [70–72]. More recently, it was shown that cortical area and cortical bone mass by HR-pQCT analysis was independently of aBMD associated with fracture risk, suggesting that HR-pQCT may have additional value on fracture risk calculation [73]. Moreover, it was demonstrated that in individuals with identical BMD at distal radius area, differences in bone microarchitecture were observed by HR-pQCT due to differences in morphological and biomechanical differences, especially at the cortical level of bone [74, 75].

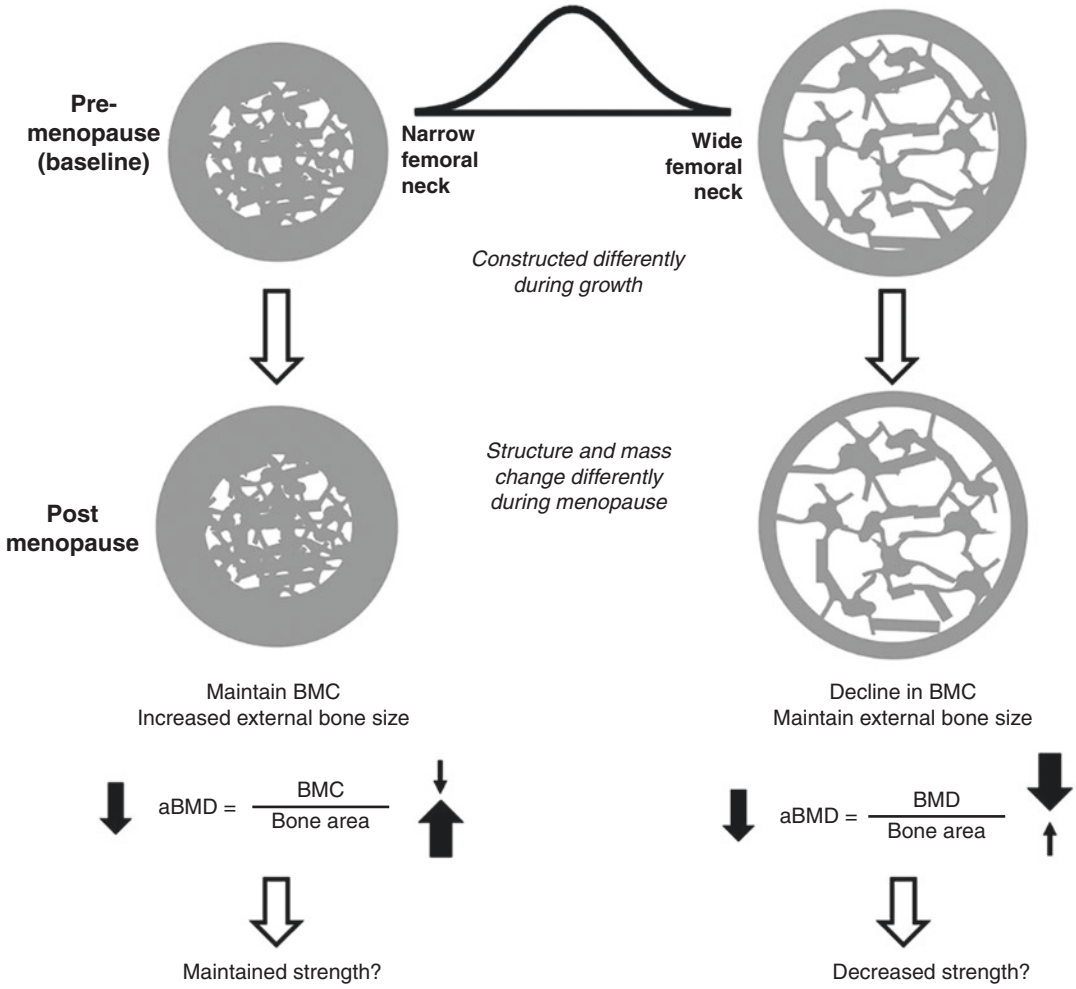

Fig. 15.2 Structural changes in bone with osteoporosis medications. The antiresorptive medications (bisphosphonates and denosumab) and anabolic medications (teriparatide and likely abaloparatide) produce very different structural changes in bone. Although both classes increase trabecular bone, their effects on cortical bone are different. Bisphosphonates and denosumab do not expand periosteal bone but do decrease the endosteal diameter by an increase in endosteal bone volume. Antiresorptives also reduce cortical porosity. Anabolic agents lead to an increase in periosteal bone with a simultaneous increase in endosteal bone resorption resulting in a bone without a large change in cortical thickness. At the same time, anabolic agents increase cortical porosity. Despite the increase in cortical porosity, the larger bone has increased strength. NC no change. (Adapted from: Choksi et al. [59] (under open access scheme)

Although promising, an important point is that some clinical questions remain: up to now, we do not know what is the most clinically relevant and prognostically optimal region of interest to report in clinical practice. Furthermore, standardization of repetitive measurements of the same region of interest needs to be improved. Therefore, incorporation of this modern diagnostic tool is promising but remains challenging. In addition, HR-pQCT may have clinical relevance for certain rheumatic diseases like ankylosing spondylitis (AS) characterized by bone formation. In AS patients, suboptimal bone microarchitecture in both axial and peripheral skeleton (distal radius) was demonstrated [76] which is an important finding, as lumbar spine bone density measure-

ment by DXA in AS patients may give an overestimation of BMD due to syndesmophytes or bamboo spine development. Recently, HR-pQCT imaging made it possible to monitor the healing process of fractures by a noninvasive manner, as this technique identified differences in cortices and trabeculae during a follow-up period of 2 years in the fractured and nonfractured site, whereas BMD was similar at both sites [77]. Moreover, a recent collaboration between different bone specialists showed that HR-pQCT imaging is a promising tool to define erosions in RA patients instead of using plane X-rays [78]. Another interesting observation is that HR-pQCT can measure changes in microarchitecture during treatment for a disease. This was illustrated in coeliac disease patients who underwent treatment with gluten-free diet, where it was observed that both BMD as microarchitectural parameters at the trabecular and cortical level improved during intervention [79]. Very recently, data were presented of an observational study in 589 French postmenopausal women with 135 incident fractures, who were followed over 9.4 years. The authors compared the structure fragility score (SFS) combining trabecular and cortical indices by HR-pQCT at the distal radius, with the BMD of the femoral neck and the FRAX® score: the predictive value seems to be comparable for all methods, with no additional value of the SFS on top of the BMD or the FRAX® [80].

Although these studies do not demonstrate that HR-pQCT is superior to DXA for fracture risk assessment, it clearly illustrates that new modern techniques may have additional value and may be promising in the future to have a better fracture risk assessment, especially in certain high-risk patient groups.

These concerns illustrate that the prevention of subsequent fractures after an initial fracture care needs to be improved. An important step forward may be intensification of collaboration between different medical specialists and general practitioners. The recommendations published by EULAR, in collaboration with the European Federation of National Associations of Orthopaedics and Traumatology (EFORT), for patients with fractures is a good example; in which ten recommendations are advocated for optimal fracture care of patients older than 50 years with a fragility fracture, to prevent subsequent fractures [81].

Challenge 6: Osteoporosis Treatment

The current treatments have one important feature in common; bone resorption and formation remain coupled [82]. This is both from a pharmacological and clinical point of view not optimal and results in unmet needs. First, antiresorptive treatments can only increase bone mineral density (BMD) to a certain extent as the decrease in osteoclast number and release of substances from the bone matrix subsequently impairs the recruitment of osteoblasts and de novo synthesis of new bone by the osteoblasts. Therefore, if the patient initially had very low bone mass, antiresorptive treatments will not be able to improve BMD enough to optimally prevent future fractures. In addition, if the patient also had deteriorated bone architecture, this will be improved, but not restored. Second, teriparatide stimulates osteoblasts and subsequently osteoclasts which limits the effect, and some patients with very low bone mass or suboptimal response to teriparatide are left with very low BMD after treatment. Third, only few studies have examined if the coupling of bone resorption and formation can be overcome by combining the therapies, and the unmet needs thereby may be improved.

Furthermore, while all antiresorptive and anabolic therapies increase spine and hip BMD, with the highest increases in the spine (Fig. 15.3), there is a discrepancy in how these therapeutic agents affect the skeleton (Table 15.4). As newer agents are studied, a trend in more efficacious BMD improvement with each new agent is apparent. Although many osteoporosis treatments have not been directly compared in head-to-head trials, the mechanisms of actions of these newer treatments often predict a superior efficacy in increasing BMD [83].

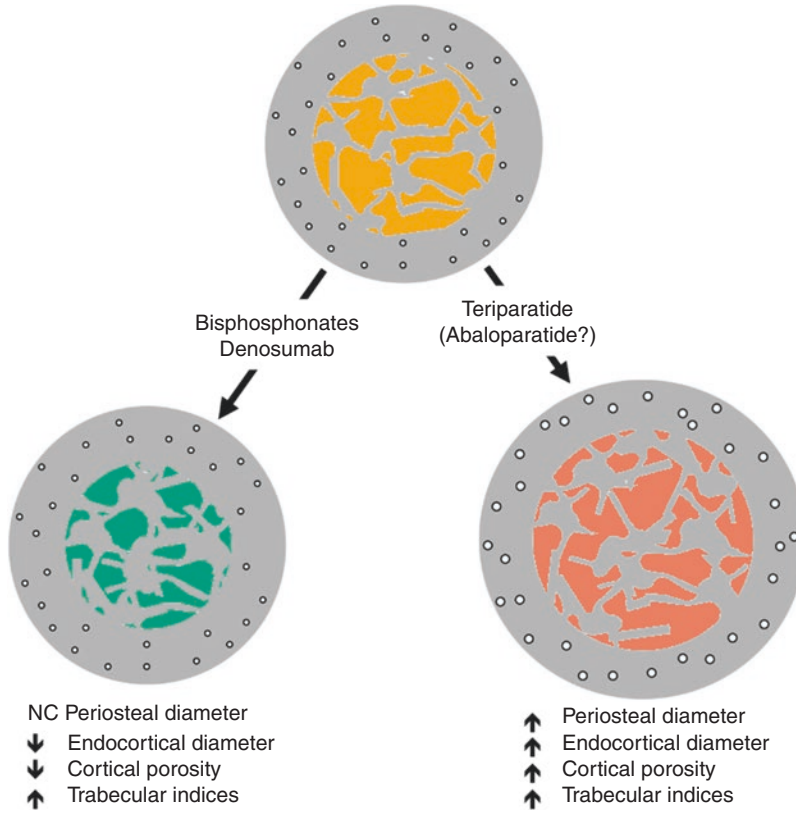

Fig. 15.3 Areal BMD as determined by DXA declines with aging for different reasons. With aging, women with smaller femoral necks tend to increase bone area through an increase in cortical thickness by an increase in periosteal and endosteal bone formation. Since BMD may only decrease slightly but bone area increases more, the result is lower areal BMD as measured by DXA despite likely having little change in bone strength. In the case of women with larger femoral necks, the endosteal cortex undergoes excessive resorption without periosteal expansion resulting in a thinner cortex. The result is a lower BMC without significant change in bone area. The DXA areal BMD decreases and may result in a bone with less strength. (Quoted from: Choksi et al. [59] (under open access scheme))

All approved osteoporosis medications produce significant increases in spine and hip BMD as measured by DXA. The degree of BMD increase in the spine is likely a consequence of the greater surface area of trabecular-rich vertebral bodies on which the agents act. Twelve months of treatment with bisphosphonates increased BMD by approximately 4% in the spine and 2% in the hip as reported in the landmark FIT, VERT, BONE, and Horizon trials [84, 85, 96, 97]. The efficacy of daily, weekly, and monthly oral and yearly IV bisphosphonate medications are similar [98–102]. Compliance with oral bisphosphonates is a common factor in those patients who fail to respond to treatment [103–105]. Denosumab has even greater effects likely owing to its enhanced ability to suppress bone resorption [89]. Teriparatide, an anabolic agent, increases spine and hip BMD [59]. Abaloparatide, another recently available anabolic agent, also markedly increases spine and hip BMD [93].

Romosozumab, recently approved for treatment, is a humanized monoclonal antibody that targets sclerostin and has been reported to increase spine BMD approximately 13.5% and hip BMD approximately 6.5% after 12 months of treatment [94, 95].

Numerous published studies have reported the architectural changes in the skeleton with such

Table 15.4 Osteoporosis therapy agents, their doses and grade of recommendation in osteoporotic fractures

Medication	Dosage	Vertebral fracture	Non-vertebral fracture	Hip fracture	BMD (approx. % increase)	
					Spine	**Hip**
Alendronate	70 mg/week	A	A	A	**4**[a]	**2–2.5**[a]
Risedronate	35 mg/week	A	A	A		
Zoledronic acid	5 mg IV/ annually	A	A	A		
Ibandronate	150 mg/month oral or 3 mg IV every 3 months	A	A[1]	Not adequately evaluated	**3.8**[b]	**0.5**[b]
Denosumab	60 mg SC every 6-month	A	A	A	**5.5**[c]	**3**[c]
Raloxifene	60 mg od	A	Not adequately evaluated	Not adequately evaluated	**2.9**[d]	**No significant change**
HRT	Several formulation available	A	A	A	**6.76**[e]	**4.12**[e]
Teriparatide	20 µg SC every day	A	A	Not adequately evaluated	**Teriparatide 9**[f]	**Teriparatide 3**[f]
Abaloparatide	80 µg SC once a day				**Abaloparatide 11**[g]	**Abaloparatide 4**[g]
Calcitriol	0.25 µg twice daily	A	Not adequately evaluated	Not adequately evaluated	**No data available**	
Romosozumab	210 mg SC qMonth × 12 months	Data only available from phase III trials			**13.5**[h]	**6.5**[h]
		Reduction by 73%	Reduction by 25%	No data available		

A: grade A recommendations
1: In subsets of patients only (post hoc analysis)
[a]12 months of treatment [84–87]
[b]12 months of treatment [88]
[c]12 months of treatment [89]
[d]12 months of treatment [90]
[e]At 24 months of treatment [91]
[f]18 months of treatment [92]
[g]18 months of treatment [93]
[h]12 months of treatment [94, 95]

agents using a variety of techniques that include HR-pQCT and QCT of in situ hip and spine as well as similar techniques of iliac crest bone biopsy samples. What has become clear is that they do not uniformly produce similar results (Table). Bisphosphonates increase cortical thickness primarily by decreasing the endosteal perimeter, partially through the filling in of previously excavated resorption pits at the endosteal surfaces. In addition, bisphosphonates also reduce cortical porosity and increase the amount of trabecular bone. Denosumab has similar effects and presumably to a higher degree owing to its improved fracture reduction compared to bisphosphonates [59].

Challenge 6: Patient Education

A plunge of around 50% from 2008 to 2012 in postmenopausal women using bisphosphonates was documented in the USA, the so-called crisis in osteoporosis [106, 107], (Fig. 15.4). The reason for the crisis is probably multifactorial: a

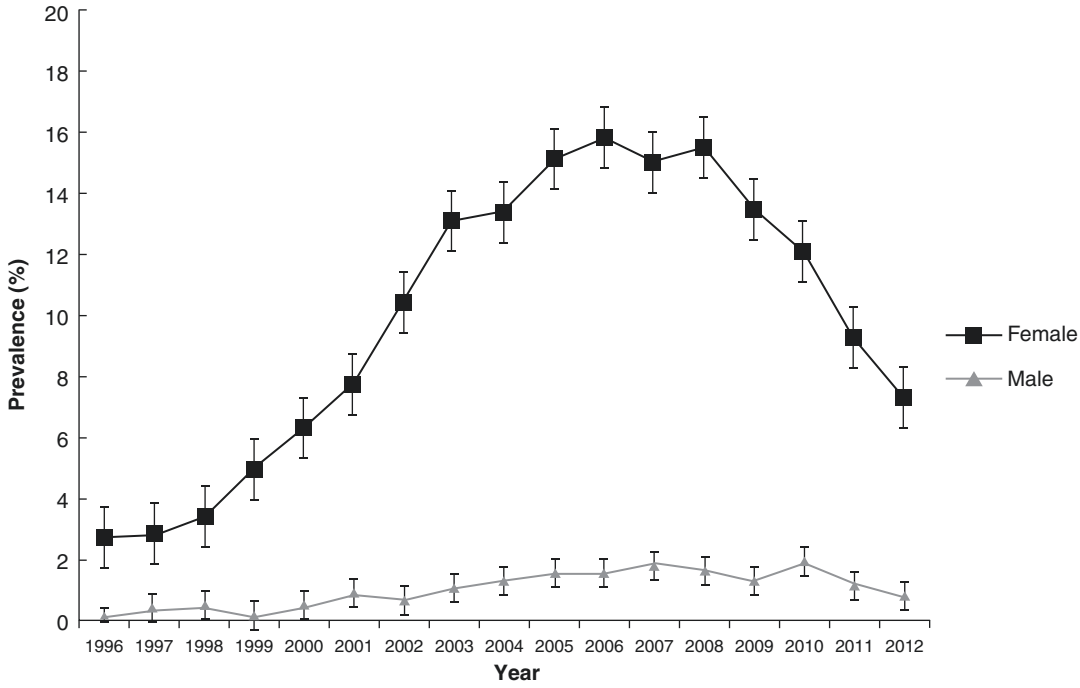

Fig. 15.4 Crisis in osteoporosis treatment: prevalence of bisphosphonate use among females and males aged 55 years and older from 1996 to 2012. Data source: Medical Expenditure Panel Survey (MEPS). (Jha et al. [37]. To get permission: the author publishing with an STM Signatory Publisher. How can we proceed?)

common public awareness about devastating side effects as atypical femur fractures and osteonecrosis of the jaw is probably the most important. Suboptimal communication by physicians that are not capable of achieving a large fracture reduction by bisphosphonates (30–70% vertebral fracture reduction) versus the very small risk of severe side effects, around 1 in 100,000 bisphosphonate users, may exacerbate this issue. It is important to realize that effective drugs reduce fracture rates, but do not fully prevent the occurrence of fractures. Other explanations are lack of education to and engagement with osteoporosis by physicians, who may regard osteoporosis as a low medical priority, poor coordination of healthcare systems, inadequate access to diagnostic tools such as DXA and VFA, low adherence and compliance to anti-osteoporotic drugs, and the treatment gap [108]. Patient education can be stratified into phases subject to the patients' age.

How to Improve Peak Bone Mass?

In general, it can be stated that peak bone mass can be influenced not only negatively but also positively during young adult age. Therefore, it is important to realize that due to welfare, there is a change in lifestyle not only due to changes in nutrition and diet, but adolescents also seem to have a more sedentary lifestyle. Nowadays, youth has changed activities during leisure to a more sedentary relaxation with game consoles and other video games. This may be a difficult but necessary challenge as several studies showed that sedentary behavior in young children is associated with a lower bone density and ultimately lower peak bone mass [109, 110]. Recently, it could be demonstrated that more hours of watching television per day was associated with a lower BMD [111].

On the other hand, there is a chance to initiate intervention programs to increase peak bone

mass for young adults, as it was observed that physical activity was associated with increased BMD levels [44]. In this study, it was shown that moderate activity, e.g., walking, cycling or exercises, for at least 4 h a week, and participation in recreational sports for at least 4 h a week or participation in hard training or sports competitions several times each week may increase BMD up to 11% and 13%, respectively in girls and boys aged 15–19 years [112]. Moreover, a retrospective cross-sectional study in prepubertal girls that observed global physical activity and not only activities related to sports was associated with a greater peak bone mass [113]. Nevertheless, although physical exercise may have a positive effect on BMD and peak bone mass, there are remaining questions about the optimal intensity and duration of therapy. Promising results were shown in a recent study by Mitchell and colleagues, as this study observed an improvement of bone after physical activity in children genetically predisposed to lower bone density [114]. Another point is how to change behavior from a sedentary type to a lifestyle with more physical exercise in large groups of young adults. Therefore, there is an urgent need for not only limiting the negative modifiable factors (low calcium, low vitamin D, smoking, and alcohol) but also investing in positive modifiable factors (mainly exercise) to aid in achieving optimal peak bone mass values in many individuals.

Proactive Non-pharmacological Measures to Prevent Fractures

Non-pharmacological supplements (including adequate calcium intake and vitamin D levels and exercise) have an important role to play in maintaining a healthy lifestyle, which is crucial for patients at high risk of sustaining a fracture, particularly, on the other hand, a nonhealthy lifestyle may have negative impact on BMD, bone quality as well as risk of falling [115].

Calcium and vitamin D and exercise: there is ample evidence showing a positive effect of healthy lifestyle elements (calcium, vitamin D, exercise) on the bone. In addition, the balance, though not yet fully proven, between a positive effect of a healthy lifestyle on bone, in combination with the absence of side effects, is attractive. An adequate calcium balance is an important factor in bone strength. Obviously, an extremely low dietary calcium intake, particularly in patients with malabsorption, for example, after bariatric surgery, may induce a strong tendency to serum hypocalcemia and a subsequent elevated bone resorption. This can be counteracted by oral calcium supplementation. On the other hand, earlier data have suggested that calcium supplementation might be associated with increased cardiovascular risk [116]. However, several other studies have not confirmed such assumed relationship between high dietary calcium intake and cardiovascular events [117, 118], leading to a continuing debate about whether calcium supplementation may lead to an elevated myocardial infarction risk. This is even more critical, as a study which included rheumatoid arthritis patients revealed that the risk of a cardiovascular event was elevated after a fragility fracture with a hazard ratio of 1.8 (95% confidence interval: 0.85–1.63) [119]. Another point is that when calcium is prescribed for osteoporotic patients with a low dietary calcium intake, it is difficult to estimate the dietary calcium intake with a simple questionnaire [120], and it is also difficult to assess the percentage of the calcium that has been absorbed in the intestine and which part of that is finally taken up and laid in the bone.

Another important modifiable risk factor is Vitamin D. Lower serum 25-hydroxy(OH) vitamin D levels have been reported to exert a negative impact on bone mineralization, consequently, on bone strength, and may also lead to muscular weakness and an increased risk of falling [121, 122]. Furthermore, low levels of serum 25(OH) vitamin D have been reported in patients who sustained a hip fracture [121]. Other studies have shown an association between low vitamin D levels and an increased risk of all-cause mortality, which could reflect a causal effect but could also result from less exposure to sunshine in elderly individuals with severe underlying diseases and comorbidities [123, 124].

In a large meta-analysis, it was shown that vitamin D supplementation (800 IU/day), in patients who received calcium supplementation, is associated with a 20% reduction in non-vertebral fractures and also with a 20% reduction in falls [125, 126]. In a randomized controlled trial observing different dosages of vitamin D, in >95% of patients, a serum level of 50 nmol/l was found after 6 months of treatment. However, it is not clear to which patients vitamin D supplementation should be prescribed: to all osteoporotic patients or only to those with a vitamin D level deficiency or insufficiency? Strikingly, very high-peak dosages of vitamin D (annually 500,000 IU/year) seem to be associated with increased fall risk and fracture risk [127, 128], while a dosage of 2000 IU per day was associated with a higher fall risk than with a dosage of 800 IU per day [129].

Smoking is another important non-pharmacological factor that has a negative effect on bone strength, mediated by direct negative impact on osteoblasts, upregulation of receptor activator of nuclear factor-kB ligand (RANKL), alterations in calciotropic hormones and decreased intestinal calcium absorption [130]. In addition, heavy smokers are often physically inactive and have a low body weight, which are also important risk factors for fractures. Thus, there is much evidence that stopping smoking and starting with a healthier lifestyle are crucial in those individuals regarded as heavy smokers; unfortunately it is not easy to stop smoking, particularly for those who are addicted to nicotine.

With regard to alcohol, more than four alcoholic beverages per day show deleterious impact on bone tissue, particularly a negative effect on bone formation [120]. However, even more than two units of alcohol per day increases the risk of osteoporotic and hip fractures, not only because of the negative effect on bone but also because of a negative effect on neuromuscular coordination and fall risk [131].

Other dietary-modifiable factors that influence bone mass and future fracture risk include other nutritional factors like protein intake and fruit. Previous studies have shown an incremental increase in bone mass with protein intake in young adults, and, recently, different diets have been identified to decrease fracture risk by improving bone strength [132]. Moreover, better milk intake improves bone mineral acquisition in adolescent girls [133]. On the other hand, ketogenic diets may cause a steady rate of bone loss, as measured in the spine, presumed to be because ketones are acidic; and so, keto diets can put people in what's called a "chronic acidotic state." These observations may implicate clinical relevance, although the main question is how much intake of proteins, fruit, or dairy is necessary in general; and the next question is whether these amounts can be applied to the individual patient in standard clinical practice.

Physical exercise, especially weight-bearing activity, has been reported to have beneficial effects on the skeleton in both adolescents [134–136] and the elderly. Many studies have shown that weight-bearing exercise can increase bone mineral density (BMD), particularly at a young age. Many previous studies have demonstrated an osteogenic effect of high impact and weight-bearing exercise on BMD using DXA [137–139]. In humans, the main stresses applied at the level of the calcaneus are ground reaction forces (GRF) as the heel strikes during locomotion [140]. Based on the GRF, swimming (GRF < 1 × body weight), dancing (GRF between 1 and 4 × body weight), and soccer (GRF > 4 × body weight) can be classified as low, moderate, and high impact exercise, respectively [141–143]. The relationship between loading magnitude and bone can be explained by the bone mechanostat theory proposed by Frost [144], who stated that exercise has a combined effect on bone modeling and remodeling, in that bone mass is increased by modeling and the added bone is retained by remodelling. Mechanical loading is also beneficial to bone structure. If a load is imposed, the bone will accommodate and undergo an alteration in mass, external geometry, and internal microarchitecture [108, 145].

Multifaceted Osteoporosis Group Education

In today's healthcare system, patients are expected to play an active role and take responsibility for their own health [146, 147]. In light of this development, disease-specific group education (GE) has become an integral and continuing part of healthcare provision [148] and a recommended way to encourage patients to become active participants in their own care [149–151]. Active participation includes making decisions about medical treatment and learning how to make lifestyle changes. The constant need to make health decisions is evident for patients with the chronic disease such as osteoporosis [152]. These patients face numerous self-care decisions, for example, whether to take medicine and to start doing weight-bearing exercises. Usually patients with osteoporosis consult their physician or general practitioner to discuss and evaluate the treatment within the first year after starting treatment. Afterward, treatment is evaluated every 2–3 years; hence, making decisions on how to manage osteoporosis in daily life relies heavily on the patient.

In the encounter between patients and physicians, decision-making is described as an iterative process including three steps: (1) information exchange, (2) deliberation about options, and (3) deciding on treatment to implement [153–155]. Research on patients with osteoporosis and decision support has shown that decision aids increase patients' knowledge of options for managing osteoporosis and help them clarify their own preferences [156, 157]. A systematic review found that tools, especially those including reminders and education support, may reduce fracture risk by increased use of osteoporosis medicine leading to increase in bone mineral density (BMD) [158]. A study of patients with osteoporosis fractures and their decisions about taking prescribed osteoporosis medication revealed that regardless of whether the decision was easy or difficult to make, patients stated that the decision was not permanent as a number of circumstances could cause them to change it again [152]. Another study explored decision-making in the context of multifaceted group education for patients with osteoporosis. During group education, patients changed their understanding of lifestyle conducive to bone health, which had an impact on their decision-making. Patients sought clear recommendations on how to manage a life with osteoporosis and were offered information regarding a variety of ways to follow the recommendations. Teachers supported the patients by providing medical information and listening to patients' experiences. Group education led to many healthy decisions on the part of the patients and to advice and directions on how the patients could implement decisions in the future to ensure bone health [159].

In conclusion, osteoporosis is a silent disease with increasing prevalence due to the global aging population. Decreased bone strength and bone quality is the hallmark of osteoporosis which leads to an increased risk of fragility fractures in elderly. This must be considered as a major health concern, as it has previously been established that fragility fracture has been associated with decreased quality of life due to increased disability and more frequent hospital admission, and, most importantly, osteoporotic fractures have been related to an augmented mortality risk. Although multiple national and international osteoporosis governing bodies have developed and updated several guidelines to aid clinical practice, there remain multiple unmet needs in the field of osteoporosis and fracture care. Tackling such challenges would definitely reflect on the patients' management and fracture prevention.

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Osteoporosis Update for Primary Care Physicians

16

Yasser El Miedany

Introduction

Osteoporosis is a skeletal disorder in which bone density and quality are reduced. Osteoporotic patients experience loss of bone mass, deterioration of bone tissue, and a decline in bone quality, which leads to increased bone fragility and a higher risk of fractures. There are approximately 9 million osteoporotic or fragility (low-trauma) fractures worldwide per year [1]. In developed nations, around one in three women and one in five men aged 50 years or more will suffer a fragility fracture during their remaining lifetime, most commonly at sites such as the hip, distal forearm, vertebrae, and humerus. For the individual, a hip fracture can be devastating with loss of independence, and less than one-third of patients make a full recovery and mortality of approximately 20% at 1-year postfracture [2]. Falls and subsequent osteoporotic fractures lead to significant morbidity and to mortality that ranges between 21% and 30% within the first year of the fracture depending on the site [3, 4].

Advances in osteoporosis management over the last two decades have included also fracture risk assessment tools, such as FRAX® and QFracture as well as the development of bone-strengthening treatments, improving the ability to identify people at risk and set up targeted treatment protocols for those most likely to fracture. While primary fracture prevention describes the prevention of occurrence of low-trauma fractures at the first instance, secondary fracture prevention describes the prevention the occurrence of a second fracture following the first one which was passed untreated. These elements provide the potential for a community-based screening program to reduce fracture rates. However, it was reported that in several occasions, small percentage of the patients who sustain low-trauma fracture receive osteoporosis therapy. For example, in Sweden, which has one of the highest incidences of such fractures in the world, only about 14% of patients with a diagnosed fragility fracture are treated with bone-specific drugs in the 12 months after their fracture [5, 6]. International guidelines identified primary healthcare (PHC) [general practitioners] as the main authority responsible for osteoporotic patients and for following up fragility fractures in this cohort of people [7, 8]. Deficiencies in transferring information about fractures from hospitals to primary healthcare contribute also to undertreatment with bone-specific drugs and, thus, to insufficient secondary prevention.

This chapter will start by discussing the primary care perception about osteoporosis, followed by presenting the gaps in care in the primary care setting and how improving osteoporosis service in the primary care and fracture liai-

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son service can help breaking barriers not bones. The chapter will present the new concept of the bone health team and the role of the osteoporosis nurse. The chapter will conclude with presenting an algorithm of management of osteoporosis in the primary care.

Primary Care Perception About Osteoporosis

While research on osteoporosis has proliferated, the field has been dominated by quantitative research such as secondary care prevention strategies [9–11], and patient decision aids quantifying care gaps [12, 13] and identifying at-risk groups [14]. Insights into individuals' experiences, particularly among the primary care professionals, their motivations, behaviors, and perceptions are less common in the literature. In fact, studying healthcare professionals' attitudes toward osteoporosis management might help explain poor management of the condition [15–18].

In a study that compared primary healthcare physicians and patients' perspectives about adherence to osteoporosis therapy, the researchers reported that physicians were worried mainly about structural barriers to care, costs, adherence to medication, as well as side effects [19]. The physicians thought patients lacked knowledge about osteoporosis and were concerned about the reliability of information patients obtained on their own. On the other hand, the patients thought both they and their primary healthcare physicians lacked sufficient knowledge [19].

When it comes to DXA scanning, which is considered the "best available predictor of future fracture risk" [20], little is known about the primary healthcare professionals' use of DXA scans. A small study [16] was carried out aiming at exploring the general practitioners' beliefs about diagnosis and management of osteoporosis, including the role that DXA scanning can play. The general practitioners included in that study were working in an area supplied by a single large hospital, where DXA scanning is available on an open access basis (with a current waiting time of 2 weeks). As far as the primary healthcare physicians' perception of the importance of osteoporosis, the general practitioners discussed osteoporosis in terms of its being a pathology, using phrases such as "thinning of the bones" and "loss of bone mass which leads to structural weakness of the bones. They all expressed the opinion that it was an important problem in terms of public health. Regarding the identification of the patients at high risk of osteoporosis, the general practitioners included in the study were able to identify some important risk factors including menopause/postmenopause, smoking, strong family history of osteoporosis, anorexia, being very thin, lack of exercise, chronic immobility, chronic steroid use, poor diet, and metabolic disease. However, the general practitioners noted that they would use these factors in order to evaluate an individual's risk. However, this was not seen as an exact science or as equivalent to diagnosis by scan, with 60% of the general practitioners considering that the only accurate way to evaluate risk was through a DEXA scan. However, when it came to referring patients for DXA scanning, primary healthcare professionals reported that it is difficult to decide who and when to scan despite guidelines for primary care. Although the "guideline route" indicates that an assessment is made of who is at risk, who should be scanned, and when as well as that the DXA result is used to decide who to treat, however, the pathway taken by primary healthcare professionals did not follow this model. Alternative routes were identified. In this study, general practitioners noted that if treatment was straightforward based on a number of strong risk factors, then confirmation through a DEXA scan was considered unnecessary. Available evidence supports this stance. Potential treatment length influences consideration of a scan, e.g., for a younger woman with probable early menopause who is likely to be on long-term treatment. Furthermore, the DEXA scan was seen as useful in providing additional information to help in the joint decision-making process, in "persuading" patients of the need for specific treatment, or in convincing patients that they had a problem. Patient's pressure was another factor that affected

the general practitioner's decision to request DXA scan. In fact, this was also a factor in the decision-making process, such that, if a patient requested a scan, the general practitioner would reassure them and then recommend a scan.

Few qualitative studies have investigated how healthcare professionals' attitudes influence osteoporosis management in primary care [15–17], but a group of Australian researchers found that primary care physicians ranked osteoporosis as less important than other conditions, such as diabetes, osteoarthritis, cardiovascular disease, and hypertension [17]. They sometimes thought the guidelines were not clear (e.g., about treatment duration) and worried that the cost of medication would be problematic for patients. However, they were confident that the medications were effective. In another study, the district nurses often felt frustrated with the management they could provide for patients with osteoporosis [15].

Gaps in Care in the Primary Care Setting

Osteoporosis is a preventable disease that physicians can diagnose and manage particularly in the early stages of low bone mass and prior to the occurrence of any fractures. Therefore, recognition of individuals at risk of osteoporosis is imperative for reducing morbidity and mortality associated with osteoporosis-related fractures. Yet osteoporosis is vastly underdiagnosed and undertreated worldwide contrary to recommendations for universal screening and treatment guidelines [20–22]. A recent study of Medicare recipients who experienced a hip fracture found that just 19% of them had been receiving a bone-active osteoporosis treatment before the fracture occurred. That number reveals an alarming trend of underdiagnosis of osteoporosis. But the figures reported from another study carried out in 2016 and published in JAMA Internal Medicine [23] were alarming, as the study revealed that after the occurrence of a fracture, the percentage of women receiving treatment barely changed, rising to just 21%.

This trend of underdiagnosis and treatment of osteoporosis has occurred in spite of the fact that effective therapy exists to reduce future fractures. This represents a gap in treatment and diagnosis of osteoporosis which could lead to an epidemic of new fractures. This crisis in healthcare needs to be addressed particularly osteoporosis is a very preventable disease. The National Bone Health Alliance and American Academy of Family Physicians reviewed the challenge of bridging the osteoporosis screening, diagnosis, and treatment gaps in primary care [24]. When it comes to bone health, several gaps in patients' care have been identified (Fig. 16.1), these include the following:

Gap 1: Failure to Implement and Follow Osteoporosis Screening Guidelines

Over the past years, evidence has been gathered denoting that physicians who should be responsible for osteoporosis screening may not be following recommended diagnostic guidelines and may be basing treatment decisions on incorrect postulations. Based on analysis of medical claims data collected in the USA from a large, nationwide cohort between 2008 and 2014, screening rates among privately insured women ages 50+ were persistently low. Only 26.5% women in the age group 65–79 and 12.8% women 80 years and older underwent bone mass measurement. Even lower utilization rates were seen among non-Hispanic black women and women of low socioeconomic status [25]. Another analysis of 5 years record of electronic health and radiological reports at a regional healthcare system revealed two-thirds of women receiving new medication prescriptions for osteoporosis therapy did not need the treatment. The diagnosis of osteoporosis was based on dual-energy X-ray absorptiometry (DXA) abnormalities of lateral lumbar spine bone mineral density, which is not a diagnostic site according to the International Society of Clinical Densitometry guidelines. In fact, one-half of the women being treated may not have qualified for screening at all, because they were

Fig. 16.1 Gaps in osteoporosis management in the primary care

of younger age and had no risk factors for osteoporosis [26]. Another study found that family physicians order bone densitometry and try to manage osteoporosis appropriately but lack a rationale for testing [27]. Surveys on physicians' learning needs indicate the majority (66.8–83.2%) want to be informed about criteria for ordering, the interpretation of densitometry

reports and T-scores, as well as the frequency of testing [28, 29].

The best approach to tackle such gap is to provide the primary healthcare physicians with the needed information regarding who and when to test, guideline-based diagnostic criteria and indications for testing, and information on how to interpret tests.

Gap 2: Failure to Address the Imminent Fracture Risk in the Primary Care Setting

Early osteoporosis therapy intervention after the occurrence of a first low-trauma fracture, especially in those with low bone density, can reduce the risk of a subsequent fracture(s) and associated premature mortality. However, disturbing data show that the percentage of patients receiving a treatment for osteoporosis, even after sustaining a hip fracture, has declined in the USA from 41% in 2001 to 21% in 2011 [30]. These numbers demonstrate a low participation of physicians in their patients' secondary fracture prevention.

One reason for this decline is the patients' and physicians' concern regarding potential drug toxicities of bisphosphonates and other anti-osteoporosis medications. However, these adverse events are rare, and the benefits for patients at risk for subsequent fractures are high [31]. Nonetheless, physicians unfamiliar with the safety profiles of osteoporosis medications are reluctant to prescribe them to fractured patients. In one study, nearly all family physicians surveyed indicated they would be more likely to treat elderly fracture patients with medication if they had a safe medication shown to reduce patients' risk of recurrent fracture [13] despite the high benefit-to-risk ratio of available interventions [32]. In addition, surveys demonstrate physicians are confused about available medications for osteoporosis, particularly when to start treatment, adequate dosing, how to decide which drug to prescribe, and how to manage patients who are at moderate-risk for fracture [27, 29].

The best approach to tackle such gap is to provide the primary care physicians with the needed information regarding the range of anti-osteoporotic agents available for treatment and how to select the appropriate one for each patient, drug safety profiles, dosing instructions, timing of initiation of medication, and how to treat patients at moderate-risk for fracture.

Gap 3: Insufficient Physician-Patient Communication/Poor Patient Education

Multiple studies demonstrated that women tend to underestimate their risk of becoming osteoporotic and are less concerned about the consequences of osteoporosis than other diseases. Among women who have multiple FRAX risk factors and a diagnosis of osteoporosis and take osteoporosis prescription medication, one-third did not believe they were at an increased risk for future fracture [32, 33]. Even when patients have had fragility fractures, more than half do not link their fractures with osteoporosis even when told they already do have the disease; nor do they appear to understand they are at increased risk for future fracture [34].

Patient education on low bone mass and osteoporosis is imperative for long-term management of osteoporosis and fracture prevention. It is crucial for physicians to communicate to patients that a diagnosis of osteoporosis, increasing age, or a fragility fracture increases the risk of future fracture. However, surveys and focus groups indicate primary care physicians feel there are barriers to communicating with elderly patients about the complexity of osteoporosis risk and fracture prevention, which include time constraints, the complexity of their other health problems, and their reluctance to add new medications to long lists of prescribed therapies [27, 29].

The best approach to tackle such gap is to provide the primary healthcare physicians with the needed training to enable them to provide clear patient education that can help patients understand their risk, empower them to actively participate in shared decision-making, and support self-care and medication adherence and persistence [35].

Gap 4: Poor Monitoring After Prescribing Osteoporosis Therapy

Several classes of effective drugs are available to treat osteoporosis. To be effective, these drugs must be taken consistently and on long-term basis. Analysis of prescribing information has shown that the relative risk of fracture is 26% lower among adherent versus nonadherent patients and 21% lower in persistent versus non-persistent patients [36]. As with other medications for chronic illnesses, adherence and persistence for anti-osteoporotic drugs are suboptimal. Over 50% of patients who are prescribed osteoporosis medications are either poorly adherent or poorly persistent with treatment within 12 months [37]. The risk of side effects and discontinuation is higher in the early months of therapy following the initiation of medication.

Confounding this problem is evidence that physicians routinely overestimate patient adherence to osteoporosis medication therapies and tend to have a poor understanding of patients' concerns leading to nonadherence. While physicians believe the experience of side effects and affordability are top reasons for nonadherence [38, 39], studies demonstrate patients' reasons for nonadherence include fear of side effects, lack of perceived benefits of medication, complex dosing requirements, and insufficient awareness of disease-related consequences [39]. Systematic reviews of interventions to improve adherence and persistence with osteoporosis medication [25, 40] have identified clear trends regarding the interaction between the study subjects and the healthcare provider, including:

- Early identification of patient with low compliance and persistence
- Definition of a shared management strategy with the objective of improving patients' adherence
- Application of standard strategies to all patients to avoid risks of interruption or suspension of the therapy

However, studies indicate that prescribing physicians are not seeing their patients within the time frame considered most effective to prevent nonadherence during which they could address side effects, clarify instructions regarding dosing, and educate patients on the benefits of osteoporosis medications [39].

The best approach to tackle such gap is to shorten the time between initial prescription of therapy and follow-up, and improving physician awareness of medication nonadherence and poor persistence to anti-osteoporotic medications may facilitate physician-patient dialogue, with the aim of reducing the risk of fracture.

Gap 5: Pitfalls in the Healthcare System

The healthcare system also adds to low rates of osteoporosis care. The lack of significant incentives for osteoporosis preventive care, limited access, financing options for allied health professionals to perform patient counseling and education, and a "handoffs" attitude among physicians who manage acute fractures all result in a challenging healthcare environment which struggles to achieve optimal bone health.

The best approach to tackle such gap is to provide the primary healthcare physicians with comprehensive computerized primary care system which has the potential to identify fragility fractures, cases of osteoporosis, and its risk factors and provide incentives such as a "pay-for-performance" (P4P) system to improve chronic disease management or "primary care quality and outcomes framework (QOF)" which rewards general practices for the provision of "quality care" and helps to fund further improvements in the delivery of clinical care.

Table 16.1 summarizes the gaps in osteoporosis management in the primary care setting and best approaches to handle them

Table 16.1 Gaps in osteoporosis service in the primary care, approaches to tackling, and expected outcomes

Gap	Approach	Expected outcomes
Failure to implement and follow guidelines for screening for osteoporosis in standard practice	1. Recognize guideline-based recommendations for osteoporosis screening and bone mineral density testing 2.Fracture liaison service	Outcome 1: providers will recognize when, who, and how to assess for fracture risk and osteoporosis Outcome 2: providers will be able to interpret assessment results to develop a patient care plan
Failure to identify and treat patients who sustain a fragility fracture to reduce the subsequent fracture risk	Identify the risks and benefits of pharmacological agents for patients with osteoporosis	Recognize appropriate individualized treatment interventions for osteoporotic patients, based on evidence-based guidelines and drug safety profiles
Poor patient education and insufficient physician-patient communication regarding risks of osteoporosis and fracture	1. Provide patient education and communication 2. Patient empowerment 3. Develop and implement shared decision-making tools	Provide patient education on disease awareness and risks, and identify resources for further education, including non-pharmacological interventions
Poor monitoring and follow-up after prescribing osteoporosis medications	Develop and implement strategies to increase patients' adherence to their care plan	1. shorten the time between initial prescription of therapy and follow-up 2. Recognize reasons/causes of the patient's nonadherence to their care plan
Pitfalls in the healthcare system	Comprehensive computerized primary care system	Identify fragility fractures, cases of osteoporosis, and its risk factors

Improving Osteoporosis Service in the Primary Care: Breaking Barriers Not Bones

One of the main challenges in osteoporosis management is that in several occasions it may not be viewed as a high priority during the in-hospital care period, leaving this to "outpatient investigation and management by primary care physicians" or to a "consultant service." In fact, there seems to be a general lack of awareness and ownership of the problem [41].

A new European survey [42] revealed that bone specialists believe osteoporosis and fragility fractures are neglected and under prioritized by their healthcare systems, and action needs to be taken. The survey led by UCB asked 401 bone specialists from 11 European countries about their experience of osteoporosis and fragility fracture management. Of those surveyed, 66% agreed that osteoporosis is a neglected condition and only 10% of specialists surveyed agreed that osteoporosis and fragility fractures are currently given a high priority by their local health authority. When asked, the majority (90%) agreed that the condition should be a public health priority, and 91% agreed that effective management can improve outcomes and reduce costs. At present, in women over 45 years of age, osteoporosis accounts for more days spent in hospital than many other diseases, including diabetes and breast cancer.

The impact of osteoporosis is compounded by the economic burden incurred due to osteoporotic fractures which has been rated as high and expected to escalate as the population ages. Overall, the medical cost of osteoporosis and related fractures in the USA is estimated to be $20 billion per year. The annual cost in the USA of caring for osteoporotic-related fractures alone parallels or exceeds the annual cost for myocardial infarction, breast cancer, and/or cerebrovascular accidents [43]. Direct costs are predicted to escalate to $25 billion by 2025 and $50 billion by 2050 due to the increase in incidence of osteoporotic fractures [44]. Similarly, in Europe, in 2010,

the cost of fragility fractures in the European Union was €37 billion [45] and based on demographic changes is predicted to double by 2050 [46]. In the UK, it runs a similar scenario, with around 536,000 people suffer fragility fractures each year, including 79,000 hip fractures, and a cost in 2010 estimated at £3.5 billion, expected to rise to £5.5 billion per year by 2025 [47].

Moving forward, osteoporosis care must be guided by medical necessity, ensuring that all subjects prone to develop osteoporosis should have access to adequate care and screened for fracture risk. Furthermore, the gap between appropriate access to BMD testing and medications should be addressed in order to provide appropriate care for individuals at high risk of developing low-trauma fractures.

Models of change that are applicable on a large scale are always preferred to limited ones, which can be applied at the local level. In an effort to develop more generalizable knowledge about what works at improving care, a new area of translational research called Dissemination and Implementation Science has been developed. Dissemination and Implementation Science (DIS) is a growing research field that seeks to inform how evidence-based interventions can be successfully adopted, implemented, and maintained in healthcare delivery and community settings [48]. Research in primary care has highlighted many new developments in the past decade including training programs, scope of care, care teams, treatments, and payment models [49, 50]. These changes have resulted in advances, opportunities, and challenges. Some of the most recent and ongoing developments in primary care include a focus on patient-centered care, the concept and implementation of the patient-centered medical home [51, 52], the use of electronic medical records and meaningful use standards [53, 54], payment redesign such as the Medicare Access and CHIP Reauthorization Act of 2015 [55] and Merit-Based Incentive Payment System [56], Maintenance of Certification requirements [57, 58], as well as practice transformation strategies to implement these initiatives. Matters may get further complicated as new developments in the patient population may occur including aging and the associated increasing burden of chronic illness, health equity and social determinants of health issues, and the coming era of precision medicine [59–61]. Primary care practitioners and researchers are in the forefront of making these changes happen.

Improving quality of care can be carried out through systems redesign, e.g., systems approaches that seek to improve the efficiency of osteoporosis healthcare delivery. A common application of this approach is the development of electronic reminders in health information systems that flag selected patients or selected health provider actions and recommend, or even mandate, particular actions. This will help to take some of the onus of osteoporosis screening out of the hands of busy generalists and avoid "reminder overload." A pilot-test assessed the "low-cost, low-tech" approach which enables the patients to directly schedule their own bone density studies using a designated call line. This approach, similar to another approach offering access to mammography, has yielded a greater than 13% increase in the rate of patients receiving dual-energy X-ray absorptiometry (DXA) scans [62]. An analogous tactic that implement service evaluation tool to interrogate the IT system can be used in the primary care surgeries. All patients over the age of 65 can be extracted from the database and FRAX analysis to be undertaken. Those with medium to high FRAX score (i.e., 10-year risk of >20% for major osteoporotic fracture and/or >3% for hip fracture) are captured and offered further evaluation and bone-sparing therapy as necessary [63].

Another approach that is of interest internationally is the implementation of fracture liaison service. This can be carried out through implementation of fracture liaison service [64] and the employment of a community-based fracture liaison nurse [65]. The intent of this popular approach is to assure that postfracture hospitalized patients are given the tools and resources they need to address their bone health at a particularly teachable moment. With successful widespread adoption of this approach, those patients who are most at risk for future fractures,

namely, those who have already had a fracture, will be better managed.

Bringing all together, provider, patient, and systems interventions is based on providing bone healthcare including home care as an important setting to interact with postfracture patients as the key window of opportunity [66] for osteoporosis intervention. Home healthcare provides services such as physical therapy, medication management, or other nursing interventions. Often this is provided post-hospitalization for a fracture, and home healthcare thus may reflect the best "teachable moment" for many fracture patients.

In general, the targets for such interventions include the triad of the healthcare provider, the patient, and the healthcare system. However, research implementation teaches that "nothing works all the time" and "many things together may work better than a single thing alone." Thus, multiple approaches are often used concomitantly in these strategies. Also important is hitting the target at a "teachable" moment, noted above, such as in the period immediately following fracture. This tactic may be considerably more powerful than educating otherwise healthy adult patients about the need for BMD testing. Successful programs have included postfracture management using posted/electronic material to providers, patient reminder calls, and educational material.

The Bone Health Team

Despite the critical need for a comprehensive osteoporosis early identification and management service, few models for the primary prevention of fragility fractures have been described, and no team-based primary interventions were reported [67, 68]. In a trial to tackle such challenge, a "bone health team" has been suggested as a link between secondary and primary care providers (Table 16.2). The team consists of osteoporosis specialist, a pharmacist, and a nurse practitioner dedicated to the screening and management of patients at risk for osteoporotic fractures and provided the service in community-based outpatient clinics. The bone health team manages the screening, diagnosis, treatment, and ongoing monitoring of osteoporosis, on behalf of the primary care, through a collaborative care agreement, using virtual and telephone clinics [69].

Table 16.2 Suggested members of the bone health team

Bone health team
Clinical osteoporosis specialist (physician)
Ortho-geriatrician
Radiologist
Orthopedic surgeon
Primary care physician with special interest in osteoporosis
Fracture liaison service nurse
Physiotherapist/occupational therapist
Clinical pharmacists—trust and community
Representative from ambulance service
Patient representative, perhaps from voluntary service such as the Royal Osteoporosis Society or National Osteoporosis Foundation
Primary care trust/trust management

Bone health team interventions include the following: identification, based on risk factors assessment in adults >65 years old, and screening, using DXA scanning and lab assessment arranging for bone profile blood check. If abnormalities were identified during this evaluation, the corresponding potential underlying conditions were evaluated further; treatment was advised by the bone health team following the national clinical practice guidelines. In addition to pharmacotherapy, the bone health team should evaluate the patient's dietary and supplemental intake of calcium and vitamin D, as well as fall history, fall risk, and weight-bearing activity history. Pertinent social history, including alcohol and tobacco use, should be also discussed. Based on patient risk factors, appropriate recommendations are made including supplementation of calcium and/or vitamin D, if, currently insufficient, referrals to physical therapy for core muscle strengthening and balance, referral to occupational therapy for a home safety evaluation, referral to smoking cessation, and encouraging weight-bearing activities.

The outcomes of such newly developed service were assessed in a study published recently [69]. Data from the cohort of primary care patients enrolled in the bone health team service

showed significantly higher rates of osteoporosis screening with DXA and therapeutic intervention than current standard primary care practice, suggesting this dedicated approach to osteoporosis screening and management may offer a viable method for the primary prevention of osteoporotic fractures.

The Role of the Osteoporosis Nurse Specialist

By the very nature and scope of the profession, nursing plays a significant role in the prevention, detection, as well as management of osteoporosis. The skills of critical thinking, effective communication, and interacting with other members of the interdisciplinary team enable nurses to understand the needs of the patients and the goals of osteoporosis management. However, in order for the nurses to be able to play these key roles, enhanced knowledge of osteoporosis within the curriculum of nursing programs and ongoing professional development opportunities are mandatory. Osteoporosis has to be given its prominent place and importance along with other key chronic illnesses, such as cardiovascular disease, diabetes, and others.

Osteoporosis nurses are the link that connects between the primary care, osteoporosis specialist, and the patients. Starting with the patients, nurses play an important role in the prevention of osteoporosis through the education of groups of individuals regarding bone health. In community settings and schools, depending upon the resources available, and the priorities of individual healthcare systems, nurses can play a key role in the education of children, youth, and parents regarding healthy lifestyles to promote bone health for the future. A renewed emphasis on physical activity and calcium intake is important, as youth become more sedentary and dietary preferences tend to exclude sufficient amounts of calcium need to achieve optimal bone health. In specialized roles, nurses have the opportunity to provide outreach education to various community and professional groups regarding bone health. These can include healthcare providers, employee health and wellness initiatives, community health forums, and seniors', women's and cancer survivor groups, to name a few.

Nurses play an integral role in facilitating the detection of osteoporosis, through their involvement in the assessment of patients at various points of contact within the healthcare system—primary care settings, emergency departments, fracture clinics, and the admission of individuals to various levels of healthcare (acute, chronic, long-term care, community home care). Incorporating simple questions into standard patient assessments or admission processes can facilitate the earlier detection of potential osteoporosis, by including, for example, a history of height loss or a fragility fracture, and other common risk factors for the development of osteoporosis.

Following the diagnosis of osteoporosis, nurses play a significant role in supporting individuals in the treatment and management of this condition through ongoing assessment, teaching, and counseling. Where resources exist, an interdisciplinary approach to providing care is optimal and may include a nurse, physical therapist (exercise), occupational therapist (fall and fracture prevention), dietitian (calcium and vitamin D intake), and pharmacist (medication), working with the physician. Where these other resources are not readily available, it is within the scope of practice for the nurse to initiate counseling and teaching regarding these issues and lifestyle factors and to coordinate and refer to other healthcare providers and community services, as available.

Nurses are instrumental in providing psychosocial support for individuals with osteoporosis. For many, this is yet another chronic condition that they are faced with, leading to anxiety regarding the diagnosis, treatment, and prognosis. Nursing assessment and support assists individuals in maintaining their commitment and compliance to lifestyle modifications and treatment over the course of their lives, and in the modification of approaches as other conditions emerge. Nurses play a role in enabling individuals to cope with chronic illness through the development of coping strategies and, as required, pain

management. With the bone health of individuals being monitored over a longer period of time, as compared with other chronic illnesses, nurses often provide ongoing remote telephone counseling and support, which poses its own unique set of opportunities and challenges [70].

The Role of the Fracture Liaison Service (FLS) Nurse

An essential component of the FLS is a nurse who would integrate and coordinate the bone healthcare for subjects who sustain a fragility fracture (low-trauma fracture). The role is not dissimilar to that of the diabetes, COPD, or heart failure nurse. Based in primary care, in addition to being involved with the person who has recently suffered a fracture (incident fracture), the nurse would need to establish a validated register of patients who have previously suffered a fragility fracture (prevalent fracture) (Fig. 16.2). Furthermore, a register of those at high risk but who, as yet, have not had a fracture (primary prevention), for example, those with a family history of hip fracture, those who have used oral steroids, or those who have rheumatoid arthritis needs to be compiled. This could be set up using the World Health Organization Fracture Risk Assessment Tool (FRAX™), available at www.shef.ac.uk/FRAX. Using clinical risk factors, the FRAX can be used to calculate the absolute risk of a patient experiencing a hip fracture or any osteoporotic fracture over the next 10 years. The FLS nurse could then refer susceptible people for a DXA scan; investigate for secondary causes of osteoporosis, if appropriate; and liaise with the secondary care/ osteoporosis specialist physician to provide a report and management plan for the primary care physician. The FLS nurse would also need to liaise with falls clinics and nursing homes [71].

As with any asymptomatic chronic condition, compliance in medicine taking is poor, side effects are increased, and the benefits of therapy are reduced if the medication is not taken in the correct way. The central role of primary care in promoting compliance has been recognized, and an FLS nurse is ideally placed to do this and offer lifestyle advice [72].

In addition to improving compliance in taking bone remodeling agents, an FLS, perhaps involving medicines usage reviews carried out by clinical pharmacists, would be ideally placed to ensure co-prescribing of calcium and vitamin D. For those patients unable to take oral treatments, a community-based intravenous administration service could be established to reduce

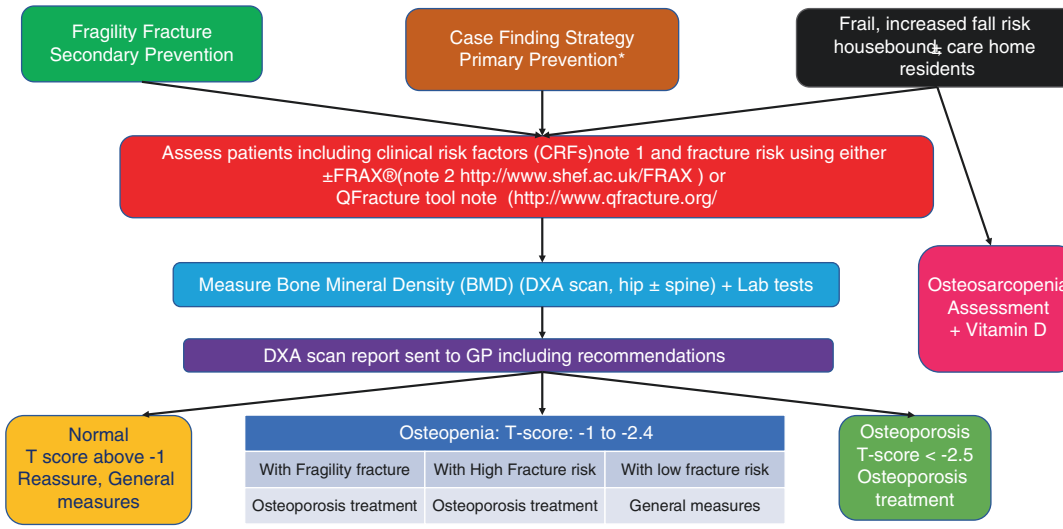

Fig. 16.2 Fracture liaison service structure and functions

costs and provide a more local service for patients. Benchmarks for quality of care need to be established against which the service can be audited.

Components of Screening Interventions

Rationale for Screening

Since individuals without prior fracture but at risk for incident fragility fracture are asymptomatic, screening should be able to identify those who are at greater risk of fracture and potential candidates for preventive intervention. Information from screening may be used, along with patient values and preferences, to inform decisions about treatment that might decrease future risk of fracture and related morbidity [73]. Thus, the aim of screening is not to detect the existence of osteoporosis but rather to reduce fracture-related burden of morbidity, mortality, and costs.

Screening to prevent fragility fractures involves a sequence of activities, not simply one test. The activities include a systematic offering of screening in a specified population of asymptomatic people with the intent to identify those at increased risk for fractures in order to provide preventive treatment and improve health outcomes.

Assessment of Fracture Risk

Fracture risk should only be assessed in certain populations. The risk of fragility fracture is commoner in women and is commoner in older patients. The risk of osteoporosis rises steeply after the menopause in women because of the loss of the protective effect of circulating estrogen.

Therefore, international guidelines suggested that the risk of fracture should be assessed in:

- All women over 65 years of age
- All men over 75 years of age

Fracture risk should also be assessed in women under 65 years of age and men under 75 years of age, with certain additional risk factors, these include:

- Previous fragility fracture
- Current use or frequent recent use of oral or systemic glucocorticoids
- History of falls
- Family history of hip fracture
- Other causes of secondary osteoporosis such as vitamin D deficiency (see below)
- Low body mass index (BMI) (less than 18.5 kg/m2)
- Smoking
- Alcohol intake of more than 14 units per week for women and more than 21 units per week for men

Causes of secondary osteoporosis include:

- Endocrine: hypogonadism (in either sex) including untreated premature menopause and treatment with aromatase inhibitors or androgen deprivation therapy, hyperthyroidism, hyperparathyroidism, hyperprolactinemia, Cushing's disease, and diabetes
- Gastrointestinal: coeliac disease, inflammatory bowel disease, chronic liver disease, chronic pancreatitis, and other causes of malabsorption
- Rheumatological: rheumatoid arthritis and other inflammatory arthropathies
- Hematological: multiple myeloma, hemoglobinopathies, and systemic mastocytosis
- Respiratory: cystic fibrosis and chronic obstructive pulmonary disease
- Metabolic: homocystinuria, chronic renal disease, and immobility (due, e.g., to neurological injury or disease)

There is no point assessing fracture risk in patients under 50 years of age unless they have major risk factors such as high dose steroid therapy.

It is also worth remembering that having osteoporosis alone is not the only reason why people sustain a fracture. There is also a risk of

falls from other comorbidities such as Parkinson's disease. Therefore, fall prevention is a large part of fragility fracture prevention, and most hospitals or community geriatric services will have a fall service that identifies patients at risk of falling and treats them with physiotherapy and exercise classes to improve their musculoskeletal fitness.

Within a consultation, assessment of fracture risk has been made much easier with the use of online tools or decision aids. There are two commonly used ones are:

- FRAX: https://www.sheffield.ac.uk/FRAX/
- QFracture: https://qfracture.org/

Most GP computer systems have these tools uploaded to the system so that they can be used quickly within a consultation. Both will provide a risk of osteoporotic fracture. In the UK, the FRAX system uses guidance from the National Osteoporosis Guidance Group (NOGG) to calculate whether the patient needs treatment or not, which is helpful. In the USA, the fracture risk is assessed based on the 10-year probability of fracture risk (>20% for major osteoporosis fracture and >3% for hip fracture probability). FRAX was developed by the World Health Organization (WHO) for assessing fracture risk in women and men taking into account several risk factors as listed above. Also, the femoral neck bone mineral density (BMD) can be used to calculate the risk if this is available, but risk can be assessed without BMD as well. FRAX was developed using data from Europe, Asia, and the USA and validated in several countries.

On the other hand, QFracture was designed using UK data, and the list of risk factors differs slightly from those in the FRAX tool and includes asthma, risk of falls, and other long-term conditions such as diabetes and the use of certain medications such as tricyclic antidepressants, so is more comprehensive. QFracture produces a 10-year risk of hip fracture and also other major osteoporotic fractures such as the wrist and spine. However, it does not give guidance on when to start treatment (i.e., the treatment threshold), whereas FRAX will give a treatment threshold or advise measurement of BMD in borderline cases to help make a decision about treatment. There is also a slight difference in the age ranges covered by each tool; FRAX can be used in the age range 40–90 years and QFracture from 30 to 84 years.

Thus, the primary healthcare physician or practice nurse can identify those subjects at high risk of osteoporosis and sustaining a fragility fracture. For patients at high risk of fracture as assessed by FRAX or QFracture or another risk tool, it is advisable to be referred for DXA scanning.

Treatment Thresholds and Decisions

Treatment thresholds vary considerably across countries and may take into account variation in population-specific risk of fracture and mortality [74], competing healthcare priorities, patient willingness to pay for fracture-related healthcare, resource availability (e.g., access to BMD assessment tools), and preexisting reimbursement criteria [75, 76]. The US National Osteoporosis Foundation [77] recommends initiating pharmacological treatment in individuals with osteoporosis or with low BMD (T-score between −1.0 and −2.5, osteopenia) and either a 10-year hip fracture probability ≥3% or a 10-year major osteoporosis-related fracture probability ≥20% (using FRAX). This decision was supported by a cost-effectiveness analysis based on assumptions from one-step BMD screening followed by treatment with a generic bisphosphonate (assumed relative fracture reduction of 35%), and a willingness-to-pay threshold of $60,000 per quality-adjusted life-year gained [78, 79].

Canadian guidelines [80], as well as those developed in several other countries (e.g., Austria [81], Greece [82], Hungary [83], Malaysia [84, 85], Mexico [86], the Philippines [87], Saudi Arabia [88], Poland [89], Slovakia [90], Slovenia [91], Spain [92–94], Taiwan [95], Thailand [96]), that are based on country-specific FRAX models, use a fixed 20% 10-year probability of major osteoporotic fracture as a treatment threshold [75]. In many (but not all) cases, the choice of the 20% intervention threshold is without a specific rationale but instead based on the threshold used in the USA. Some guidelines also use a fixed 3% 10-year hip fracture probability

as an alternative intervention threshold. Another less common approach is to use intervention thresholds that increase with age [75]. The threshold is based on the rationale that because individuals with a prior fracture can be considered for treatment without the need for further assessment, other individuals of the same age with a similar fracture risk but no prior fracture should also be eligible [97]. Recent strategies adopt a hybrid approach (i.e., incorporating both fixed and age-dependent intervention thresholds) [97–99]. For example, the National Osteoporosis Guideline Group for the UK recommends that the treatment threshold increase with age for individuals up to 70 years to align with the level of risk associated with a prior fracture (ranges from approximately 7 to 24% 10-year probability of fracture, equivalent to the risk probability of a woman of the same age with a prior fragility fracture). After age 70, a fixed threshold is used to account for the reduced sensitivity of the risk probability algorithm for those without a prior fracture, which becomes most apparent at advanced age [97].

Treatment decisions may best be based on patient preferences, including their competing priorities and assessment of the relative importance of benefits and harms, and shared decision-making between patients and their healthcare providers [100]. Although treatment efficacy appears to be an important variable when choosing between different treatments, a major factor impacting the effectiveness of any treatment, and therefore screening program, is medication adherence. A study in the USA showed that close to 30% of patients provided with a prescription for osteoporosis treatment do not fill their prescription [101]. Of those initiating treatment, only half are still taking their medication at 1 year [102]. Predominant factors affecting adherence include dosing frequency, side effects of medications, costs, and lack of knowledge about the implications of osteoporosis [93]. One study conducted in the USA showed that in 2009, half of women (mean age 69 years; 30–40% with osteoporosis or prior fracture; perceived risk for 10-year fracture about 40%) who were provided information regarding fracture risks and treatment risks and benefits reported that they would accept prescription osteoporosis treatment at the threshold currently recommended by national physician treatment guidelines; 18% of the women would not accept treatment even at 50% fracture risk levels [103]. Willingness to accept treatment increased at higher levels of fracture risk and was higher in those with greater acceptance of the risks of medications [103]. There is large variation between patients regarding their treatment preferences, which support a shared decision-making approach in place of recommended treatment thresholds based on fracture risk [100].

Osteoporosis Management Guidelines for the Primary Care

Until first fragility fracture, osteoporosis is a silent disease. Frailty, falls, independence, and previous fragility fracture, which increase patient demand for bone density screening, are more prevalent concerns for older patients. In order to provide comprehensive and practical guidance for the management of osteoporosis in primary care setting, treatment decisions should be based on patient preferences, including their competing priorities and assessment of the relative importance of benefits and harms, and shared decision-making between patients and their healthcare providers [91]. Although treatment efficacy appears to be an important variable when choosing between different treatments [91], a major factor impacting the effectiveness of any treatment, and therefore screening program, is medication adherence. An unsatisfactory response following treatment for secondary prevention of osteoporosis, i.e., after a fragility fracture, is defined as occurring when a woman has another fragility fracture despite adhering fully to treatment for 1 year, and there is evidence of a decline in BMD below her pre-treatment baseline.

Osteoporosis management to reduce fracture risk includes pharmacological and non-pharmacological strategies. It has been addressed by various organizations in the past decade, so there are different approaches; some areas may have local protocols defining which patients can access which treatments. Figure 16.3 shows Management algorithm of osteoporosis in postmenopausal women and men (over 50 years) in the primary care setting.

Note 1: Clinical Risk Factors / Indicators of Low Bone Mass Density (BMD)

These should be taken into account when assessing the patient.

- Parental history of hip fracture
- Alcohol intake of 4 units or more per day
  smoking
- Rheumatoid arthritis
- Low body mass index (defined as BMI <18)
- Medical conditions such as inflammatory arthritis, Crohn's disease
- Conditions that result in prolonged immobility
- Untreated premature menopause

Other clinical risk factors include therapy with breast cancer drugs, prostate cancer drugs, coeliac disease / malabsorption syndromes, inflammatory arthritis.

Note 2: Investigations:

FBC, ESR

- Bone and liver function tests (Ca, P, Alkphos, albumin, ALT/γGT)
  Serum vitamin D
- Serum creatinine
- Serum TSH
- Serum PTH
- serum paraproteins and urine Bence Jones protein
- Anti TTG (coeliac antibody)
- Additional test if indicated:
- Serum testosterone (morning sample), LH and SHBG
  Prolactin
- Lateral thoracic and lumbar spine X rays

Note 3: Compliance Issues / Intolerance / Poor Response Definitions

Compliance –Emphasise administration advice specific to bisphosphonates (see BNF). If patient not willing to follow the timing schedule, consider alternative treatment.

Intolerance –. If oesophageal irritation occurs, consider prescribing a proton pump inhibitor unless contra-indicated. Intolerance is defined as persistent upper GI disturbance that is sufficiently severe to warrant discontinuation of treatment, and that occurs even though the instructions for administration have been followed correctly

Poor response–on-going rapid decline in BMD.

Note 4

DXA Scans

Consider a repeat DXA post treatment. Exact frequency will vary depending on clinical risk factors (see below) then consider repeating every 2-3 years:

- ongoing steroid use –repeat DXA in 1 year
- oral bisphosphonate treatment –repeat after 2-3 years
- IV Zoledronic acid –repeat after 3 years

Note 5: Prescribing Points

- Clinicians should consult electronic BNF or Summary of Product Characteristics (SPC) for full prescribing details (e.g. licensed indications, contra-indications, use in elderly, renal, hepatic impairment, contraindications, counselling, adverse effects etc.)

- Compliance with oral bisphosphonates should be checked after the first month of therapy and rechecked periodically thereafter to ensure compliance.

- The choice of treatment should be made on an individual basis after discussion between the responsible clinician and the patient, or their carers, about the advantages and disadvantages of the treatment available. Where generic products available, start treatment with the least expensive formulation, taking into account administration costs, the dose needed and the cost per dose

Fig. 16.3 (**a**) Management algorithm of osteoporosis in postmenopausal women and men (over 50 years) in the primary care setting (stage 1)

STAGE 2: MEDICAL MANAGEMENT

1. Choice of therapy should be tailored to the individual and patient choice must be factored in.
2. Consult electronic BNF or Summary of Product Characteristics (SPC) for full prescribing details (e.g. licensed indications, contra-indications, use in elderly, renal, hepatic impairment, counselling, adverse effects etc.
3. Ensure dental examinations are carried out as appropriate before starting bisphosphonate/ denosumab therapy and give advice regarding dental hygiene etc. due to risk of Osteonecrosis of the Jaw (ONJ) associated with these medications. (see supporting notes for more information)
4. Clinicians should seek specialist opinion if patient sustains a fracture on therapy

Osteoporosis therapy: First Line Choices

Use an oral bisphosphonate: either alendronic acid 70mg WEEKLY tablets (generic) or risedronate sodium 35mg WEEKLY tablets(generic)

If intolerant to oral or concerns regarding adherence: Use either an IV bisphosphonate; IV zoledronic acid once a year or go for Denosumab (second line choice).

Additional Prescribing notes:

□ - Alendronic acid 70mg weekly dosage is not licensed for use in men but is commonly used.
- RENAL IMPAIRMENT (GFR < 35ml/min) – denosumab (Prolia®) s/c should be used FIRST LINE as po/IV bisphosphonates should be avoided.

Second Line Choice (when using oral therapy)

An alternative oral bisphosphonate can be used as a 2nd line option if contraindications, intolerance, poor compliance or poor response to the initial choice of oral bisphosphonate occurs.
If oral therapy is intolerant: Denosumab 60mg (PROLIA) 6-monthly injections SC

Third Line Choices (choice to be determined by Specialist) or in case of severe osteoporosis with multiple vertebral fractures:

Use: Parathyroid hormone e.g. abaloparatide or Teriparatide SC daily injections for 18-24 months

Additional Prescribing notes:

□ - All patients on treatment for osteoporosis must be prescribed Calcium 1-1.2g + colecalciferol 20mcg (800IU) daily UNLESS clinician is confident patient has adequate calcium intake and is vitamin D replete.
- General Measures
- □ Recommend good nutrition esp. with adequate calcium and vitamin D
- □ Recommend regular weight bearing exercise
- □ Maintain body weight
- Denosumab- Initial dose to be given by specialist team then GP to take over prescribing, monitoring responsibility and arrangement of administration (See separate guidance on denosumab for prescribing and monitoring requirements). NB: Denosumab prescribing, administration and monitoring responsibility should stay with secondary care if patient has renal impairment – no GP prescribing for this patient group

• IV zoledronic acid secondary care prescribing only
– Teriparatide and abaloparatide: secondary care prescribing only

Stage 3 Consider specialist referral for:
• Premenopausal women
• Male osteoporosis if considering a drug unlicensed for indication
• Male osteoporosis if less than 50 years old
• Intolerance or poor response to treatment with oral bisphosphonates
• If patient fractures on treatment

Fig. 16.3 (continued)

In conclusion, with osteoporosis being the most common bone disease in the world, resulting in more than 9 million fragility fractures each year around the globe, more need to be done to help educate and support general practitioners as well as patients on osteoporosis and the importance of timely referral and effective management.

The literature is emerging on the barriers to care. Several patient-related barriers of initiation of effective osteoporosis management have been identified: age, dementia, medical comorbidities, polypharmacy, lack of adherence to treatment, postoperative delirium, language barriers, inadequate support, lack of access to care by a primary care physician, and social economic status [104]. On the other hand, physician and system-related barriers have been acknowledged also, including lack of time, cost of resources for diagnosis, lack of knowledge and concern about osteoporosis treatment, as well as lack of clarity whose responsibility is it to initiate and promote osteoporosis care. Furthermore, inadequacy of communication between orthopedics and the primary healthcare professionals, insufficient means of transportation for patient follow-ups, and uncertainties in applying disease-specific guidelines to older patients with comorbidities contribute to these barriers [105]. One study reported that most orthopedic surgeons believe that while they are primarily responsible for the surgical care of their hip fracture patients, the management of osteoporosis is considered the responsibility of the primary care physician [106].

The importance of the role of primary care in following up patients who present in secondary care has been emphasized. Reducing osteoporotic fractures is a manageable goal for primary care. Using a primary care-based fracture liaison service can provide the mechanism to ensure that this happens.

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Part IV

New Treatment Concepts

Bone Modulation

17

Yasser El Miedany

Introduction

In spite of its inert appearance, the bone is an extremely dynamic tissue that is continuously being remodeled to adapt to changing mechanical demands. Such remodeling, which is carried out on a microscopic scale, consists in the removal of low-performing bone and its replacement by new, fully functional bone. The first symptom and considered the major characteristic of osteoporosis is a decrease in the bone mass and quality [1], rendering people prone to sustaining osteoporotic fracture (fragility fracture) caused by low-energy trauma [2]. Osteoporosis is more prevalent in older adults, with nearly 200 million patients are diagnosed to have osteoporosis annually, and an estimated nine million new osteoporotic fractures occur in a given year [3–5]. Surgery is the primary treatment approach for osteoporotic fractures; however, poor prognoses have been reported and attributed to a combination of biological and surgical factors [6]. Fractured osteoporotic bones are usually compromised and comminuted, which makes it hard to achieve an optimum reduction and stable fixation [5, 7]. Osteoporotic fractures mostly occur in elderly patients, who usually live with other comorbidities or unfavorable systemic conditions and most likely take medications that make them prone to complications [8]. Furthermore, the abnormal remodeling status of the bone with osteoporosis would deteriorate after getting bed bound while admitted to the hospital and very limited mobility after discharge, which poses a disadvantage with respect to fracture healing and bone callus strength; consequently, the refracture risk following surgery increases significantly [9]. Therefore, it is not surprising, bearing in mind the complexity of treatment, length of hospital admission, and poor prognosis, that the annual facility-related hospital cost of osteoporotic fractures is the highest (up to $5.1 billion), followed by that of myocardial infarction and stroke [10].

In the course of the past three decades, several drugs have been developed that can prevent fractures; however, although the effect of these treatments on vertebral fractures is impressive, the effect on non-vertebral fractures is less than satisfactory [11, 12]. Moreover, significant reduction of vertebral fractures occurs early in the course of therapy, typically within 6 months, whereas reduction of non-vertebral fractures and hip fractures specifically has not been observed before at least 1 year of therapy [13]. Furthermore, although the results of the clinical studies remain controversial, the majority have reported decrease in the callus area (20–40%) and bone mineral density (BMD) at the fracture sites in elderly osteoporotic patients. Studies have indicated that the delayed or nonunion of osteoporotic fractures

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is implicated in the scarce capacity of bone regeneration with aging [14, 15]. Additionally, the bone properties of such patients are quite different from those of normal individuals and are manifested in the decrease of bone mechanics and mechanosensation, as well as the abnormal bone metabolism caused by immune disorders [16].

Pharmacological interventions aim to decrease this risk and the associated clinical consequences by correcting the imbalance between bone resorption and bone formation that constitutes the pathophysiological basis of the disease. Most currently available agents inhibit bone resorption and formation to varying degrees and decrease the risk of fractures but cannot replace already lost bone, and they only modestly decrease the risk of non-vertebral fractures, the most frequent osteoporotic fractures. Parathyroid hormone (PTH) peptides, the only approved bone-forming agents, stimulate bone formation but also bone resorption and have not been shown to reduce the risk of hip fractures, the most devastating clinical consequence of osteoporosis. These unmet needs have led to efforts for the development of new therapeutics for osteoporosis based on improved knowledge of the local regulation of bone remodeling arising mainly from the study of rare bone diseases and genetically modified animal models [17]. This chapter will discuss the concept of dynamic skeleton, coupling of bone remodeling, as well as principles of bone modulation. It will then discuss implications from research studies and clinical practice on bone modulation, as well as new aspects of the bone-protecting effects of vitamin D. It will conclude by elaborating some nontraditional molecules with anti-osteoporotic potential.

The Dynamic Skeleton

The unique character of the bone tissue is attributed to its mix of elasticity and strength that permits deformation under a certain level of loading stress before failing [18]. The strength of bone depends mainly on both the density and distribution of the inorganic matrix mineralization [19]. Cortical bone, which consists of dense and well-organized lamellae, has higher strength but a lower capacity to withstand a load that exceeds the elastic deformation range compared to that of trabecular bone, which is composed of unparallel lamellar units with variable porosity (50–90%) [20]. The mechanical competence of trabecular bone is based largely on the BMD, while the stiffness of cortical bone is highly dependent on its porosity [5, 21]. In contrast to calcified matrix mineralization, the organic matrix (e.g., collagen and non-collagenous proteins) is considered the main factor responsible for controlling bone ductility and its capacity to withstand an impact without cracking [22]. A large proportion (90%) of the organic matrix is composed of type I collagen, which undergoes numerous posttranslational modifications [23]. Among them, enzymatic modifications positively affect the biomechanical stability of the bone, while nonenzymatic cross-linking is associated with a deterioration in these properties [22]. Non-collagenous proteins, including osteopontin (OPN) and osteocalcin (OCN), account for 10% of the organic matrix and limit crack energy through the control of hydroxyapatite size and orientation [24]. Whereas bone material properties provide only a static snapshot of bone quality, the abilities of self-regeneration and remodeling provide a dynamic profile of bone health [25].

As the bones are not completely developed at birth, they continue to be formed slowly out of cartilage or connective tissue, which are converted into the hard, lamellar components of the bone. Growth of the bones (modeling) comes to an end at puberty with ossification of the "growth plates." Modeling is of particular interest as the bone is much more capable of reacting to external loads during growth than at any other time. About 90% of adult bone is formed by the end of adolescence, and subsequent gains during adulthood are very small. Later, in the adult life, the adult skeleton is renewed by remodeling. Bone remodeling is a process where osteoclasts and osteoblasts work sequentially in the same bone remodeling unit. The basics of both bone model-

ing and remodeling will be reviewed in the coming section.

Bone Modeling

Bones, mostly, are composed of an outer shell of protective and supportive cortical (compact) bone, inside of which is a network of trabeculae (plates) that comprise the cancellous, or spongy, part of the bone. Bones are formed during embryonic development by the process of endochondral ossification, in which they are first modeled in a mold or anlagen of cartilage [26]. Blood vessels invade the cartilage, which is resorbed by chondroclasts, to form a medullary cavity. The precise origin of these chondroclasts is still uncertain, but they may be in the hematopoietic cell lineage. They are not required to be osteoclasts because endochondral ossification is normal or only slightly impaired in mammals that do not form osteoclasts. The cartilage is replaced by cortical bone formed by periosteal apposition and by trabecular bone, which is laid down within the medullary space at the epiphyseal growth plate. Hematopoietic, stromal, and adipocytic bone marrow cells fill the remaining space within the bones. A network of endothelium-lined sinusoids and feeding blood vessels nutritionally supports these cells and the trabecular bone. Up to approximately 30% of the volume of the space inside the bones of the axial skeleton is composed of trabecular bone, which contributes significantly to the supportive role of bones in the maintenance of normal posture. In contrast, trabecular bone is confined largely to the ends of most long bones, their diaphyseal cavities filled mostly with fatty marrow in adult humans [27].

Bone Remodeling

Following bone modeling (growth), the integrity of bones is maintained by the process of bone remodeling, in which worn-out sections of bones are removed by osteoclasts and replaced with new bone laid down by osteoblasts (Fig. 17.1). Osteoclasts are multinucleated cells derived from mononuclear precursors in the mononuclear-phagocyte lineage that fuse with one another by cytoplasmic, but not nuclear, fusion [29]. Their formation and activity are regulated predominantly by osteoblasts and stromal cells. The stromal cells are derived from precursors in the mesenchymal cell lineage that also gives rise to chondroblasts, adipocytes, fibroblasts, and muscle cells.

Osteoclasts remove packets (trenches) of the bone (approximately 60 μm deep) from the surfaces of bone trabeculae at remodeling sites, and osteoblasts fill in these defects by laying down and mineralizing the new bone in a process simi-

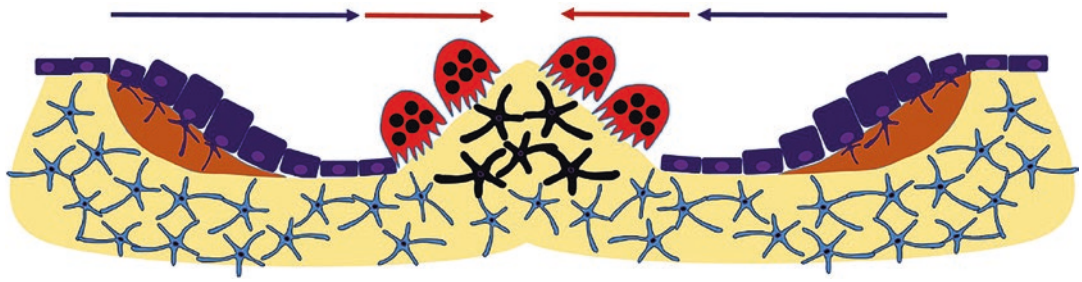

Fig. 17.1 A sketch of BMU operation after a group of osteocytes has undergone apoptosis near bone surface. Bone resorption (red arrows) and bone formation (blue arrows) are performed in this order. Bone remodeling is initiated when osteoclast precursor cells are recruited to the altered bone surface (black stellate cells) and fuse to form mature, bone-resorbing osteoclasts (red cells) that attach to the surface. Mature osteoclasts degrade the mineralized matrix (light yellow) and produce resorption pits also called resorption bays or Howship's lacunae. Once osteoclasts have degraded the target area, they undergo apoptosis, and osteoblasts (dark blue cells) situated behind them first secrete osteoid matrix (dark yellow) and subsequently differentiate into mature osteocytes (light blue stellate cells). (Quoted from: Arias et al. [28] under open access scheme)

lar to that used to replace sections of damaged roadways. Thus, osteoclasts typically do not resorb through the full thickness of trabecular elements during normal bone resorption and, consequently, leave a base of bone matrix to which osteoblasts are attracted and upon which they can lay down new bone matrix. The resorption phase lasts up to approximately 30–40 days; the formation phase takes about 120–170 days [30]. Recent studies have indicated that bone-lining cells in the osteoblast/stromal cell lineage clean up the resorbed surfaces and prepare them for new matrix deposition by removing projecting collagen fibers and laying down a thin layer of matrix to form the cement line that can be seen marking sites of resorption. The collagen fibers are degraded by matrix metalloproteinases secreted by these bone-lining cells, which do not appear to differentiate into the osteoblasts that subsequently fill in the resorption cavity [27].

Coupling of Bone Remodeling

Bone remodeling occurs in an orderly fashion by the basic multicellular units (BMUs) and temporary anatomical structures comprising a team of osteoclasts in the front and a team of osteoblasts in the back, supported by blood vessels, nerves, and connective tissue. Osteoclasts resorb the bone by removing bone mineral and degrading the organic matrix, while osteoblasts move to the resorbed area and lay down new bone matrix that subsequently mineralizes, a process known as coupling. The mechanisms regulating this coupling are not entirely clear, but it is thought that growth factors mobilized from the bone matrix during resorption might contribute to intercellular signaling and subsequent stimulation of bone formation (Fig. 17.2). Alternatively, or in addition, the osteoclasts produce factors that might contribute to generation and differentiation of osteoblast precursors [32, 33]. It is now generally accepted that osteocytes are the main regulators of bone remodeling due to their location in the bone allowing them to sense mechanical signals and to respond to chemical signals regulating bone and mineral metabolism by secreting factors that can modulate the number and function of osteoblasts and osteoclasts [34].

An increased number and life span of osteoclasts and a decrease in the formation and life span of osteoblasts induce an imbalance between bone resorption and bone formation, the cellular basis of osteoporosis. This imbalance, in favor of resorption, results in bone loss and deterioration of bone architecture. The decline in the ability of osteoblasts to refill the resorption cavity leads to reduction of the thickness of the bone packets and thinning of the trabeculae. In addition, the enhanced osteoclastic resorption per unit time that occurs at the menopause results in perforation and removal of trabeculae and loss of their connectivity [35]. Cortical bone becomes wider in diameter and thinner, due to the move of the endosteal surface outward at a greater pace than the bone placed in the periosteum but also more porotic due to enhanced intracortical remodeling [36].

Principles of Bone Modulation

Bone construction is achieved mainly by bone modeling, which lead to a change in both the external as well as the internal shape and dimensions of the bone. Commonly, bone modeling is considered as being formative; however, in fact, it can be either formative or resorptive. Formative bone modeling takes place on the periosteal surface and usually occur during growth. Formative bone modeling is carried out by osteoblasts, which are able to synthesize and deposit a volume of bone upon a bone surface that has not undergone prior bone resorption [36, 37]. On the other hand, resorptive bone modeling takes place on the endocortical surface which consequently excavates the medullary canal of long bones during growth and is not followed by bone formation. Resorptive modeling occurs also on the periosteal surface during growth to enable integration of the metaphysis with the diaphysis of long bones [37]. The resorptive bone modeling is carried out by osteoclasts, which are able to resorb a volume of the bone upon a bone surface. Modeling helps to give the bone its strength for

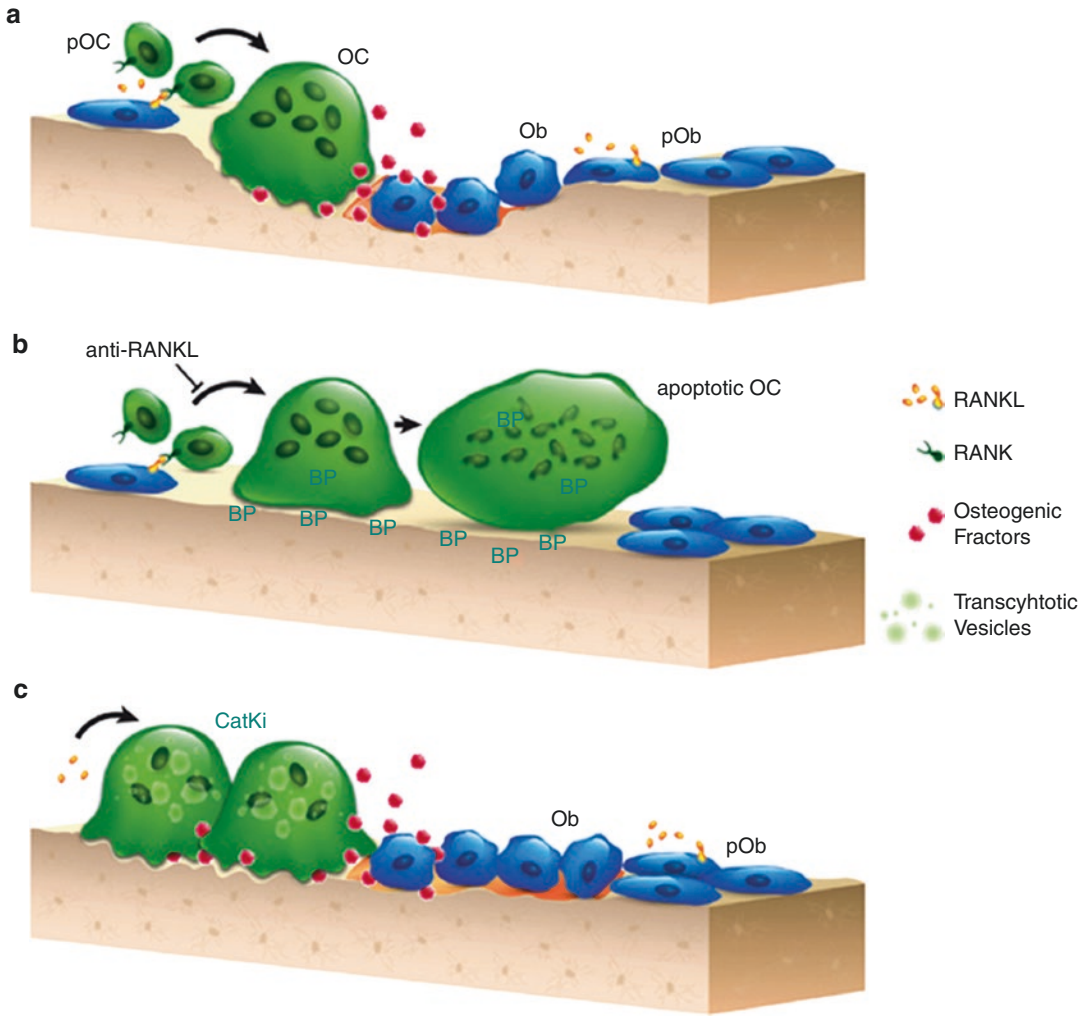

Fig. 17.2 Schematic representations of the normal coupling process of bone resorption and formation during the remodeling process. (**a**) RANKL promotes differentiation and activation of osteoclasts at remodeling sites. Coupling factors derived from the resorbed bone matrix or directly from the activated osteoclasts stimulate the recruitment and maturation of osteoblasts to initiate bone formation on the existing resorption surface. (**b**) Denosumab blocks osteoclastogenesis, and bisphosphonate induces the loss of ruffled border and eventual osteoclast apoptosis. These therapies lead to little-to-no resorption surface and fewer numbers of osteoclasts on bone. (**c**) Treatment with a cathepsin K (CatK) inhibitor reduces osteoclastic resorption efficiency and retards transcytotic trafficking of matrix removal. This does not prevent other osteoclast functions, such as the generation of a shallow resorption surface and the release of osteogenic factors; together, these functions initiate osteoblast bone formation (BP bisphosphonate, CatKi cathepsin K inhibitor, Ob osteoblast, OC osteoclast, pOb osteoblast progenitor, pOC osteoclast progenitor, RANK receptor activator of nuclear factor kappa-B, RANKL RANK ligand. (Reproduced with permission from (le Duong [31]). Still awaiting the permission (email resent on first of August 2020))

loading, resistance to deformation, and lightness of weight to facilitate mobility [36].

On another front, renewal or reconstruction of the bone is achieved by bone remodeling. Bone remodeling is carried out by bone multicellular units, which is composed of teams of osteoclasts and osteoblasts which resorb, respectively, a volume of older or damaged bone and then replace it with a newly synthesized bone [37]. Remodeling is a bone surface-dependent process. Primarily

this includes the intracortical surface of the Haversian canals, the endocortical surface of the medullary canal, and the opposing trabeculae surfaces [36].

Remodeling balance is always achievable during young adulthood when nearly equal volumes of the bone are removed then replaced upon these three components of the endosteal surface so that no permanent bone loss or microstructural deterioration occurs (Fig. 17.3) [38].

The net outcome of the imbalance between bone resorption and formation, which occurs at the menopause, is increased bone fragility. This provides the rationale for the development of pharmacological agents for the management of osteoporosis. It is clear from the described changes that reduction of bone resorption must be an essential component of any therapeutic approach for the maintenance or improvement of bone strength. However, this approach cannot replace already lost bone, which is required for better fracture protection in women with severe disease. For this, specific stimulation of bone formation is essential. Thus, in theory, optimal pharmacological management of osteoporosis should aim at decreasing bone resorption (endosteal and intracortical) and stimulating bone formation at all skeletal envelopes, including the periosteum. Such approach will not only prevent the structural decay of bone tissue but will also increase bone mass and may lead to improved reduction of the risk of non-vertebral fractures, which occur predominantly at cortical bone sites [39].

Concurrent treatment of women with osteoporosis with teriparatide and the inhibitor of bone resorption, denosumab, increased BMD at all skeletal sites considerably more than either monotherapy alone after 2 years [39, 40]. The difference in response between teriparatide and teriparatide/denosumab treatment is probably

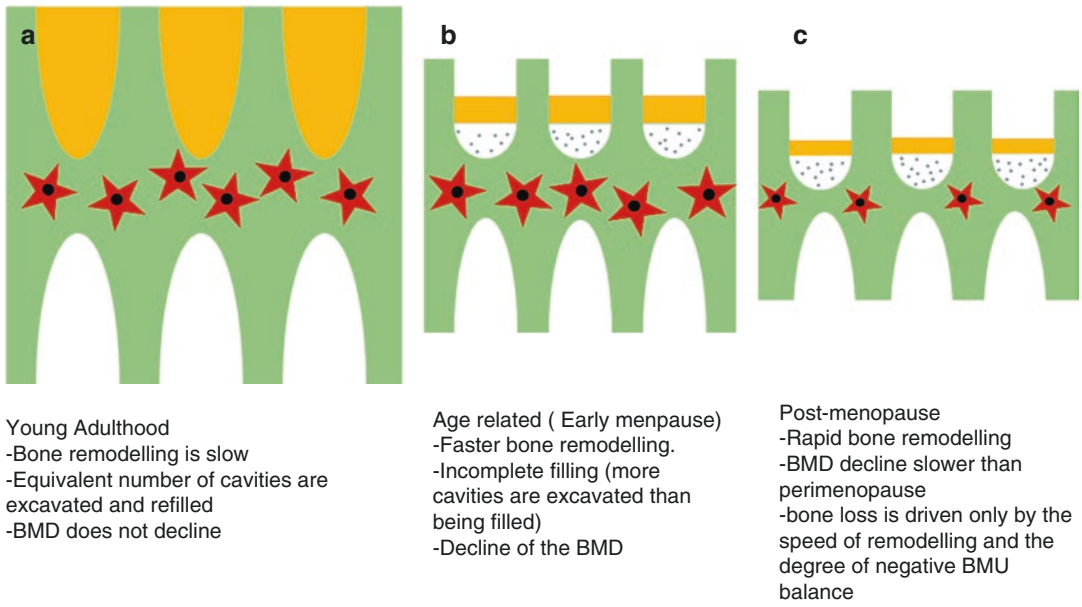

Fig. 17.3 (**a**) Reversible deficit in bone volume: at any time BMUs at different sites are at different stages of their remodeling cycle. Deficit is the result of cavities which are completely refilled with osteoid but still incompletely mineralized. So the reversible deficit is a deficit of mineral not matrix. (**b**) Age-related (early menopause): rapid increase in the rate of bone remodeling. The reduction in the volume of the bone resorbed by each BMU but even greater reduction in the volume of bone deposited at the same location resulting in BMU imbalance and morphological basis of irreversible bone loss. (**c**) Postmenopause: Rapid remodeling continues, but BMD declines more slowly than during early menopause. This is explained by the finding that bone loss is driven mainly by the speed of remodeling and the degree of the negative BMU balance, not by the greater difference in the number of cavities being excavated and not concurrently being incompletely refilled as occurs during early menopause

due to inhibition of teriparatide-stimulated RANKL (receptor activator of nuclear factor kappa-B ligand) production by denosumab that reduced bone resorption and allowed teriparatide to exert a stimulatory effect only on bone formation. These results reinforce the hypothesis that for optimal therapeutic outcome, bone formation and bone resorption should be modulated in different directions. The results of the studies of cathepsin K inhibitors illustrated that this may be feasible. Cathepsin K inhibitors, however, may preserve bone formation but are not anabolic agents, an important unmet need in the management of osteoporosis [38].

The design of a genuine anabolic treatment for osteoporosis must address the possibility of stimulating bone formation without concomitant stimulation of bone resorption and ensuring that formation is stimulated at quiescent bone surfaces. Human and animal genetics indicated that this may be feasible. In particular, the recognition of the pivotal role of the Wnt signaling pathway in bone formation provided a number of potential targets for the development of new pharmaceuticals. For clinical use, however, treatments should not only modify the expression of target molecules but need also to have bone specificity to avoid potential off-target effects [41, 42]. One such target is sclerostin, a negative regulator of bone formation produced exclusively in the skeleton by osteocytes [43]. The restricted expression of sclerostin in the skeleton and the lack of abnormalities in organs other than the skeleton in patients and animals with sclerostin deficiency made this protein an attractive target for the development of a new bone-forming therapy for the management of osteoporosis. This approach was further supported by studies of heterozygous carriers of sclerosteosis who have increased serum levels of P1NP and high, normal, or increased BMD but no clinical symptoms, signs, or complications of sclerosteosis [44, 45]. This will be discussed in further details in another chapter in this book.

The concept of bone modulation in osteoporosis management was further supported by the findings of recent studies documenting that the effectivity on fracture healing has been strengthened when teriparatide is combined with other anti-osteoporotics. Casanova et al. [46], using micro-CT and quantitative histomorphometry, showed that a 3-week administration of teriparatide together with zoledronic acid significantly increased bone volume and reduced trabecular spacing in mice with operatively induced fractures. Leder et al. [47] in a randomized control trial described more significant increases in BMD at the hip and at the lumbar spine in postmenopausal women treated for 2 years with teriparatide and denosumab, when compared with women on single administration of these medicaments. Furthermore, better fracture repair could be obtained using a combination of teriparatide and anti-sclerostin and/or anti-cathepsin K antibodies [48].

Implications from Research Studies and Clinical Practice

Inhibitors of Bone Resorption

Inhibitors of osteoclastic bone resorption, such as bisphosphonates, denosumab, and selective estrogen receptor modulators (SERMs), reduce the rate of bone resorption to varying degrees by different mechanisms of action. The reduction of the rate of bone resorption is invariably followed by reduction of the rate of bone formation due to the coupling of the two processes. The final result is an overall decrease of the rate of bone turnover to a level that depends on the potency of the individual agent used and is maintained during the whole period of treatment. The introduction of the most potent inhibitor of bone resorption, denosumab, into clinical practice made any further development of this class of agents obsolete. However, studies of humans and animals with osteopetrosis indicated that reduction of bone resorption may not necessarily be coupled with reduced bone formation if the osteoclasts remain intact [49].

Loss of function of a number of molecules regulating removal of bone mineral or degradation of bone matrix was shown to be associated with a decrease of bone resorption without, how-

ever, affecting or even stimulating bone formation [50, 51]. Cathepsin K (CatK), a protease abundantly expressed in osteoclasts responsible for the degradation of the organic matrix of the bone, is the most extensively studied molecule in preclinical and clinical studies.

Cathepsin K Inhibitors

Cathepsin K (CatK) is a member of a family of cysteine proteases that is synthesized as a proenzyme before being transported to lysosomes where it is cleaved to produce the active enzyme that degrades collagen type I and other bone matrix proteins within the acidic environment of resorption lacunae [52]. Congenital absence of CatK in patients with pycnodysostosis, a rare, autosomal, recessive osteochondrodysplasia, is characterized by increased bone density, bone deformities, and increased bone fragility, complications that are not present in heterozygotes [53]. CatK-deficient mice develop a high bone mass phenotype in the presence of fully differentiated osteoclasts, while mice overexpressing CatK had increased bone turnover and decreased trabecular bone volume [54, 55]. The discovery that loss of function of CatK decreases bone resorption with increased number of viable osteoclasts and the surprising finding of preservation or even increase in bone formation provided the rationale for the development of a new class of antiresorptive agents that target this enzyme (Fig. 17.2) [31, 56, 57]. The mechanism responsible for the maintenance or increase in bone formation in the presence of reduced bone resorption by CatK inhibition may be due to stimulation of osteoblasts by osteoclast-derived factors (clastokines, such as sphingosine-1-phosphate) or matrix-derived growth factors (such as IGF-1) that are not degraded [58, 59]. Initial studies of CatK inhibitors showed off-target inhibition of other cathepsins due either to their lack of specificity for CatK or to their accumulation in lysosomes of cells other than osteoclasts and led to the design of new agents potentially devoid of such effects. Two CatK inhibitors have been studied for the treatment of osteoporosis, namely, odanacatib (Merck & Co) and ONO-5334 (Ono Pharmaceutical Company).

Odanacatib is a selective, orally administered CatK inhibitor [60]. Unlike basic CatK inhibitors, odanacatib is neutral and does not accumulate in the acidic environment of lysosomes which could lead to off-target inhibition of other cathepsins [56, 61]. Odanacatib is metabolized by CYP3A4 and its absorption is not impaired by food intake [31, 62]. In animal models, odanacatib reduced bone resorption while preserving bone formation in trabecular and endocortical surfaces. In addition, odanacatib reduced cortical remodeling and increased modeling-based bone formation and improved the cortical area of the femur and its strength [63, 64]. Odanacatib was further superior to alendronate in increasing cortical thickness, possibly through increased periosteal bone formation, an action that was also observed during treatment with another CatK inhibitor [65, 66]. However, in 2016, Merk has published that it has decided to discontinue development after an independent adjudication and analysis of major adverse cardiovascular events confirmed an increased risk of stroke. Phase III results showed that while the drug could reduce fractures, it also increased the risk of atrial fibrillation and stroke.

Stimulators of Bone Formation

The only currently available bone-forming agent, PTH, stimulates bone formation but also bone resorption. PTH binds to the PTH/PTHrP type I receptor and activates several signaling pathways, including the canonical Wnt signaling pathway, having both anabolic and catabolic effects on the bone that are probably exerted via signaling in osteocytes [67]. Teriparatide, given by daily subcutaneous injections, increases cancellous and endocortical bone formation, mainly at sites undergoing active bone remodeling, but has limited effect on periosteal bone formation and increases cortical porosity [68]. PTHrP 1–36 and their analogue abaloparatide, which bind to

the PTH/PTHrP 1 receptor, also increase bone formation and bone resorption markers, but to a lesser extent than teriparatide, and improve hip BMD significantly more than teriparatide [69, 70].

New Aspects of the Bone-Protecting Effects of Vitamin D

Vitamin D positively influences not only the mineralization of the bone matrix but via genomic and non-genomic effects modulates the function of some nonskeletal systems, including muscles. D-hormone metabolites have been shown to influence bone homeostasis directly. Bioactive 25(OH) D3, 1,25 (OH)2D3, as well as 24R,25 (OH)2D3 stimulated osteoblast growth and differentiation in vitro [71]. 1,25(OH)2 D3 administered in vivo for 28 consecutive days significantly increased bone formation, reduced bone resorption, and increased trabecular bone volume in mice [72].

Long-term treatment with 1α,25[OH](2)-2β-(3-hydroxypropyloxy) vitamin D3 metabolite (eldecalcitol) suppressed bone turnover, decreased the risk of bone microstructure deterioration, and increased bone biomechanical strength in ovariectomized rats [73]. Yamasaki et al. [74] found that eldecalcitol increased bone formation at the endocortical surface in female rats.

In clinical studies, significant increases in BMD in the spine of osteopenic women were found at the end of the first, second, and third years of treatment with 1,25(OH)2D3, while no positive effects in cholecalciferol-treated women were observed [75]. Thus, it can be said that D-hormone metabolites have unambiguously positive effects on bone mass and microstructure.

Further Nontraditional Molecules with Anti-osteoporotic Potential

Osteoclast formation is increased after the activation of T cells through NF-κB, NFATc1, or c-Fos signaling. In bone tissue culture, this process was inhibited by β-carboline alkaloid harmine. Additionally, the alkaloid increased osteoblast differentiation via Runx2, osterix, and bone morphogenetic peptide (BMP) [76]. Thus, harmine inhibits bone resorption and simultaneously activates bone formation. According to our knowledge, no study analyzing anti-osteoporotic effectivity of the alkaloid in vivo has been published yet.

Certain anti-osteoporotic activity was recorded in neoflavonoids, isolated chromatographically from *Dalbergia sissoo* heartwood. The flavonoids significantly stimulated calvarial osteoblast proliferation and mineralization [77]. Similarly, caviunin-based isoflavonoid stimulates bone formation via BMP2 and Wnt/β-catenin pathways, effectively inhibits osteoclastogenesis, and repairs cortical bone. In ovariectomized mice caviunin increased the mechanical strength of the vertebra and femur [78]. Similar anabolic effects on the skeleton mediated by Wnt/β-catenin signaling have been registered experimentally in aglycone of icariin. Micro-CT analysis showed that icariin after 12 weeks of treatment increased BMD, trabecular bone number, trabecular thickness, reduced trabecular separation, and increased biomechanical strength in oophorectomized rats [79]. Some flavonoids could be positioned as potential pharmaceuticals or food supplements for fracture repair in postmenopausal osteoporosis.

Strong bioactivity in the culture of osteoblast-like cells has been shown in the three-dimensional calcium-bearing structure CaP1 (which has three molecules of water). In vivo, the substance increased bone mineralization without any toxicity [80]. Bone regenerative effects were also found in synthetic diether molecules inhibiting RANKL-induced osteoclast formation [81], as well as in octacalcium phosphate, which increased bone mineralization via an irreversible transition into hydroxyapatite [82].

Furthermore, the food-derived compound sulforaphane and natural isothiocyanate promote osteoblast activity via epigenetic mechanisms. The molecule activates DNA demethylation increasing matrix mineralization. In mice it stimulates the expression of osteoblastic markers, such as Runx2

and collagen I A1 or ALP1, while inhibiting the nuclear factor-κB (RANKL) in osteocytes with subsequent increases in the trabecular number [83]. New strategies in therapy for osteolytic diseases consist of targeting noncoding microRNAs (miRNAs), which control gene expression in osteoclasts. Thus, miRNAs appear to be the key molecules in the regulation of bone resorption [84]. Bone homemostasis is determined by the osteogenesis/adipogenesis ratio in mesenchymal cells. Prevailing adipogenesis over osteogenesis is a principle pathological factor in accelerated bone loss. A strong modulator of osteogenic differentiation is the glutamate exchanger xCT (SLC7A11) sulfasalazine, which enhances the osteogenic potential via an increase in BMP2/4 expression. Sulfasalazine administered in vivo inhibited bone loss in hypoestrogenic mice [85]. Thus, sulfasalazine is a further candidate useful in the treatment of postmenopausal osteoporosis.

Potential bone-protecting candidates are also growth factors, such as BMP, fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) [86]. Some of these mediate the action of other molecules [85]. The beneficial effects of erythropoetin or statins on fracture healing are under investigation; however, sufficient evidence of their anti-osteoporotic action in vivo is still lacking [87].

Implications of Remodeling and Modeling on the Long-Term Effects of Osteoporosis Drugs on Bone Mass and Strength

Bone mass, as evaluated by aBMD, remains the most important determinant of bone strength, explaining up to 80% of the failure load [88]. Hence greater gains in aBMD, and thereby higher aBMD values, have been associated with lesser fracture risk, both in the presence and absence of osteoporosis therapy [89, 90]. However, large differences in BMD gain, particularly at sites of predominantly cortical bone such as the hip, have been noted between osteoporosis drugs, and even among antiresorptives. Hence relatively weak antiresorptives such as selective estrogen receptor modulators induce a small (1–2%) initial gain of hip BMD, pertaining to the partial refilling of the remodeling space, but later do not prevent the loss of hip aBMD [91], because new bone resorption units continue to be activated and remodeling-based bone loss continues, particularly intracortically, which is not fully compensated for by the amount of modeling-based bone formation (Fig. 17.3). With more potent bisphosphonates, greater inhibition of bone remodeling allows greater gains in aBMD initially, but long-term clinical trials have consistently shown a plateauing effect after 2–3 years at the hip [92, 93]. This phenomenon could be explained by a new equilibrium reached between the amount of bone removed by the residual bone remodeling and the amount of new bone deposited by modeling-based bone formation, even though the latter may be somewhat negatively affected by bisphosphonates [94] (Fig. 17.4). However, with a complete suppression of bone remodeling, as achieved with denosumab, and provided bone modeling is sustained, as suggested by the studies on monkeys [95], then a positive bone accrual could be maintained long term, thereby potentially explaining the continuous BMD increase observed with this drug for up to 10 years [96]. Eventually, with new compounds such as odanacatib and particularly romosozumab, that both inhibit bone remodeling while promoting bone modeling, even if transiently, an even greater gain of aBMD could be observed.

In conclusion, the two components of bone remodeling, resorption, and formation constitute the primary target of pharmacological interventions for the management of the disease. It is now clear that bone resorption and formation can be differently modulated by new classes of anti-osteoporotic medications that provide a novel, personalized perspective for the management of patients in clinical practice.

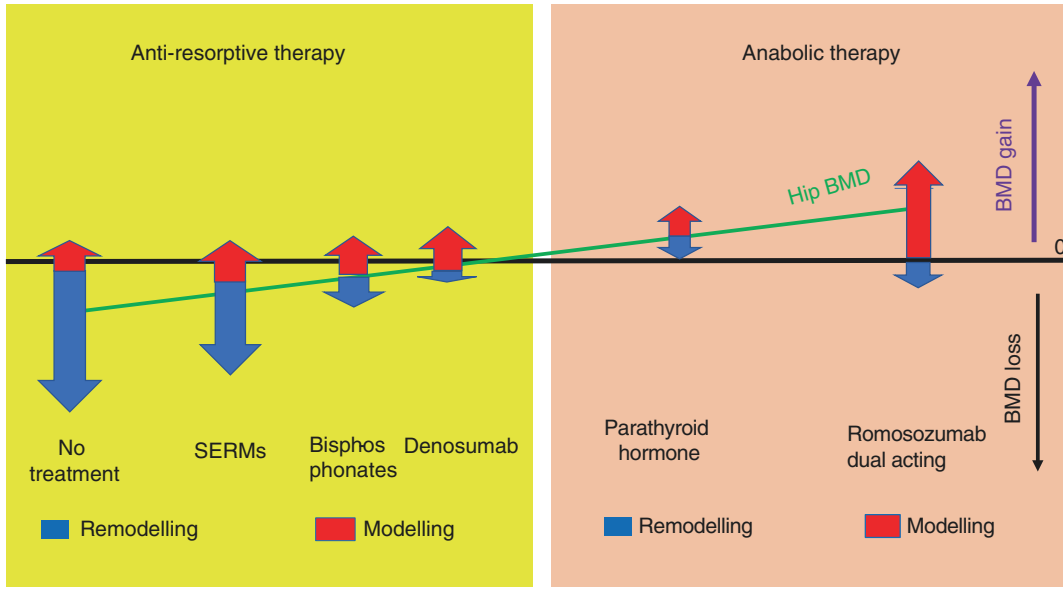

Fig. 17.4 The theoretical contribution of bone remodeling and modeling to the change in hip bone mineral density (BMD) in postmenopausal women with or without existing osteoporosis treatment. Bisphosphonates [93, 97]; denosumab [98]; romosozumab [99, 100]; SERMs, selective estrogen receptor modulators [91]; parathyroid hormone [101]

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Treat-to-Target in Osteoporosis

18

Yasser El Miedany and Sami Bahlas

Introduction

Recently, it has been proposed that a treat-to-target strategy could be useful in the management of osteoporosis [1, 2]. In general, in medical practice, the strategy of treating to a pre-specified target involves the definition of a level of a chosen disease marker/biomarker that is associated with optimal protection against the detrimental effects of a particular disease. In several medical conditions such as diabetes mellitus, hypertension, hypercholesterolemia, as well as gouty and even rheumatoid arthritis have had a specified treatment targets which appeared to facilitate disease management decisions and optimize treatment outcomes. In fact, having a gold standard is mandatory in the treat-to-target strategy to facilitate monitoring the patient's condition and make decisions regarding the medication efficacy. The proposal of treat-to-target in osteoporosis has sparked discussions about would be the treatment goals and its impact on the management approach in standard practice [3, 4].

The aim of treat-to-target is to simplify management and ultimately reduce organ damage and improve clinical outcomes. Thus, in people living with hypertension, reducing blood pressure to below the recommended targets (140/90 mm Hg) reduces the risk of clinical events such as stroke [5]. In diabetes, the target of glycated hemoglobin (HbA1C) <7% is generally applied in patients with Type II diabetes to reduce risk of microvascular and macrovascular events [6]. In concordance, in patients having dyslipidemic state, the total cholesterol/HDL-C ratio has been identified the best predictor of ischemic heart disease (IHD) risk in several observational prospective studies, including the Quebec Cardiovascular Study [7]. Therefore, evolving osteoporosis management, establishing a more individualized, goal-directed approach to managing osteoporosis may foster better drug therapy selection, improve patient follow-up, and help in developing new management approaches such as cycling or sequential therapy.

This chapter will discuss the treat-to-target concept in osteoporosis and potential value of goal-directed treatment and sets out several principles to guide this approach to selecting as well as monitoring treatments.

Treat-to-Target as a Strategy in Osteoporosis

Treat-to-target strategies set a biomarker value associated with a sufficiently reduced level of risk for the consequences of the disorder being

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treated. The therapy that has the highest probability of reaching that target in a reasonable time frame is then selected. Progress toward the target is reassessed periodically, facilitating decisions to stop, continue, or change therapy [8]. Consequently, the hallmark of effective osteoporosis treatment, particularly for the patient, is the absence of an intercurrent fracture. As no therapy can reduce fracture risk by 100%, it is to be expected that fractures might occur while on treatment. The occurrence of a fracture during treatment may simply reflect residual fracture risk in a patient receiving an effective treatment, for example, a risk (e.g., falls) that is not modified by the current treatment. It may also reflect poor compliance or a true suboptimal response to the treatment with both perhaps indicating the need for a change in management strategy. Such complexities suggest it is unrealistic to apply the occurrence of incident fracture in a treat-to-target strategy. Furthermore, the lack of incident fracture, though gratifying, cannot provide a signal to change management [9].

As the ultimate goal of any management strategy in osteoporosis is the prevention of fracture, treating to target implies that there is a surrogate measure that confirms a lower fracture risk in the individual osteoporotic patient. Such surrogate measures might include bone mineral density (BMD) and fracture risk probability, e.g., FRAX® [10] bone turnover markers (BTMs).

Establishing Treatment Goals

The principles of goal-directed treatment are founded on the identification of a target BMD or fracture risk to guide decisions about initial treatment and treatment decisions during the course of therapy. Currently, the NOF suggests initiating treatment in patients with hip or vertebral fractures, patients with a *T*-score in the lumbar spine, patients with total hip or femoral neck −2.5, and those with a 10-year probability of hip fracture >3% or 10-year probability of major osteoporotic fracture >20%, using the US-adapted World Health Organization (WHO) absolute fracture risk model (FRAX) [10]. Osteoporosis treatment goals parallel indications for initiating treatment; logical treatment goals are BMD levels above and fracture risk levels below those for which treatment is usually recommended.

In a patient with an incident fracture while on osteoporosis medication, treatment should be continued regardless of the *T*-score because the risk of another fracture in the next few years is very high [11–13]. Once a fracture-free interval of 3–5 years has been documented, other treatment targets can be considered.

Bone Mineral Density/*T*-Score as a Goal

Bone mineral density is the leading candidate for a treatment target. It is used for the diagnosis of osteoporosis and is strongly correlated with risk of fracture in patients left untreated, with an approximate doubling of risk for fracture for each SD decrease (approximately equal to 1 *T*-score unit) in bone mineral density [14]. Although absolute BMD (in g/cm^2) is used for quantitative comparison of serial BMD measurements by DXA, *T*-score is preferred as a goal because *T*-scores mitigate much of the BMD variability associated with different skeletal sites, regions of interest, and DXA make and model. This approach is feasible in clinical practice. A *T*-score goal is attractive because it is measurable and improved by treatments.

There is usually an increase in bone mineral density with osteoporosis therapies. Because greater treatment-related increases in bone mineral density are associated with greater decreases in the risk of fracture [15–21], the bone mineral density gained with therapy is a logical target, while acknowledging that in some cases improvement in bone mineral density alone does not capture the full benefit of therapy. This has been supported by the outcomes of several research studies published earlier. Research studies showed that decreases in spine BMD during treatment with alendronate have been associated with a higher risk of vertebral fracture than in those whose spine BMD improved [21]. Changes in femoral neck BMD in individual patients dur-

ing 3 years of treatment with denosumab were correlated with reductions in risk of non-vertebral fracture [17]. Furthermore, for the purpose of predicting the results of clinical trials of antiresorptive drugs, greater increases in mean vertebral and femoral neck BMD in trials of antiresorptives are significantly associated with greater of reductions in the risk of vertebral and hip fractures, respectively, in those trials [18, 19, 22].

Of greater importance than the association between BMD gain and fracture risk reduction, however, is identification of a *T*-score value above which there is an acceptably low risk of future fracture. Evidence from the Fracture Intervention Trial Long-Term Extension (FLEX) trial of alendronate and the HORIZON extension trial of zoledronic acid indicates that a persistently low femoral neck *T*-score ≤ -2.5 in women who had received 5 years of treatment with alendronate or 3 years of zoledronic acid was associated with a high risk of future vertebral fracture [11, 23, 24]. Furthermore, in a post hoc analysis of a high-risk subset of subjects in the FLEX trial, continuing alendronate beyond 5 years reduced the risk of non-vertebral fractures in women with femoral neck *T*-score ≤ -2.5 but not in those with a femoral neck *T*-score > -2.5 [25]. With continued zoledronic acid treatment beyond 3 years, there was a suggestion that continued vertebral fracture risk reduction was limited to those with *T*-score ≤ -2.5, with the absolute risk of fracture very low in those patients who attained BMD above that level [11]. Similarly, data from the FREEDOM extension study of denosumab also suggest that fracture risk while on denosumab treatment is a function of the hip *T*-score achieved during treatment [26]. A target *T*-score > -2.5 is also consistent with the recommendations of the ASBMR Working Group on long-term bisphosphonate treatment, (3) which state that after treatment for 5 years with alendronate or 3 years with zoledronic acid, postmenopausal women with low fracture risk (hip *T*-score > -2.5) may be considered for discontinuation of bisphosphonate therapy, with reassessment of fracture risk 2–3 years after discontinuation [27]. In the Spanish consensus on treat-to-target for osteoporosis, there was consensus that scores higher than -2.5 and -2.0 SD should be established as a therapeutic objective [28].

Despite the predictive value of BMD for fracture and the good correlation between fracture risk and BMD, a number of features make it a less than ideal choice for a target. First, many fractures arise in individuals with BMD that lies above the definition of osteoporosis [29]. Second, for a given value of BMD, the risk for fracture increases markedly with age, so that age would also need to be taken into account. Third, for some skeletal sites, such as the femoral neck, achieving a goal *T*-score > -2.5 might be unlikely or impossible with current medications. Furthermore, a clinician might decide to set a goal of *T*-score > -2.5 at the lumbar spine because of discordance in BMD between the lumbar spine and hip, with a lower spine BMD indicating a greater risk of vertebral fracture [14, 30]. A lumbar spine *T*-score goal may be particularly important when the treatment being considered, such as teriparatide, improves spine BMD substantially more than hip BMD. Forth, there are no data about continued benefits of treatment or risk of future fracture for lumbar spine BMD. While most osteoporosis treatments tend to increase BMD up to a plateau—and this is associated with fracture risk reduction—it is unknown whether switching to another osteoporosis treatment to obtain even greater increases in BMD actually translates into additional fracture benefit [1]. Fifth, measurement of BMD, as with any measurement, has inherent variability because of factors that include instrument calibration, patient positioning, and analysis. Moreover, lumbar spine BMD in the elderly may increase because of degenerative changes that are not associated with improvement in bone strength. For individual patients, serial BMD measurements by DXA typically have a "least significant change" in the range of 3–5% (about 0.3–0.5 *T*-score units) with a 95% level of confidence [11]. Therefore, reaching a *T*-score > -2.0 on a single measurement provides a very high degree of confidence that the *T*-score is truly > -2.5. Confidence that the goal

T-score > −2.5 has been achieved is also enhanced when the *T*-score at a skeletal site is > −2.5 on more than one measurement. In consideration of technical differences with DXA systems of different manufacturers and sources of measurement variability, measurements should ideally be made on the same device at the same facility, using the same reference databases to calculate *T*-scores, provided there is adherence to well-established quality standards [31] and DXA Best Practices [32]. With future advances in knowledge, other methods for assessing bone strength, such as finite element analysis, may someday play a role in determining treatment targets.

Fracture Probability as a Goal

If the primary reason for starting treatment is a high absolute risk of fracture, then the goal is a level of fracture risk below the risk threshold for initiating treatment. Fracture risk tools such as the fracture risk assessment tool (FRAX) [10] combine information from bone mineral density and selected clinical risk factors to provide an estimate of the risk of fracture in untreated individuals. For example, if the treatment threshold were a 10-year risk of major osteoporotic fractures (hip, humerus, wrist, and clinical spine fractures) >20%, then the treatment goal would be a 10-year risk below 20%. A patient's risk of fracture will, on average, decrease by the amount observed in clinical trials in a patient who is adherent to therapy. For example, a patient with a 5% 10-year risk of hip fracture will reduce that risk to about 3% by treatment with an agent that reduces hip fracture risk by 40% [27]. However, using fracture risk as a goal of therapy for individual patients is limited by the absence of a validated approach for estimating the risk of fractures in individual patients who are receiving treatment [33]. The Spanish consensus on treat-to-target for osteoporosis was in favor of a therapeutic objective of a 10-year risk of fracture measured with a tool such as FRAX, with certain adjustments. If fracture risk reduction measured by FRAX is used as the principal parameter for defining an adequate therapeutic objective, the consensus opted for the risk of major fractures (hip, vertebral, femur, humerus, and radius) has to be lower than 10% [28]. With regard to this hypothetical situation, Leslie et al. [34] demonstrated in the Manitoba cohort population that analysis of a subset of the same cohort, comprising more than 11,000 women undergoing baseline and follow-up DXA scans, confirmed that FRAX scores were strongly predictive of incident major fracture and hip fracture over 4 years of treatment but also reported that the change in FRAX score on treatment was not independently associated with the subsequent risk of a major fracture ($p = 0.8$) or hip fracture ($p = 0.3$). These data were supported by another study [35]. However, this hypothetical situation is almost impossible in the real life, as Leslie et al. [34] demonstrated in the follow-up of Manitoba cohort that a small percentage of patients, even with a medication possession rate >0.8, achieved reduction in major fracture probability of 4% or higher. FRAX fracture risk calculations do not take into account how recently a fracture occurred. Clinical trial and observational data in individuals treated for osteoporosis suggest that a history of recent fracture during treatment is associated with an increased risk of another fracture during treatment [11–13]. Despite its logical appeal as a treatment goal, fracture risk is currently not feasible for clinical practice. Better methods for assessing fracture risk for patients on treatment are needed to enable use of fracture risk goals to guide therapeutic decisions.

Indices of Bone Strength as a Goal

As fragility fracture is a consequence of impaired bone strength, an obvious related target, such as the restoration of bone strength with bone volume, trabecular architecture, or cortical thickness, could be considered as targets for treatment. The trabecular bone score is a measure of bone texture correlated with bone microarchitecture and a marker for the risk of osteoporosis. Introduced in 2008, its main projected use is alongside measures of bone density in better predicting fracture risk in people with metabolic

bone problems. Limitations of using bone strength as a goal include the invasive nature of traditional assessments (e.g., transiliac crest bone biopsies) or newer techniques (e.g., microindentation [36]) and the relative cost and radiation exposure of other techniques (e.g., computed tomography and finite element analysis). In terms of fracture prediction, the added value of these approaches above that of simple measurement of areal BMD appears limited; whether the same holds true for assessing the response to therapy has been the focus of a few studies. For example, in a subset of patients from the FREEDOM study of denosumab, finite element analysis showed significant improvements in bone strength at both the spine and hip in the active treatment group but the correlation between sites was weak (r = 0.38) [37]. Although TBS changes with osteoporosis treatment, the magnitude is less than that of aBMD of the spine, and it is not clear how change in TBS relates to fracture risk reduction [38].

Bone Turnover Markers (BTM) as a Goal

Bone turnover markers (e.g., C-telopeptide, a marker of bone resorption; N-terminal propeptide of type I collagen, a marker of bone formation) are biological by-products of bone remodeling that change rapidly with treatment, allowing for assessment of treatment response within weeks to months of starting or changing therapy [39]. In a meta-analysis, a 70% decrease in bone turnover markers was associated with an approximate 40% lower risk of fracture with bisphosphonate therapy taken for a year [21]. A suggested target for antiresorptive therapies has been the reduction of bone turnover markers below the mean premenopausal level [40].

Although the changes in bone turnover markers may be useful to monitor therapy, there are many limitations, including preanalytical and analytical variability and limited availability and affordability. Furthermore, contrary to the position of BMD, there is no consensus on the characterization of high and normal bone turnover. In a recent meta-analysis, the predictive value of s-P1NP was a 1.23 (95% CI: 1.09–1.39) increase in fracture risk per SD increase in analyte. The hazard ratio per SD increase in risk of fracture for s-CTX was 1.18 (95% CI: 1.05–1.34) [41]. These gradients of risk are substantially lower than those reported for the use of femoral neck BMD in the prediction of fracture. Although the decrease in fracture risk on antiresorptive treatment is associated with significant reductions in BTMs [21], data from clinical and population-based studies have proved difficult to translate into accurate targets for individuals, and the use of BTM targets has not been widely translated into clinical practice (Table 18.1).

Table 18.1 Shows a summary of the main considerations of the main variables in the treat-to-target osteoporosis management

Indication for treatment	Treatment target
T-score ≤ −2.5	T-score > –1.5 – –2.0 [8, 28]
High risk for fracture (FRAX) >20% (major osteoporosis fracture probability)	Fracture risk below the treatment threshold [8] or FRAX (major osteoporosis fracture probability) <10% [28]
Fragility fracture: (independent of T-score and fracture risk algorithm)	Fracture-free interval of 3–5 years [27]

Comparison Between the Standard Treatment and Goal-Directed Treatment

With current guidelines for managing osteoporosis, once a decision has been made to treat a patient with a pharmacological agent, a "first-line" drug, usually an oral bisphosphonate, is prescribed. BMD is often repeated 1–2 years later to evaluate for response to therapy. Stabilization or improvement of BMD is usually accepted as validation that the patient is responding appropriately to treatment. The same treatment is then continued; after 3–5 years of oral or intravenous bisphosphonate therapy, a bisphosphonate "holiday" may be considered [42]. If there is a statistically significant decline in BMD

Table 18.2 A comparison of the two main strategies for treating osteoporosis patients

Treatment stage	Standard management protocol	Treat-to-target
Treatment decision	*T*-score < −2.5 FRAX (major probability >20%, Hip fracture probability >3%) Imminent fracture risk Low-trauma fracture	*T*-score < −2.5 FRAX (major probability >20%, Hip fracture probability >3%) Imminent fracture risk Low-trauma fracture
Assessment of secondary causes of osteoporosis	Carried out	Carried out
Treatment goal	Response to treatment	Treatment target is identified before treatment is started Achievement of the target
Initial treatment choice	Usually a generic oral bisphosphonate unless a contraindication is present	Treatment chosen as the most appropriate to achieve the target
Monitoring of management	BMD assessment Occurrence of low-trauma fracture Bone turnover markers ? FRAX	BMD assessment Occurrence of low-trauma fracture Bone turnover markers ? FRAX
Treatment success	Stability or increase in BMD No fracture occur in 3–5 years after therapy	Achievement of the treatment target
Markers of treatment failure	Significant decrease in BMD (more than the least significant change) Occurrence of fractures on therapy Lack of expected Change in bone turnover marker	Failure to achieve the treatment target
Managing treatment failure	Change to a treatment more likely to achieve better response	Change to a treatment more likely to achieve the treatment target

1–2 years after starting therapy, clinicians may evaluate for factors contributing to a suboptimal response to therapy and consider switching to a different agent. Sometimes bone turnover markers are used to monitor response to therapy, with a significant change in the expected direction (decreased with antiresorptive agents, increased with osteoanabolic agents) taken as an acceptable response [27].

In contrast, goal-directed treatment is a strategy where (1) a goal of treatment is established for a patient, (2) the initial choice of treatment is based on the probability of reaching the goal, and (3) progress toward reaching the patient's goal is reassessed periodically, with decisions to stop, continue, or change treatment based on achievement of the goal or progress toward achievement of the goal. Goal-directed treatment differs from standard practice in a fundamental way. The overriding goal of treatment is to achieve freedom from fracture or at least a low risk of fracture. If a fracture, including a morphometric vertebral fracture, occurs during treatment, despite evidence of response to treatment by improvement in BMD and markers of bone turnover, then the patient has an increased risk of a recurrent fracture for at least several years [11–13], warranting consideration of switching to a more potent treatment or combination of treatments or, at a minimum, continuing an effective therapy. Table 18.2 shows a comparison of the two main strategies for treating osteoporosis patients.

Goal-Directed Selection of Initial Therapy

There are several factors governing the choice of treatment medication, including the local management policies or treatment recommendations, personal factors such as age, comorbidities, concomitant medications, organ functions, falls risk, frailty, severity of osteoporosis, or presence of contraindications to certain medications as well as severity of osteoporosis.

For patients with imminent fracture risk, it is critical to prevent fractures during the next years,

when the risk of another fracture is substantially high [43–50]. Therapeutic agents that reduce fracture risk rapidly are the most appropriate and preferred line of therapy for these patients. For patients with a *T*-score < −2.5, treatments with the potential to attain a significant increase in BMD should be considered. The acceptable probability of achieving the treatment goal has been suggested as the initial treatment should offer at least a 50% chance of achieving the treatment goal within 3–5 years of starting therapy.

If initial treatment with an oral bisphosphonate offers a low probability of reaching the target *T*-score of > −2.5, then an agent with substantially greater effect on BMD, if available, should be considered for initial therapy. Similarly, if initial treatment with an oral bisphosphonate offers a low probability that the patient will reach a goal of reduction in fracture risk, an agent or sequence or combination of agents with greater effect on fracture risk should be considered for initial therapy. Choice of initial therapy should also consider the balance of expected benefits and potential risks, patient preference, and cost [27].

Goal-Directed Assessments and Treatment Decisions During Treatment

Assessing Adherence to Treatment

To achieving the treatment goal, adherence to treatment is an important factor to consider. In general, taking less than 80% of prescribed oral medications is associated with a suboptimal therapeutic effect, which may be recognized by a decline in BMD, occurrence of a fracture, or failure of bone turnover markers to respond as expected. Poor adherence should warrant interventions to improve adherence [51]; for example, when adherence to an oral agent is inadequate, parenteral therapy should be considered. Electronic pharmacy records are the best approach to assess levels of adherence to therapy. Comparisons of adherence with oral and injectable therapy showed that patients treated with subcutaneous denosumab every 6 months [52] and intravenous ibandronate every 3 months [53] had better adherence than did weekly oral bisphosphonate.

Monitoring Response to Therapy

A treatment goal can be achieved only when the patient responds to therapy, although response to therapy is not a guarantee that the goal has been achieved. A fracture occurring while on therapy warrants further evaluation to confirm whether there are hidden underlying secondary causes of osteoporosis. Patients who have had fractures on treatment should not be considered to have achieved treatment goals until they have remained free of fracture for at least 3–5 years past the fracture. Guidelines recommend repeating a DXA study 1–2 years after starting therapy and/or measuring a bone turnover marker [54, 55] to ensure that there is a treatment response. However, a patient may be a good responder with improvement in BMD or an appropriate change in bone turnover marker, yet still have an unacceptably high level of fracture risk. This could be attributed to the BMD which remains at very low state, the patient had a recent fracture, or there are associated comorbidities or medications that increase fracture risk substantially. With the goal-directed approach, despite a treatment response being confirmed, consideration should be given to modifying therapy to help achieve treatment goals.

Patients whose BMD does not improve on treatment cannot achieve a *T*-score goal. Loss of BMD during treatment warrants evaluation of adherence and other causes of inadequate response to treatment [31, 54, 55]. Treatment monitoring should also include assessment of possible adverse effects of therapy, interval fracture history, assessment of back pain, and body height measurement to determine whether vertebral fracture assessment should be repeated [56].

There have been no analyses of the best frequency for reassessing fracture history, rescreening for vertebral fractures, or measuring height. Furthermore, the ideal interval for assessing

Table 18.3 List of incidences that might happen while receiving osteoporosis therapy and approaches to assessment and management of these patients

The incidence	Assessment	Management approach
Occurrence of new vertebral fracture: new vertebral fracture occurs (whether clinically evident or incidental findings on vertebral imaging)	History of back pain (particularly acute): imaging Measure height in every follow-up visit at least after 2 years of treatment to screen for asymptomatic new vertebral fracture. (>2 cm loss of height indicates an increased probability of a new vertebral fracture and warrants spine imaging/repeat VFA) [56, 59]	Evaluation for factors contributing to skeletal fragility (regardless of evidence of achievement of a *T*-score goal) Continuation of treatment for up to 5 additional years Treat with an agent that maximizes the prevention of another vertebral fracture
Occurrence of non-vertebral fracture during treatment	In untreated patients, the fracture risk following an incident non-vertebral fracture is greatest in the first 5 years postfracture and wane with time [43–50] In patients receiving zoledronate, incident non-vertebral fracture is an important risk factor for future non-vertebral fractures over the next 3 years if therapy is discontinued [11]	Appropriate evaluation for factors contributing to skeletal fragility, regardless of achievement of a *T*-score goal Even if the *T*-score goal has been reached, continue treatment or change to one with greater efficacy for reducing non-vertebral fracture risk or addition of therapy, at least until the patient has been fracture-free for 3–5 years
Change in other risk factors for fracture risk while on treatment	Changes in other risk factors for fracture, such as change in medications, weight loss, or development of a diagnosis that influences fracture risk, suggest a change in risk of fracture during treatment. These changes may influence the decision to continue or switch to a more potent agent	Requires development of models that accurately estimate risk of fracture during treatment
Achievement of a *T*-score goal	BMD should be maintained above the goal (i.e., *T*-score > −2.5) Benefits of continuing treatment appear to be very small when the patient has achieved a femoral neck *T*-score > −2.5 [60]	The concept of a "drug holiday" applies only to patients taking bisphosphonates because of a transient residual antiresorptive effect after discontinuation due to skeletal retention of drug For non-bisphosphonates, a drug holiday is not appropriate because BMD declines rapidly after treatment is stopped [57, 58]

BMD has not been studied and would depend on the difference between the patient's *T*-score and *T*-score goal and expected effects of the treatment. However, in general, it would be reasonable to reassess patients yearly for assessment of adherence, interval medical history, and height measurement and at least every 2–3 years to determine whether the goal has been achieved or if there is a high likelihood that it will be achieved soon. Timely achievement of the treatment goal is desirable, although there is no analysis indicating an acceptable duration of treatment to achieve the goal. It is rational to utilize the medication most likely to achieve the BMD goal quickly in patients at highest risk for fracture [27].

While patients receiving bisphosphonate therapy for osteoporosis, drug holiday can be considered after achieving the treatment target; for patients treated with non-bisphosphonates, a drug holiday is not appropriate because BMD declines rapidly after treatment is stopped [21, 41, 57, 58]. Therefore, after a *T*-score goal is achieved with a non-bisphosphonate, treatment should generally be continued with an agent that maintains BMD, possibly a bisphosphonate (at least short term) [14].

Additional medications that can maintain treatment effects after achieving treatment goals would enhance the goal-directed treatment strategy. Treatment is to be restarted if a fracture occurs, a patient's BMD at the hip or spine decreases, or risk of fracture increases to a level that would warrant initiation of treatment (e.g., the use of glucocorticoids or new parental history of hip fracture). A patient's risk of fracture rises with age and may reach a level that warrants resumption of pharmacological therapy even in the absence of other factors. Table 18.3 shows a

list of possible incidences that might occur while treating osteoporosis patients, approaches to assessment, and management of these patients.

Drug Holiday

It is unusual to contemplate a drug holiday in the treatment of most chronic diseases because, as expected with most therapies, the beneficial drug effects rapidly diminish upon discontinuation. However, the long skeletal residence time of bisphosphonates and concern about the risks of rare adverse events with long-term therapy raise the possibility that bisphosphonate therapy may be interrupted for a "drug holiday," during which anti-fracture benefit might persist for a period of time while potential risks are minimized [61]. Table 18.4 lists the basic principles of drug holiday in osteoporosis management. Intuitively, upon bisphosphonate discontinuation, both the potential benefit and risks of the residual bisphosphonate effect would decrease over time as the drug is gradually removed from the skeleton. Ideally, the optimal approach to assess the potential utility of a drug holiday for osteoporosis patients would be clinical trial data comparing fracture risk between patients who continue or stop therapy. Only three prospective studies have addressed this issue for patients who received alendronate (fewer clinical vertebral fractures than the subjects who went for drug holiday after 5 years of therapy (5.3% vs 2.4%, respectively)), zoledronate (fewer morphometric vertebral fractures than the subjects who went for drug holiday after 3 years of therapy (3.0% vs 6.2%, respectively)), and risedronate (fewer morphometric vertebral fractures than the subjects who went for drug holiday after 3 years of therapy 6.5% vs 11.6%, respectively)) [24, 62]. Outcome of the studies showed increased risk of fracture with discontinuing bisphosphonates compared to continuing the osteoporosis therapy. However, post hoc analysis of the data revealed that after bisphosphonate exposure of 3–5 years in postmenopausal women with osteoporosis, protection from fractures persists for an unknown interval of time when therapy is withdrawn, that this protection wanes within 3–5 years of discontinuation, and that the risk of atypical femoral fractures increases with duration of therapy but may decrease upon withdrawal of treatment [63].

Table 18.4 Principles of drug holiday in osteoporosis management

Principle	Concept
Patient-centered	Selection of candidates for the drug holiday and monitoring during a drug holiday needs to be tailored to the individual patients
Duration of the holiday	A drug holiday should be viewed as a temporary, not permanent, suspension of active therapy
Transient residual effect	Discontinuing a bisphosphonate may not necessarily be a "holiday" from treatment because persistence of the antiresorptive effect is expected for an undefined period of time

The scenario is different in patients taking denosumab or teriparatide therapy where the medication positive effect on the bone turnover does not last for long period after stopping the medication, in contrast to bisphosphonates where the concept of a "drug holiday" applies because of a transient residual antiresorptive effect after discontinuation due to skeletal retention of drug. For non-bisphosphonates, a drug holiday is not appropriate because BMD declines rapidly after treatment is stopped. Discontinuation of long-term denosumab was reported be followed by a rapid rise in bone remodeling, decrease of bone mineral density, and return of fracture risk to baseline [64]; a drug holiday is not appropriate with denosumab as it may be with bisphosphonates. Rather, treatment should be continued or transitioned, 6 months after the last denosumab injection, to another antiresorptive medication.

There are currently no data about the effects of withdrawing therapy in men or patients receiving glucocorticoids. While there is little reason to think that the response to withdrawing treatment would differ between men and postmenopausal women, it is not clear what would be the BMD or fracture response to stopping therapy in steroid induced osteoporosis.

The variable antiresorptive potency and binding affinity of each bisphosphonate are owing to their unique side chains. Zoledronic acid has the highest potency, followed by risedronate, ibandronate, and alendronate. Binding affinity is highest for zoledronic acid and decreases in order of magnitude for alendronate, ibandronate, and risedronate, respectively [65, 66]. This may be owing to a greater affinity of alendronate and zoledronic acid to hydroxyapatite, compared with risedronate and ibandronate [67]. The skeletal binding sites for bisphosphonate are nearly unsaturable, thereby leading to a significant accumulation of bisphosphonates, whereas release of bisphosphonates may be small, as it partly depends on bone turnover, which is reduced by the use of bisphosphonates [21]. For example, after 10 years of alendronate use at a dose of 10 mg daily (70 mg weekly), the amount of alendronate released over several months or years would be equivalent to taking one-quarter of the usual dose [68]. In general, zoledronic acid and alendronate maintain a prolonged effect after discontinuation, whereas others, such as risedronate, have a more rapid offset [21]. Another factor to consider in the drug holiday is a demonstration of compliance with the therapy. A recent retrospective register study about the residual treatment effect of alendronate and risedronate in Swedish clinical practice suggests that the duration of bisphosphonate therapy is significantly inversely associated with the incidence of hospitalized fractures following discontinuation [69]. Specifically, during the first 6 months after terminating treatment, the adjusted fracture rates were considerably lower in patients who had been persistent with treatment for more than 12 months, compared with those who had stopped treatment within 1 month (hazard ratio [HR] = 0.40). In one study, it was reported that 70% of bisphosphonate users discontinued their prescriptions after 1 year of use [70]. Therefore, the decision to go on drug holiday after 3–5 years should be after assurance of continuous use of bisphosphonates during the initial therapy period [71].

In the absence of guidance from clinical trials about how to monitor osteoporotic patients who went for osteoporosis therapy drug holiday, empiric approaches might be of help to guide the treating healthcare professionals. An option is to measure the BMD and fracture risk probability 2–3 years after discontinuation of therapy. A significant decrease in bone density or significant increase of the 10-year fracture risk suggests that the benefits of bisphosphonate therapy may be diminishing and that it may be time to return to active therapy. Another approach is to re-evaluate the patient's fracture risk without including the BMD measurement 2–3 years after discontinuation, making the decisions to re-DXA scan and consequently restart therapy based on an updated assessment of fracture risk using algorithms initially developed for untreated individuals [72].

If a drug holiday is advised, reassessment of risk should occur sooner for drugs with lower skeletal affinity, with a suggestion to reassess after 1 year for risedronate, 1–2 years for alendronate, and 2–3 years for zoledronic acid [73]. Although it has been proposed that a decrease in BMD or an increase in bone turnover marker (BTM) might be used to decide when to end a drug holiday, there is lack of data on risk for fracture when these surrogate markers begin to change off bisphosphonates. The risedronate study showed that fracture risk remained reduced despite what appeared to be unfavorable changes in these parameters. Conversely, there is no evidence that fracture risk is reduced if BMD is stable or BTM is low off treatment. That being said, in clinical practice, monitoring BMD and BTM is the only means of gaining some sense of the loss of the effect of the bisphosphonate on bone remodeling, but ultimately the duration of the holiday should be based on clinical judgment [74] (Table 18.5).

Proposed Algorithm to Monitoring Osteoporosis Therapy

There is no standard commendation that applies to all patients, and therefore duration decisions need to be individualized. Initially treatment review should be performed after 1–2 years for

Table 18.5 Who would be good candidate for drug holiday in osteoporosis management

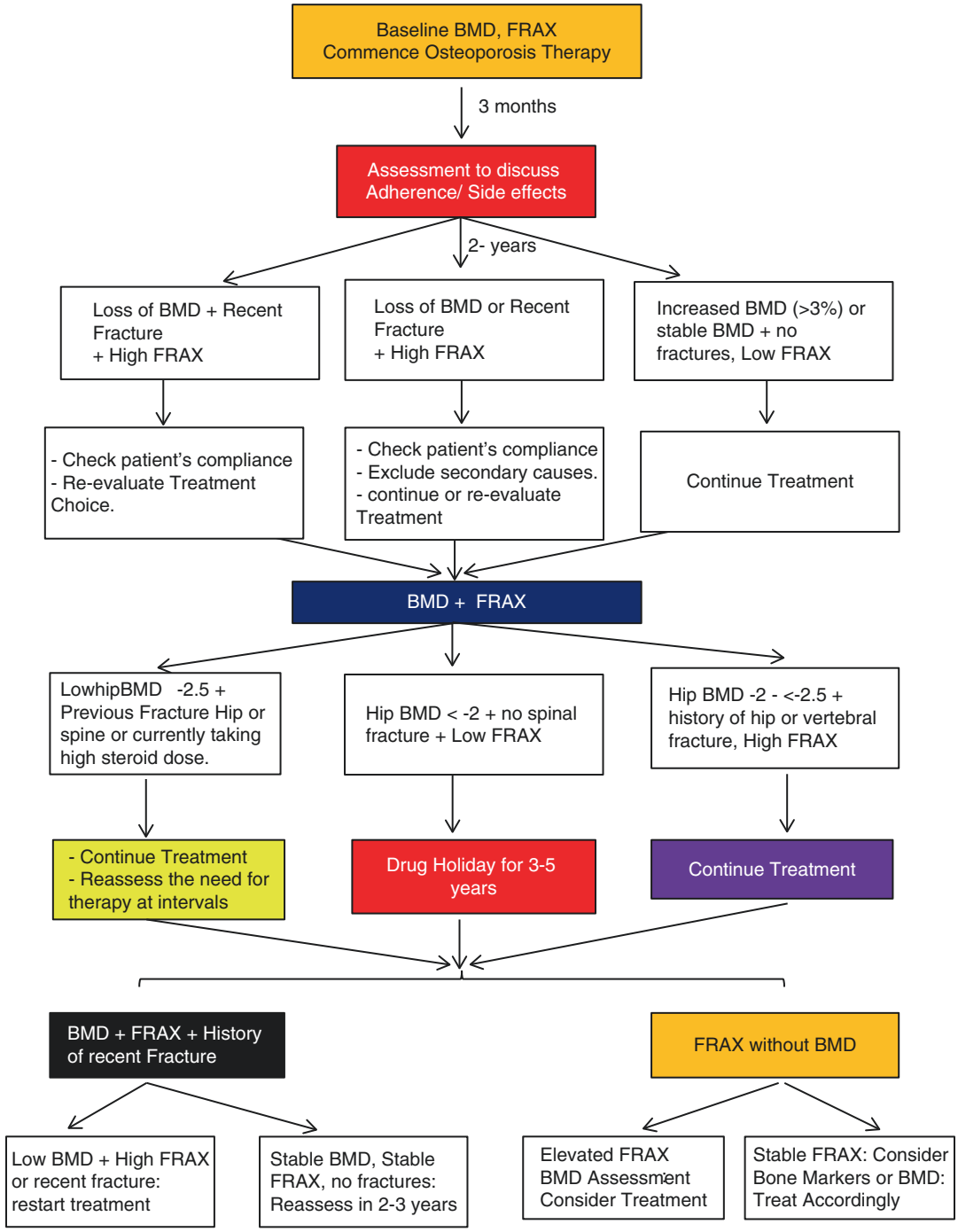
Consider drug holiday	Consider continued drug therapy	Average duration of therapy
Consider a drug holiday after 5 years of alendronate and risedronate treatment and after 3 years of zoledronic acid, in individuals without high risk	Consider the continued treatment in individuals with high risk	Drug holiday from alendronate and risedronate may be considered after 5 years
	High-risk patients: 1. *T*-score at any site still ≤ −2.5 after bisphosphonate therapy (5 years for alendronate and risedronate, and 3 years for zoledronic acid) 2. Previous fracture of the hip or spine 3. High risk of fracture because of secondary osteoporosis from chronic diseases or medication[a]	Drug holiday from zoledronic acid may be considered after 3 years
	Alternative therapy might be used for individuals with high risk	

[a]For example, steroid therapy, diseases such as hyperthyroidism, hyperparathyroidism, rheumatoid arthritis, or other disease states than can cause severe immobility, for example, multiple sclerosis

risedronate or ibandronate and after 3 years for alendronate and zoledronic acid when decisions to be made regarding continuation or change of osteoporosis therapy. Further review is to be carried out 3 years later (a total of 5-year treatment period), and a comprehensive risk evaluation should be carried out. This should include interval clinical history, particularly with respect to new chronic diseases or medications, intercurrent fracture history, and as well as height measurement. Bone mineral density measurement and vertebral imaging should be performed if height loss or acute back pain attributed to vertebral fracture was identified at any stage during the treatment period. In addition, the 10-year fracture probability should be assessed. A drug holiday for a period of 2–3 years may be considered for patients on bisphosphonate therapy, who are no longer at high risk of fracture. If treatment is stopped, serial monitoring may include clinical assessment for fractures, falling, as well as occurrence of chronic disease. While serial BMD testing can be used to monitor the patient's BMD status, 10-year fracture risk assessment without the inclusion of BMD can be used to identify patients at high risk or those who need further scanning. The use of biochemical markers may be also of help at this stage (Fig. 18.1).

Limitation and Expectations of Treat-to-Target Approach

Although several principles of goal-directed therapy could be applied to clinical practice, the concept has limitations, yet it can also offer new approach of management. For example, while, it may not be feasible for patients with a very high risk of fracture or very low BMD to achieve goals with current treatments, the treat-to-target approach might guide the need to start management with more potent treatments. For example, with current treatments, it may not be possible for a patient with a very high baseline risk of fracture, such as a 10% 10-year probability of hip fracture, to reduce that risk to <3% or for a patient with a baseline femoral neck *T*-score of −3.5 to achieve a *T*-score > −2.5. For these patients, treatment with the most potent agents should be considered. Changing standard treatment paradigms and optimizing treatment sequences, such as starting management with anabolic therapy followed by a potent antiresorptive drug, could potentially achieve BMD goals (even in patients who start with very low BMD). This highlights the importance of selecting the most appropriate initial therapy in patients who are far below the ultimate *T*-score goal [27].



- This algorithm which isbased on FRAX and BMD assessmentmight change as additional data about long-term risks of bisphosphonate therapy become available.
- Not all bisphosphonates are alike, so recommendations for discontinuation of bisphosphonates need to be drug-specific.
- Recommendations about monitoring after discontinuation and reinitiating anti-fracture therapy await further studies.

Fig. 18.1 Algorithm for long-term osteoporosis therapy

A goal of *T*-score > −2.5 (or higher if measurement variability is considered) does not apply to patients who initiate treatment because of high fracture risk with baseline *T*-scores > −2.5. A more aggressive treatment goal (*T*-score > −2.0 instead of > −2.5) may be desirable for patients with a very high baseline risk of fracture, such as those with a recent vertebral fracture or those older than 70 years [75]. Applying treat-to-target management approach for these patients requires development of methods for assessing fracture risk in patients receiving drug treatments.

Evidence and recommendations regarding the use of BMD for making clinical decisions to continue or withhold treatment with alendronate or zoledronic acid and the value of BMD for predicting fractures while on treatment are based on femoral neck or total hip BMD. There are no such data for lumbar spine BMD or other measurement sites. Nevertheless, including lumbar spine *T*-score as a goal of treatment is consistent with recommendations that the diagnosis of "osteoporosis" be made when the *T*-score is ≤ −2.5 at the femoral neck, total hip, or lumbar spine [76]. Maintaining treatment goals attained with non-bisphosphonate agents requires continuing the agent or switching to a bisphosphonate. Additional data are needed about the relative merits and safety of continuing treatment or switching to a different agent. Table 18.6 summarizes the pros and cons of potential treat-to-target osteoporosis parameters.

There are important caveats to these principles. Clinician judgment and patient preference may sometimes override numerical goals. These proposed recommendations are not intended to describe comprehensive care for patients, which should also include regular physical activity, assurance of adequate nutrition, avoidance of smoking, and excessive alcohol intake. Patients with a history of falls warrant assessment of risk of future falls and, perhaps, a program of fall prevention that includes regular weight-bearing exercise [77, 78]. Importantly, the establishment of targets should not be interpreted to deny insur-

Table 18.6 the Pros and cons of potential treat-to-target osteoporosis parameters

Target	Value	Pros	Cons
T-score	Absolute	WHO diagnostic tool for osteoporosis Valid cutoff values for therapy Main inclusion criterion in several osteoporosis clinical trials	Is not the sole risk factor for fracture risk Values vary with different instruments and at different skeletal sites
	Relative	An increase in BMD is associated with reduction in fracture risk Primary endpoint for several clinical trials	An absolute target may not account for improvement when the baseline fracture risk is very high No change in BMD with therapy is also associated with reduction in fracture risk
FRAX	*Absolute*	*WHO tool to assess for fracture risk* *Has been assessed in several clinical trials*	*FRAX does not include all risk factors for fracture*
	Relative	*Can be used for monitoring patients receiving osteoporosis therapy and its clinical implications* *Has value for guiding the need for continued treatment or treatment withdrawal*	*Does not differentiate between old and recent fractures* *Categorical scoring of risk factors*
Bone markers	*Absolute*	*May reflect the bone remodeling status*	*Diurnal variation* *Must be assessed in the same lab* *Sample must be taken early in the morning* *Not applicable on individual bases*
	Relative	*Changes above the least significant change have value for assessing the response to therapy when the baseline Value is extremely high or low*	*High values for least significant change* Least significant change value *vary for each biomarker*

ance coverage or reimbursement for further treatment if a patient has achieved a goal.

In conclusion, development of a treat-to-target strategy is a potential approach for improving osteoporosis care and reducing the burden of osteoporotic fractures. If treatment targets could be identified, they should be included in clinical practice guidelines, and the impact of the recommendations on patient outcomes should subsequently be evaluated. As new treatments and new evidence become available, it is likely and desirable that the recommendations be revised and implementation of new treatment approaches such as cycling and sequential therapy be implemented to meet the treat-to-target aims. BMD and fracture probability assessment are so far the most practical targets available for use in standard clinical practice to assess the osteoporosis therapy outcomes. Careful attention must be taken to ensure that patients prescribed osteoporosis therapy as well as those who go for drug holiday are likely to benefit. However, treat-to-target for osteoporosis should not be overly prescriptive and should allow for individualization of treatment decisions.

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19 Geroscience and Management of Osteoporosis in Older Adults

Yasser El Miedany

Introduction

Being old shares some attributes of a disease, but is this enough for old age to be considered a disease? Aging is a universal phenomenon, which results in common phenotypic manifestations for all individuals, including changes in the physiology and tissue structure, reduction in the performance of most organs, and increased vulnerability. Musculoskeletal diseases, in particular, represent a significant burden in older persons and a major cost to health systems worldwide. Of those, osteopenia/osteoporosis (characterized by low bone mass) increases with age alongside the number of osteoporotic fractures [1] while, on the other hand, sarcopenia (low muscle mass and function) confers a high risk of falls and disability in older persons [2].

Bone loss with is a natural phenomenon. Bone mass peaks around ages 25–30 years and declines gradually thereafter in both men and women [3]. The amount of bone in older people is determined by the peak bone mass, together with the rate of bone loss with age. Peak bone mass, in turn, is determined by many factors, including diet, particularly calcium nutrition; exercise; gender; and genetic makeup [4, 5]. The rate of bone loss varies from individual to individual but is broadly similar in women and men [6] except for the 5- to 10-year period of more rapid postmenopausal bone loss in women [7] that affects both cortical and trabecular bone [8]. This phase of increased loss in bone mineral content coupled with the typically smaller peak bone mass in women than in men presumably accounts for the greater frequency of bone fractures among older women than among older men.

Given the rapid growth of the aging population and the fact that the world is getting older, at the same time that birth rates have declined, the net effect of these trends is that nearly every nation is experiencing a dramatic "graying" of the population [9]. Therefore, it got critical to study the pathophysiological processes underpinning aging-associated bone loss, in order to develop, test, and validate therapeutic strategies targeting the problem of bone thinning and preventing the possibility of sustaining a fracture. In light of this, the chapter will discuss the concept of geroscience, as well as the age-related alterations to the bone tissue, and mechanisms of age-related bone loss. It will expand to discuss bone changes with aging and bone mineral density changes with aging. It will also present an approach to management of osteoporosis in the older adults including traditional osteoporosis therapy agents as well as future therapies aiming at bone marrow stromal cells.

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Geroscience: The Intersection of Basic Aging Biology, Chronic Disease, and Health

Older age is usually associated with chronic diseases, which could share similar pathophysiology and risk factors. Understanding and elucidation of those common mechanisms have enabled the development of geroscience. Geroscience examines the molecular and cellular mechanisms that might explain why aging is the main risk factor for most chronic diseases affecting the elderly population. Geroscience is based upon finding connections between the so-called hallmarks of aging, a term that refers to stress adaptation, epigenetics, inflammation, macromolecular damage, metabolism, proteostasis, stem cells, and regeneration as well as nutrient sensing to elucidate processes damaged in chronic diseases highly prevalent in older people [10].

Over the past few decades, researchers have made impressive progress in understanding the genetics, biology, and physiology of bone aging. Pathophysiologically, osteoporosis has been attributed to the imbalance between bone formation conducted by osteoblasts and bone resorption conducted by osteoclasts. Recent research provided evidence demonstrating that changes in number and function of bone marrow stromal cells (BMSCs) are also one key cause for senile osteoporosis [11, 12]. Study showed that BMSCs normally differentiate in a proper manner into osteoblast, chondrocytes, and adipocytes, but during old ages, there is comparatively less differentiation of BMSCs into osteoblast than adipocytes. Such a shift in cell differentiation of BMSCs results in reduced bone formation, which contributes to senile osteoporosis (Fig. 19.1) [13]. The underlying mechanism behind this abnormal decision in old ages is still under investigation. However, some achievements have been made in the form of identification of peroxisome proliferator-activated receptor γ (PPARγ) and core binding factor α1 (CEBPα/β/δ) as master regulators of differentiation toward adipogenesis, while osterix and runt-related transcription factor 2 (Runx2) toward osteogenesis [14].

In addition, recent evidence demonstrates that the senescence of BMSCs is also one important cause of senile osteoporosis (Fig. 19.2). Cellular senescence was first discovered by Hayflick in the 1960s, which is a phenomenon where the cells halt to divide in response to various stresses causing DNA damage and begin to secrete chemokines, cytokines, and extracellular matrix proteins, creating a toxic microenvironment called senescence-associated secretory phenotype (SASP) [15]. Such toxicity of SASP affects neighboring normal cells, resulting in further senescent cells accumulation, and, thus, damages the residing tissue [16]. The expression of senescence biomarker p16Ink4a is also enhanced [17]. Cellular senescence has been demonstrated to play a crucial role in age-related pathologies, such as atherosclerosis, type II diabetes, Alzheimer's, and Parkinson's diseases [18]. Like the senescence of other cells associated with age-related pathologies, the exact mechanism behind BMSCs senescence during senile osteoporosis is still unclear. However, telomere shortening, oxidative stress, and some genetic and epigenetic regulations have been found to contribute to BMSCs senescence during senile osteoporosis [19]. Therefore, both abnormal differentiation and senescence of BMSCs lead to the reduced number of osteoblasts in old ages, which result in decreased bone formation, thus, cause senile osteoporosis. To date, numerous medicines have been used to treat senile osteoporosis, but there are still some limitations, due to their side effects [20–24]. Therefore, in order to find out proper treatments, it is the focus of new era cell-based therapy research to uncover the molecular mechanisms behind the differentiation and senescence of BMSCs.

Aging and Bone Loss

In contrast to the well-known mechanisms of bone loss during menopause, which have been studied extensively, the triggers of an age-related transition from a steady state to one of negative net bone loss (both in women and men) are gradually elaborated. Bone remodeling is a continu-

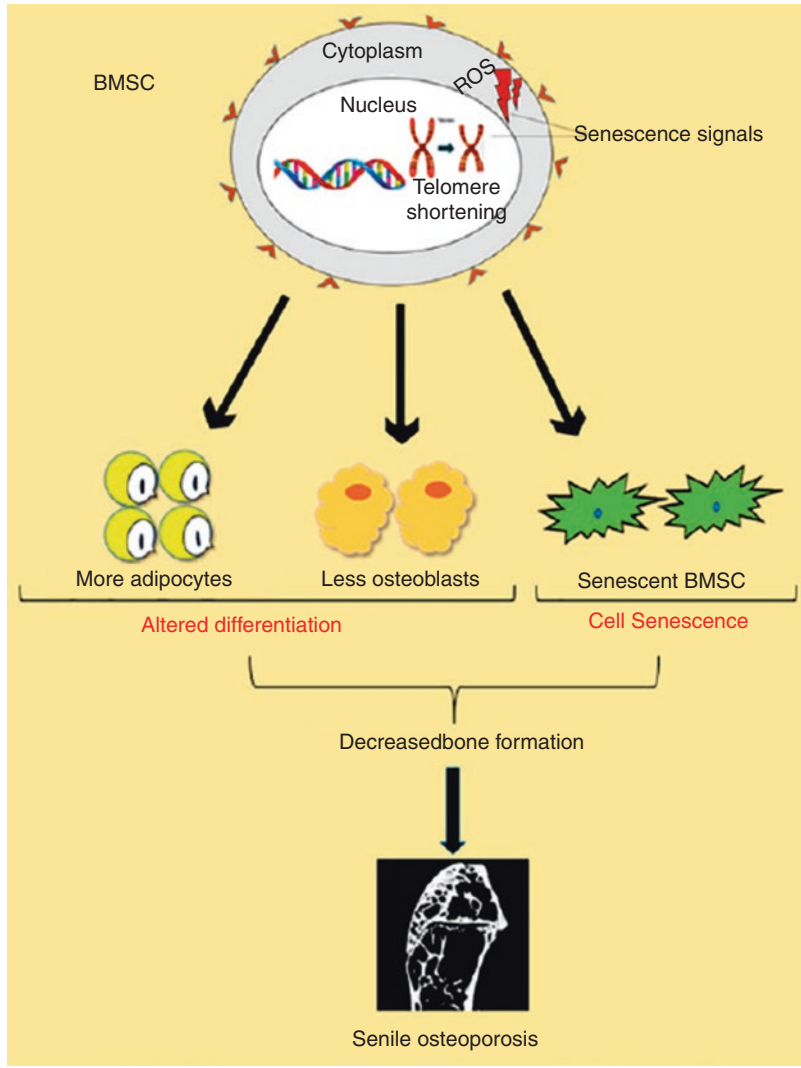

Fig. 19.1 Schematic diagram of differentiation and senescence of bone marrow stromal cells (BMSCs). (Quoted from [11] under open access scheme)

ous process throughout life. In the first three decades of life, bone turnover is coupled tightly to maintain a steady state between bone resorption and bone formation. With increasing age, bone remodeling is reduced leading to a negative bone balance at individual BMU sites. After the fourth decade of life, there is a reduction in the formation of periosteal bone, and at the same time, there is increasing number of remodeling units within endosteal bone resulting in a linear increase in endosteal bone resorption in both sexes. The overall consequences of these age-related changes are cortical thinning, increased cortical porosity, thinning of the trabeculae, and loss of trabecular connectivity, all of which reduce bone quality and consequently bone strength [25]. However, bone loss reflects the net result of all of the periosteal bone formed during aging minus all of the bone irreversibly removed from the endosteal surface, a process that seems to be independent of hormones and closely related to potential age-related mechanisms [26]. In terms of the effect of aging on periosteal bone formation, the increasing levels of endosteal bone loss are concomitant with steady levels of periosteal apposition somewhat compensating for the loss of bone mass. Therefore, cortical bone loss is less in men than in women because periosteal

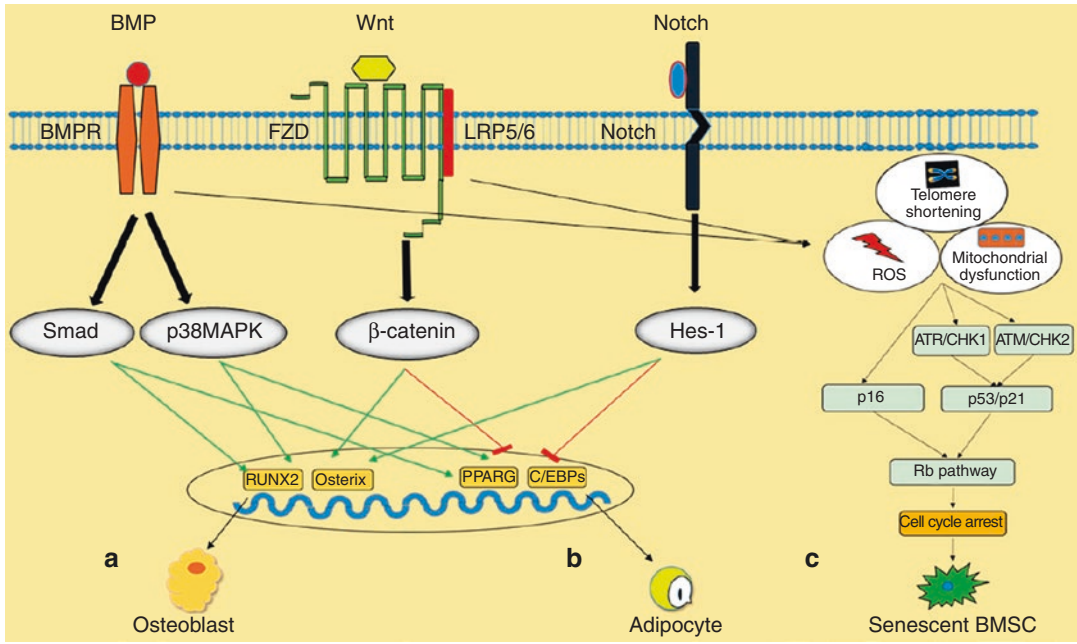

Fig. 19.2 The schematic program of signaling pathways involved in regulating differentiation and senescence of BMSCs. BMP, Wnt, and Notch signaling pathways regulate BMSCs differentiation into osteoblast (**a**) or adipocyte (**b**) either by promoting or inhibiting their respective transcriptional factors. Telomere shortening, accumulation of reactive oxygen species (ROS) or mitochondrial damage activate p53/p21 and p16/Rb pathways in BMSCs to push them into senescence (**c**) (BMSCs, bone marrow stromal cells; BMP, bone morphogenic protein; Wnt, wingless-type MMTV integration site; Notch, the notch signaling pathway is involved in regulating adipogenic and osteogenic differentiation of BMSCs; p53/p21 and p16/Rb, tumor suppressor retinoblastoma protein; these are the two interrelated key pathways involved in regulating senescence of BMSCs). (Quoted from [11] under open access scheme)

bone formation is greater and is independent of endosteal bone resorption [27].

These opposing processes are consistent with longitudinal and cross-sectional studies which showed a relatively slow rate of decline in areal bone mineral density (aBMD) in both sexes beginning at age 40 and continuing throughout the adult life [28]. Large decreases in lumbar spine volumetric BMD (vBMD) secondary to predominant vertebral trabecular bone loss beginning in the third decade and linear decrease in cortical vBMD in the wrist were also demonstrated in both sexes with advancing age [29]. The changes were greater in women than men, owing to accelerated bone loss in the menopausal stage. In terms of vBMD in the hip, a study by center and colleagues in 852 women and 635 men (60 years and older) without fractures reported an age-related decline in vBMD in the hip [30]. In addition, vBMD was more sensitive than areal BMD in older men and similar to that in women, in whom sensitivity was similar for both areal (73%) and estimated volumetric (78%) BMD cutoffs. This might explain why men and women have hip fractures at the same estimated femoral neck vBMD suggesting that vBMD can provide a useful single measure that could be used in both men and women [27].

Mechanisms of Age-Related Bone Loss

Role of Menopause in Women

It is well-known that sex steroids have significant effects on skeletal health. The cessation of ovarian function associated with reduced estrogen

levels at menopause is the start of rapid bone loss in women. During the menopause transition, serum 17b-estradiol levels decrease by 85–90%, and serum estrone levels decrease by 65–75% from mean premenopausal levels [31]. In fact, there may be a threshold level of serum bioavailable (non-sex hormone-binding globulin [non-SHBG]-bound) estradiol below 11 pg/ml at which trabecular and cortical bone loss occurs [28]. This phase of accelerated bone loss may persist for up to 10 years after menopause in most women.

The mechanisms of estrogen deficiency-related bone loss are multiple, and their relative importance in the pathogenesis of this process remains poorly understood [32]. In general, effect of estrogen deficiency on bone is the result of loss of restraint, and control estrogen has over mediators of bone resorption. Usually, estrogen may inhibit osteoclast formation and activity by increasing the production of osteoprotegerin (OPG) or transforming growth factor β (TGF-β) [33]. OPG is a soluble decoy receptor for receptor activator of nuclear factor kappa-B ligand (RANKL), and TGF-β induces osteoclast apoptosis [34]. In vitro and in vivo studies have also shown that estrogen suppresses RANKL production by osteoblastic cells and T and B lymphocytes [35, 36]. Estrogen also directly stimulates apoptosis of osteoclast precursor cells and decreases osteoclast precursor differentiation by blocking RANKL/macrophage colony-stimulating factor (M-CSF)-induced activator protein 1-dependent transcription by reducing c-jun activity [37]. Indirectly, estrogen may suppress the production of bone-resorbing cytokines such as interleukin (IL)-1, IL-6, TNF-α, M-CSF and prostaglandins [38]. Finally, estrogen is also capable of inhibiting the activity of mature osteoclasts by direct, receptor-mediated mechanisms. In addition to changes to estrogen levels, a reduction in ovarian inhibin B across the menopause transition and perimenopausal elevated follicle-stimulating hormone (FSH) also increase bone turnover [39].

Role of Sex Steroid Deficiency in Men

Although men do not have the equivalent of the menopause, total testosterone levels do decline with aging [40, 41]. More importantly, a number of studies have demonstrated that the biologically available fraction of testosterone and estrogen (i.e., the fraction not bound to sex hormone-binding globulin) declines markedly with aging in men, due in large part to a near doubling in sex hormone-binding globulin levels over life, combined with an inadequate compensatory response by the aging hypothalamic-pituitary-testicular axis to appropriately compensate for the declining bioavailable sex steroid levels [40, 41]. Thus, in a population-based sample of 350 men between the ages of 20 and 90 years, it was reported that bioavailable testosterone decreased over life by 64%, bioavailable estrogen by 47%, and sex hormone-binding globulin rose by 124% [40].

Although both serum-free or bioavailable testosterone and estradiol levels decline with age in men, it had generally been believed that because testosterone is the major sex steroid in men, it was the decrease in bioavailable testosterone levels that would be associated most closely with bone loss in men. However, Slemenda and colleagues [42] found that in aging 93 health men more than 55 years old, there was better correlations between serum estradiol and BMD than testosterone and BMD at various skeletal sites BMD (assessed by DXA). BMD correlated with serum estradiol levels (correlation coefficients, depending on the site, of +0.21 to +0.35, $p = 0.01–0.05$) and, inversely, with serum testosterone levels (correlation coefficients of −0.20 to −0.28, $p = 0.03–0.10$). Subsequent to this report, other similar cross-sectional studies have demonstrated significant positive associations between BMD by DXA and estrogen levels in men [40, 43–48], particularly circulating bioavailable estradiol levels. These cross-sectional findings have subsequently been validated by longitudinal data [49]. Another study [50] demonstrated that in aging men, estrogen is the dominant sex steroid regulating bone resorption, whereas both estrogen

and testosterone are important in maintaining bone formation.

Further studies looking at differential effects between estrogen and testosterone confirmed that estrogen deficiency was more important than testosterone deficiency in causation of bone loss in aging men [50, 51] and that the effects of estrogen on bone were independent of FSH [52]. Another large prospective study of older men again showed a low bioavailable estradiol level that was reported to be associated with significant increased fracture risk and that testosterone in the presence of high SHBG is associated with significant increased fracture risk when adjusted for estradiol levels [52]. Nevertheless, testosterone contributes to reduced fracture risk in men because of its influence on increasing bone size in men during growth and development [53, 54].

Bone Marrow Fat

The predominant feature of age-related bone loss is the accumulation of bone marrow fat at the expense of osteoblastogenesis [55]. This accumulation of marrow fat appears to be an active process independent of estrogen since it is evident during the third and fourth decade of life [56]. Biopsy studies with animal models [57] and humans [58] have consistently demonstrated a significant increase in marrow fat in aging bone. MRI studies have also demonstrated an age-related increase in marrow fat [59, 60]. In addition, there is an inverse relationship between marrow fat volume and bone volume that was independent of sex and correlated with the changes seen in people with osteoporosis [61]. Therefore, aging per se, independently of hormonal changes, appears to contribute significantly to bone marrow adipogenesis raising the possibility that senile osteoporosis is a type of lipotoxic disease [62]. Bone marrow adipocytes appear to exert a toxic effect on osteoblasts [63]. Cocultures of adipocytes and osteoblasts reveal that adipocytes inhibit osteoblast activity and survival, possibly secondary to the release of adipokines and fatty acids by the increased number of adipocytes within the bone marrow [64].

Mechanistically, the predominant differentiation of mesenchymal stem cells (MSCs) into adipocytes comes at the expense of osteoblasts [65]. A range of transcriptional factors has been identified to participate in adipogenic differentiation in BMSCs. The most well-known transcription factor is PPAR Y. In addition, early B-cell factor-1 (EBF-1), Twist-1, Twist-2, CCAAT/enhancer binding protein α (C/EBPα), chicken ovalbumin upstream promoter transcription factor II (COUP-II), PR domain containing 16 (PRDM16), sex determining region Y-box 2 (Sox2), and octamer-binding transcription factor 4 (Oct4) also play roles in regulating adipogenic differentiation of BMSCs [66]. PPAR Y belongs to the nuclear receptor (NR) superfamily of ligand-activated transcription factors that regulates the genes involved in adipocyte differentiation of BMSCs [67]. It has been demonstrated that upregulation of PPAR Y suppresses osteogenesis and promotes adipogenesis in BMSCs [68].

Further evidence of the lipotoxicity of marrow adipocytes on bone comes from the observation of PPARγ induction by thiazolidinediones. The use of thiazolidinediones in diabetic patients was associated with bone loss and higher incidence of fractures. The increasing levels of PPARγ induced by thiazolidinediones within the bone marrow not only affect bone formation but also induce bone resorption [69].

Secondary Hyperparathyroidism

Deficiency of calcium and vitamin D can contribute to secondary hyperparathyroidism [70]. Vitamin D deficiency is prevalent in the older population irrespective of latitude [71]. A low serum 25(OH)D concentration leads to a small decrease in serum 1,25-(OH)2D and calcium absorption which then stimulates an increase in parathyroid hormone (PTH) secretion. In addition vitamin D is required for osteoblastogenesis and bone formation [62]. The increased serum PTH subsequently increased osteoclastic activity and bone resorption, resulting in primarily cortical bone loss [70]. A chronic negative calcium balance state can also occur independently of

vitamin D as a result of age-related reduced intestinal calcium absorption [72] associated with reduced dietary intake. This deficiency, when not adequately compensated through dietary means or calcium supplements, contributes to physiological secondary hyperparathyroidism.

With age, a number of other factors can also cause an increasing PTH levels. Common factors include impaired renal function and the use of loop diuretics such as furosemide and estrogen deficiency. In women, there is some suppression of PTH secretion during the rapid phase of bone loss in early postmenopausal period. In the later stage, however, there is gradually increasing PTH secretion which increases bone turnover [73].

PTH secretion also increases in aging men, similar to what is seen in aging women. Normal circulating gonadal sex steroid levels in aging men may help to protect against bone resorption promoted by increased PTH levels. Thus, it has been more difficult to demonstrate a direct role for PTH in causation of age-related bone loss in men [74].

Other Contributing Factors

Body Fat Several clinical studies revealed a direct relation between the body fat and bone mass [75–78]. Furthermore, it was observed that serum leptin levels were increased in obesity and correlated positively with fat mass [79]. Subsequently the hormone mediating the relationship between fat mass and bone mass was demonstrated to be leptin. An in vitro study showed that leptin acted on human marrow stromal cells to enhance osteoblast differentiation and inhibited adipocyte differentiation [80]. Further animal studies also reported a central regulatory role of leptin [81, 82]. Another study, carried out on mice, revealed that in a loss of function of its receptor, leptin was shown to regulate bone mass accrual in vivo by acting through neuronal means [83].

Serotonin was also shown to regulate bone mass in rodents [84]. In humans the role for circulating serotonin in regulating bone mass was suggested by the findings from a study which included premenopausal and postmenopausal women [85]. Serotonin levels were inversely associated with body and spine aBMD and with femoral neck total and trabecular vBMD. Serotonin levels remained significant negative predictors of femur neck total and trabecular vBMD, as well as trabecular thickness at the radius, after adjusting for age and BMI.

Peak Bone Mass Attainment of peak bone mass is another factor contributing to later age-related bone loss. Those people who achieve a higher peak bone mass are less likely to develop osteoporosis later in life as age-related bone loss ensues, whereas those with low levels are at greater risk [86]. Numerous other factors such as corticosteroids usage; diseases such as malabsorption, anorexia nervosa, and idiopathic hypercalciuria; as well as behavioral factors such as smoking, alcohol abuse, and inactivity can also contribute to fracture risk in 40% of men and 20% of women in the older population [87]. Finally, sarcopenia, through reduced muscle loading on bone, also contribute to age-related bone loss [85, 86].

Bone Changes with Aging

Mechanical and Morphological Changes with Age

The components of bone are maintained in a balance to resist fracture while optimizing the weight of the skeleton. Stiffness (resistance to deformation) and strength (maximum stress to failure) are required to carry large loads, while toughness, or ductility, is required to absorb the energy from impact loads (Fig. 19.3). A shift in the balance to a higher tissue mineral content will generally yield stiffer but more brittle bones. It is important to recognize that changes in collagen structure may also contribute to increased brittleness due to the shift in its cross-linking profile, which not only stiffens the organic matrix but also affects the morphology of the mineral component [88]. It is also important to realize that,

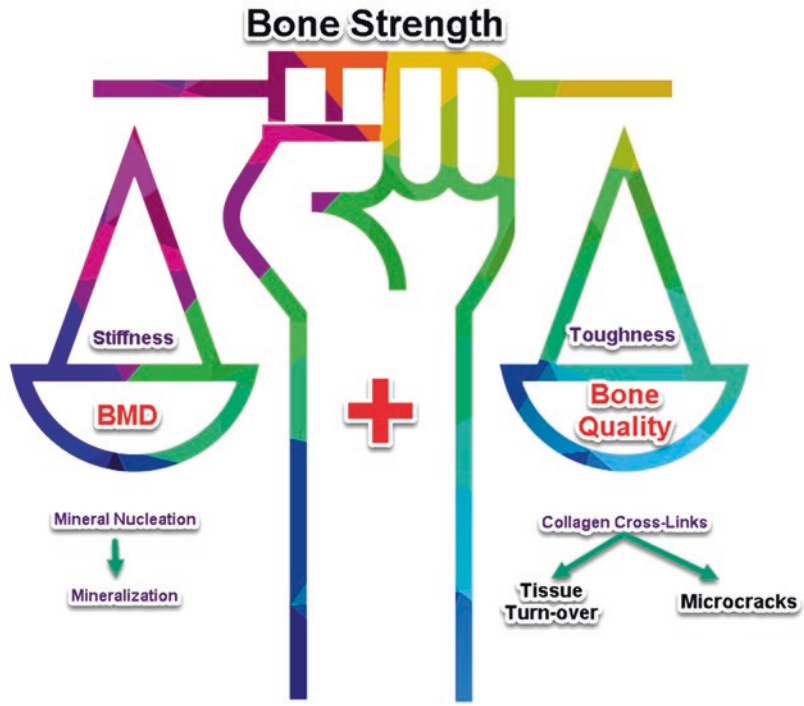

Fig. 19.3 Bone mineral density accounts for 60% of bone strength, while bone quality accounts for the rest. Collagen cross-linking is not just a determinant of bone quality; it also affects tissue turnover, microcrack propagation, and mineral nucleation, all of which influence bone strength

although bone mineral density (BMD) decreases in some fragility diseases such as osteoporosis [89], it is increased in others such as osteopetrosis [90]. Thus, it is the tissue-level properties in combination with the bone geometry that determine fracture risk.

The strength of bone as a tissue is determined by the amount of mineral that is there (usually provided clinically as a two dimensional BMD and a T- or Z-score comparing the value with that of healthy sex-matched 25-year-olds or with healthy age-matched control individuals, respectively) and the way that mineral is distributed relative to the forces applied to the bone [91]. With aging, sex-related differences in the distribution (geometry and morphology) become more pronounced, and these differences are believed to contribute to increased fracture incidence in the extremely elderly population [92].

The bone that is repetitively loaded (by normal activities of daily life, by extreme exercise, or in ex vivo experimental situations) develops cracks, initially at the submicron level, but eventually these cracks become visible, and if they are not repaired by the bone remodeling process, they can lead to failure [93]. The cause of the initial damage is hypothesized [94] to be either disruption of bone mineral crystallites, debonding at the mineral organic interface, disruption of collagen fibrils, or some combination of all three. Disruption of the structure of the bone cells that are embedded in mineral, the osteocytes, also can contribute [95]. The extent of this microdamage increases exponentially with age in humans [96], as the microcrack densities and lengths also increase [97]. It is likely that both the inability to repair the cracks [98] and their increasing propagation with age contribute to the reduced toughness of both cortical and trabecular bone [99].

Changes in bone morphology occur also with aging. Morphology describes the shapes (geometry) of bones, in terms of whether they are long bones (such as the femur and tibia), short bones (such as the bones of the feet and hands), or flat bones (such as the calvaria or breast bones). The morphological traits that determine strength are the sizes and the shapes of the bones [100]. There are compact areas (cortices) and spongy areas (trabecular) found in the ends of all long bones and in the central region of other bones.

Bones change in shape to facilitate their mechanical functions—being strong enough to withstand large forces and streamlined enough to minimize energy demands [100–102]. In the healthy individual, bone formation and resorption are in a state of balance. The variations in bone morphology are related to the changes in this balance between bone formation and bone remodeling. While these changes do not affect all bones equally, the general trends are similar. For example, in terms of hip structure, men and women older than 85 years of age have been reported to have the most "unfavorable" hip geometry, narrower cortices, and decreased resistance to bending/buckling [92]. Similar "unfavorable" properties also exist in tibias [103], and perhaps in other bones, but this might not be detected in bones that are loaded to a lesser extent than tibias and femurs. The reason for these morphological changes is related to genetics, the loading of the bones, and the activity of the cells.

Bone Protein Changes with Age

The organic matrix of bone consists of collagen (mainly type I) and approximately 5% (by weight) non-collagenous proteins. The collagen provides the flexibility (toughness) to the bone structure, which provides resistance to impact loading, and serves as a template for the oriented deposition of mineral crystals (Fig. 19.3). Collagen is secreted from the cell as triple-helical fibrils which self-associate to form larger fibrils and then fibers. Extensive posttranslational modifications (hydroxylation, glycation) occur before the fibrils associate within the cell. Once extruded from the cell, globular domains that help keep the fibrils soluble in the cell are cleaved. These fibrils are then stabilized and modified extracellularly by the formation of cross-links, based both on reduction of Schiff bases and aldol condensation products within and between the fibrils and by the addition of sugars to the collagen fibrils (advanced glycation end products) [104]. It is the cross-linking of the collagen fibrils that has the greatest impact on the strength of collagen fibrils.

There are two different categories of collagen cross-links, and they vary differently with age (Fig. 19.4). The cross-links that are formed enzymatically by lysyl hydroxylase and lysyl oxidase (enzymatic cross-links) connect the N- or C-terminus of one collagen molecule to the helical region of another. They then mature, with age, to trivalent pyridinoline (PYD) and pyrrole (PYL) cross-links, which connect two terminal regions and a helical region, thereby increasing

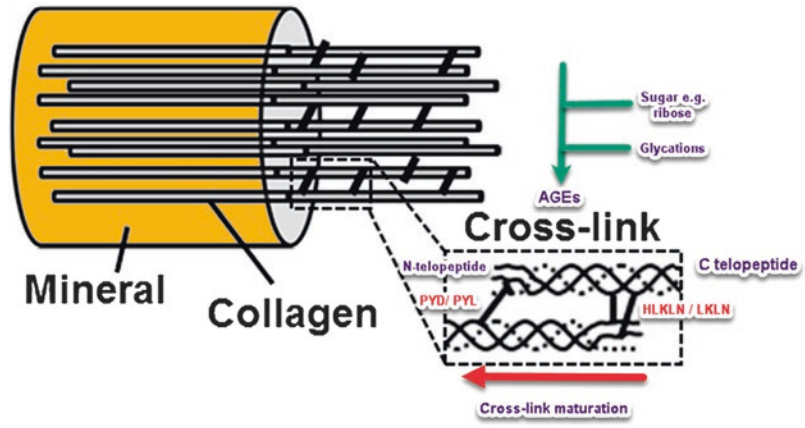

Fig. 19.4 Type I collagen is the major component of the organic phase. Enzymatic cross-linking binds neighboring collagen molecules to form collagen fibrils, which is a template of bone. Chronological formation of collagen cross-links: as collagen matures, reducible cross-links become non-reducible. Advanced glycation end products (AGEs) also accumulate between the helical parts of the molecules as the collagen persists in the tissue. Both contribute to the stiffening of the collagen matrix with age, which may contribute to bone tissue properties

the stiffness of the collagen [105]. Those formed by glycation- or oxidation-induced nonenzymatic processes and advanced glycation end products (AGEs), such as glucosepane and pentosidine, increase in formation as the collagen persists for longer times in the tissue. Limited numbers of nonenzymatic cross-links were found to be structurally related to the morphology of the trabecular bone [106].

Formation of cross-links affects both the way the collagen mineralizes and the way microdamage is propagated. There is also evidence to suggest that the accumulation of AGEs within bone tissue can be removed only by bone resorption and their presence increases osteoclast activity while decreasing formation by osteoblasts, thereby contributing to the fragility of bone with age [107]. Important features of the bone collagen network include the orientation of the collagen fibrils and the co-alignment of mineral crystals with the fiber axis of the collagen. Collagen orientation increases with tissue age [108]. Similar to the accumulation of nonenzymatic cross-links, orientation is an age-dependent feature.

There are also age-dependent changes in the expression and relative presence of the noncollagenous proteins [109]. Such proteins, reviewed in detail elsewhere, are for the most part multifunctional proteins important for regulating cell matrix and mineral matrix interactions, as regulators of mineralization, and for playing a role in signaling. Much of their multifunctionality is related to the extensive posttranslations they undergo (fragmentation, glycosylation/de-glycosylation, phosphorylation/dephosphorylation). Thus, it is important to note that not only do their distributions change with age but also the extent of their posttranslational modification decreases with increasing age [110, 111].

Decreased protein production with age was reported by Grynpas et al. [112], where a comparison of trabecular bone from human femoral necks showed that younger individuals (ages 18–37 years) had more extracellular bone matrix proteins than individuals aged 51–79 years and that there were increased bone matrix protein fragments in the older group.

Mineral Changes with Age

The mineral content of bone (also referred to as "mineralization" or "ash content") increases with age, and classic studies have shown that the breaking stress of bone increases exponentially with ash content, while the toughness of bone (resistance to fracture or the inverse of brittleness) declines as the ash content reaches a maximum [113]. The mineral found in the bone is an analogue of the natural occurring mineral, hydroxyapatite [Ca10(PO4)6(OH)2]. Bone mineral crystals contain a variety of inclusions and substitutions that also vary with age. Prevalent among these substituents is carbonate, which substitutes for hydroxyl and phosphate within the apatite surface and the crystal lattice [114]. Age-dependent changes in bone mineral composition with increasing animal or tissue age include (1) increasing mineral content, (2) increasing carbonate substitution, (3) decreasing acid phosphate substitution, (4) increasing hydroxyl content, (5) increasing Ca/P molar ratio, and (6) increasing crystal size and perfection [88].

Changes in BMD with Aging

Aging causes changes in cortical bone microstructure and higher bone porosity, and age correlates negatively with BMD and bone strength [115]. Fragility is the result of bone loss and degradation of bone structure [116]. Assessment of Haversian canal and osteon area produced by an increase in osteon-remodeling rates with age indicates an increase in intracortical porosity, which may be used as an indicator for the diagnosis of osteoporosis and age-related risk of fracture [117, 118]. Moreover, cortical BMD aging changes vary by skeletal site, and the severity of BMD decline also depends on tissue mineralization, defined as the percentage of BM in the solid phase, along with the aforementioned porosity [115]. An early study conducted on humeral cortices from cadavers noted that cortical porosity increased with age, from 4% to 10% from 40–80 years, yet BMD did not demonstrate age-related variation [119]. Riggs et al. [120] found

overall BMD reduction of 47% in the spine and 30–39% in mid- and distal radii across the human life span. Especially marked decreases were seen in females >65 years of age. In a large South Korean sample, BMD demonstrated an accelerated phase of decline for the femoral neck during early adulthood. Therefore, differences in normative values for different populations and other extrinsic influences should be considered when assessing and comparing age trajectories for BMD values [121]. Moreover, discrepancies in results reported by different studies might be due to the variables used (measurements of BMD corrected for vascularization and resorption spaces) and other factors, such as skeletal site and methodological approaches, which may also partly account for different outcomes.

In general, an increased skew of the balance of bone remodeling toward bone resorption produces a decrease in BMD and bone strength in males and females [115, 122]. Peak bone mass will be reached at different ages depending on the skeletal site, with the earliest age being 14–18.5 years for the hip in both sexes [123]. Adult bone strength depends directly on skeletal development and growth during the first decades of life. Males tend to reach peak bone mass at an older age than females, with higher bone content and density being accomplished at a later maturational stage [124]. Both sexes gain 40% of their skeletal mass between 12 and 16 years of age. However, males will demonstrate a slight increase in aBMD at the lumbar spine and mid-femoral shaft in the late years of adolescence, while females will not [125]. Underlying differences in physiological bone growth and peak bone mass between males and females play an important role in BMD sex variation.

After reaching peak bone mass at the end of skeletal maturation, BMD begins to decline. BMD values later in life represent the influence of skeletal development and changes in the rate of bone loss, with both factors being determinants of osteoporosis development in postmenopausal females [126]. Estrogen deficiency causes an increase in remodeling and subsequent bone loss in this group, with low estrogen levels also reducing skeletal tissue formation in response to mechanical stimuli [127]. At older ages, higher incidence of osteoporosis is seen in females in comparison to males, regardless of females' hormonal status, linking the disorder not only to hormonal deficiency but also to lower female skeletal mass reached at puberty or inherently higher BMD loss with aging [128, 129]. Nonetheless, skeletal fragility also increases with age in males, as demonstrated by the increasing frequency of minimal-to-moderate trauma associated with other risk fracture factors, such as previous trauma and bone strength, among others [130]. For example, in individuals >55 years old, BMD differences in weight- and non-weight-bearing bones have been correlated with variations in age and sex [131]. Moreover, males in the same age cohort present bone failure (fracture), especially on the lumbar spine, at higher BMD measures than females [124]. Sex differences in bone loss due to age exhibit regional variation. Warming et al. performed a cross-sectional and longitudinal study on healthy subjects (not suffering from metabolic disease). The cross-sectional data demonstrated a similar percentage of bone loss at different sites (hip, spine, ultradistal forearm) in males and females aged 20–80 years, with the exception of the distal forearm, where females had a 50% greater bone loss in old age compared to males. Cross-sectional and longitudinal data for females both support minimal premenopausal bone loss only at the hip, an obvious postmenopausal bone loss at the distal forearm and hip that lasts throughout postmenopausal life, and a bone loss at the lumbar spine that is only found in the first decade after menopause [132].

Males in the same study exhibited continuous bone loss at the hip throughout life, whereas an accelerated bone loss was found at the distal forearm. This research reported some discrepancies between cross-sectional and longitudinal data but in general was in agreement with previously published studies [133, 134]. In order to ensure accurate assessment of BMD values, age- and sex-related standards might be adjusted to body size, peak bone mass, skeletal size, and, as shown in the next section, population-specific references [135, 136].

Approach to Management of Osteoporosis in the Older Adults

Treatment Goals The goals of treatment for patients with osteoporosis include bone strengthening, optimizing physical function, prevention of new fractures, and decreasing symptoms of prior fractures [137]. Non-pharmacological interventions should be advised to all patients who have osteoporosis. Inactivity and immobility promote reduced bone mass, and even moderate (or more vigorous) walking programs help reduce the risk of hip fractures [138]. Those who are at high risk of falls may benefit from a home occupational therapy safety assessment. Smoking cessation and moderation of alcohol intake are also recommended. It is estimated that one-third of falls can be prevented with fall prevention strategies. Among the particular exercise programs, challenging balance training (particularly tai chi) may help to reduce the risk, fear, and number of falls, [139, 140] core stability exercises are recommended for those with a prior vertebral fracture, and resistance training (appropriate for functional capacity) is recommended even for those who are at risk for osteoporosis. Combining weight-bearing exercises with strength training will help prevent bone loss [140]. A Bayesian approach revealed that hip protectors decrease the risk of incident hip fractures in elderly nursing home residents [141], and these protectors should be considered in patients at high risk for falls**.**

Medications

Based on the mechanisms underlying age-related bone loss, the main goals of therapy should include the inhibition/restriction of osteoclastic activity, the enhancement of osteoblastic activity, and the regulation of bone marrow adipogenesis. In addition, contributing factors should be corrected or minimized. Currently the main classes of agents are antiresorptives, which suppress osteoclastic activity, and anabolic agents, which target osteoblasts (Table 19.1).

Calcium and Vitamin D

The recommendations regarding calcium and vitamin D supplementation may cause confusion. With reference to vitamin D, most of the circulating vitamin comes from exposure to sunlight, not from diet. Certain factors, such as use of sunscreen, darker skin color, and being elderly, decrease the efficiency of vitamin D production in the skin. The targeted level for a serum 25-hydroxyvitamin D level of 75 nmol/L likely cannot be maintained during the winter time in the western world without supplementation [142]. In concordance, the American Geriatrics Society Workgroup on Vitamin D Supplementation for Older Adults concluded that a serum 25-hydroxyvitamin level of 75 nmol/L should be a minimum goal for elderly adults (particularly frail ones) [143]. For every 1000 IU of vitamin D3, the average serum 25-hydroxyvitamin D level will rise by approximately 20 nmol/L [144]. In elderly patients at moderate risk for vitamin D deficiency, we typically supplement with 1000 IU of vitamin D3 daily. Higher doses may be required, and doses up to 2000 IU a day are considered safe. For elderly patients who would be at risk for fractures due to vitamin D deficiency (typically those with comorbid conditions that inhibit absorption of the vitamin D supplement or patients with ongoing bone loss or recurrent fractures despite adequate treatment), higher supplemental doses may be required, and serum 25-hydroxyvitamin D levels can be used to guide dosing.

There has been extensive discussion regarding the timing and necessity of measuring serum vitamin D levels. Testing should be conducted 3 months after initiating therapy and should not be repeated once the recommended level of 75 nmol/L is reached (unless there is a change in clinical status). Ongoing bone loss or new fragility fractures would be considered a change in clinical status. The American Geriatrics Society Workgroup recommends monitoring of serum 25-hydroxyvitamin D levels in individuals who take medications that bind vitamin D, who are obese, who have malabsorption syndromes, or who limit their overall vitamin D intake [143].

Table 19.1 Pharmacological effect of osteoporosis treatments on the typical features of age-related bone loss

Bone cells	Bisphosphonates	SERMs	Denosumab	Parathyroid hormone	Romosozumab	Vitamin D
Osteoblasts	↑ Differentiation ↑ Activity ↓Apoptosis			↑ Activity ↑ Survival ↑ Differentiation	↑ Activity	↑ Activity ↓ Differentiation ↓ Apoptosis
Osteoclasts	↓ Differentiation ↓ Activity ↑ Apoptosis	↓ Differentiation ↓ Activity	↓ Differentiation ↓ Activity ↑ Apoptosis	↑ Activity		↑ Activity
Adipocytes	↓ Differentiation			↓ Differentiation		↓ Differentiation ↑ Trans-differentiation to osteoblasts

The daily total intake of elemental calcium should be 1200 mg. When possible, patients are encouraged to achieve their daily target through calcium-rich foods but acknowledge that not all older adults can, or want to, change their diet. The evidence behind vitamin D and calcium supplementation is strong. It increases bone mineral density, reduces falls, and decreases the risk of hip and non-vertebral fractures in elderly, institutionalized individuals [145]. Community-based clinical trials with calcium and vitamin D supplementation have poor compliance and tend to be negative [146], though a 2005 meta-analysis on vitamin D supplementation of 700–800 international units a day did reduce the risk of hip and non-vertebral fractures in both ambulatory and institutionalized individuals [147]. On the other hand, most trials that examine high doses of vitamin D are not properly designed to assess long-term harms [148]. The studies that investigated whether vitamin D and/or calcium supplementation led to an increased risk of certain malignancies were either inconsistent or not relevant to our patient population [149]. Table 19.2 shows the threshold levels of 25-hydroxy-vitamin D in the serum and their impact on bone health.

Table 19.2 Threshold levels of 25-hydroxy-vitamin D in the serum and their impact on bone health

Serum 25-OH-D level	Definition	Impact on bone health
<25 nmol/L (<10 ng/L)	Vitamin D deficiency	Mineralization defects
<50 nmol/L (<20 ng/L)	Vitamin D insufficiency	Increased bone turnover and/or PTH
50–75 nmol/L (20–30 ng/L)	Vitamin D sufficiency/ optimum	Neutral effect (bone turnover and PTH normalized), desirable benefits on fracture, falls, and mortality
>75 nmol/L (>30 ng/L)	Normal	Desirable target in the fragile individuals or oldest old Due to the optimal benefits on fracture, falls, and mortality
125 nmol/L (50 ng/L)	Upper limit of adequacy	Possibility of adverse effects above this level

Adapted from Rizzoli et al. [148]

The purported association between calcium supplementation and cardiovascular disease is controversial. One reanalysis of the Women's Health Initiative database revealed an increased hazard ratio for those patients who were assigned to calcium supplementation (and were not taking calcium supplements at the time of randomization) [150]. It is important to determine how much calcium a patient is receiving in their diet before deciding on the supplementation dose. For women over the age of 50 and men over 70 years of age, an appropriate recommended dietary intake is 1200–2000 mg/day of elemental calcium [151]. Dietary calcium intake may have less adverse cardiovascular effects than supplements because they are taken in less concentrated boluses and are absorbed more slowly since they are eaten with fat and protein [152].

Antiresorptive Osteoporosis Therapy

Who Need to Be Treated The decision to initiate antiresorptive therapy depends on the patient's overall risk. *There are two main authorities, the national osteoporosis foundation and the national osteoporosis guideline group (NOGG) which have published intervention guidelines to guide osteoporosis therapy intervention* (Table 19.3). Those who are at high 10-year fracture risk should be treated. Those who fall into the moderate-risk category should be managed on a case-by-case basis. They should undergo a comprehensive evaluation to determine if there are any other factors that might lead the physician to consider therapy (e.g., repeated falls, disorders associated with osteoporosis, women receiving steroids or aromatase inhibitor therapy). Patients who are in the low-risk category generally do not require any further therapy, aside from lifestyle modifications (exercise, smoking cessation, falls prevention) in addition to optimization of their calcium and vitamin D intake (diet and supplemental).

Table 19.3 Shows a comparison between the osteoporosis intervention guidelines as suggested by the national osteoporosis foundation (NOF), US and National Osteoporosis Guideline Group (NOGG), UK with a focus on older individuals

	NOF	NOGG
BMD	All women aged ≥65 years and Men aged ≥70 years should be offered a DXA scan Initiate therapy in those with T-scores ≤2.5 (at femoral neck, total hip or lumbar spine)	Case finding using FRAX in all postmenopausal Women and men aged ≥50 years That risk of fracture should be expressed as an absolute risk, i.e., probability over a 10-year interval
Vertebral imaging	Women aged ≥70 years Men aged ≥80 years	Vertebral fracture assessment should be considered in postmenopausal women and older men if there is a history of ≥4 cm height loss, kyphosis, recent or current long-term oral glucocorticoid therapy, or a BMD T-score ≤−2.5. It should also be considered in individuals with a history of non-vertebral fracture after the age of 50 years
FRAX	Its use is warranted in patients with low femoral neck BMD	NOGG intervention thresholds are based on FRAX probability

NOF: National Osteoporosis Foundation (USA) [NOF's Clinician's Guide to Prevention and Treatment of Osteoporosis. https://my.nof.org/bone-source/education/clinicians-guide-to-the-prevention-and-treatment-of-osteoporosis]

NOGG: National Osteoporosis Guideline Group (UK) [NOGG 2017: clinical guideline for the prevention and treatment of osteoporosis. https://www.guidelines.co.uk/musculoskeletal-and-joints−/nogg-osteoporosis-guideline/453250.article]

Bisphosphonates, the most commonly used antiresorptive therapy, are generally well tolerated, and, for most patients who suffer from osteoporosis, the treatment benefits outweigh the risks [153]. The bisphosphonates reduce the incidence of new vertebral fractures by up to 50%, non-vertebral fractures by 20%, and hip fractures by 40% [154]. The time to onset of benefit for the bisphosphonates is around 6 months for clinical vertebral fracture prevention and 18 months for hip fracture prevention [155].

In postmenopausal women, alendronate, risedronate, and zoledronic acid are all appropriate first-line therapies for the prevention of vertebral and non-vertebral fractures (including hip). The choice of which particular medication to use can be determined by patient preference. Risedronate and alendronate are available orally; they both can be taken daily or weekly, with risedronate also having a once-monthly pill. Risedronate also has a once-weekly pill that can be taken with food. Zoledronic acid is available as a once-yearly intravenous infusion.

An important issue is the long-term safety profile of bisphosphonates. Bisphosphonate binding to skeletal bone is unsaturable, so that the medication accumulates over time and may be released even after therapy has been stopped [156]. The likelihood of atypical femur fractures is low, even in women who have received treatment for up to a decade [153]. Nonetheless, these concerns have led to the idea of a drug holiday after several years of therapy.

Not much data exist to guide decisions regarding duration of drug holidays. For those who have moderate 10-year risk of fracture, it may be reasonable to discontinue intravenous bisphosphonate use after 3 years and oral bisphosphonate use after 5 years. So long as there has not been a significant loss of bone mineral density (or fracture) on subsequent testing, the holiday may be continued for up to 5 years. The FLEX trial showed that 10 years of alendronate therapy did not significantly reduce the risk of non-vertebral fractures, compared to 5 years of alendronate therapy. The benefit in continuing alendronate therapy for 10 years occurs in the population whose femoral neck T-scores are −2.5 or less, who have a lower incidence of novel vertebral fractures [157]. Patients who are at high risk for future fractures should be treated for up to 10 years before a shorter drug holiday can be offered (typically 2 years at the most). Patients should be monitored for significant bone loss or

novel fractures. The other option is for those at high risk for future fractures and who are receiving antiresorptive therapy to switch to bone formation therapy after 5–10 years of use. For all patients, regardless of risk, the decision of when to hold bisphosphonates and for how long should be made on a case-by-case basis.

Denosumab is a fully human monoclonal antibody RANKL inhibitor. This ultimately prevents the differentiation and function of osteoclasts and leads to increased bone mass [158, 159]. It is administered as a subcutaneous injection every 6 months. For patients who cannot take oral bisphosphonates (typically due to gastrointestinal side effects or the need to take on an empty stomach), denosumab has been shown to have similar bone mineral density improvements as alendronate [160].

Unlike bisphosphonates, which incorporates into bone, denosumab does not, and cessation of therapy may lead to a more rapid decline of bone mineral density compared to bisphosphonates. A 2012 review showed that denosumab is efficacious and safe as a first-line treatment for postmenopausal women, particularly those who cannot take bisphosphonates [137]. While rare, cellulitis was significantly more common in patients receiving denosumab compared to placebo; it occurred in 12 out of 3886 patients in the FREEDOM trial, compared to one in 3876 patients in the placebo arm [158]. Atypical femur fractures, although rare, have also been observed with denosumab therapy.

HRT and SERMs have largely fallen out of recommendation in recent years. Although hormone therapy reduces vertebral, non-vertebral, and hip fractures, this is offset by increased risk of breast cancer and cardiovascular diseases [85, 86]. While raloxifene, the only SERM-approved for the prevention and treatment of postmenopausal osteoporosis, only has vertebral fracture efficacy [87] and is associated with increased risks of venous thromboembolic events and hot flushes.

Calcitonin Calcitonin nasal spray was withdrawn from several countries/markets after a review of risks and benefits. Those who were treated with nasal calcitonin had a low, but observable, increased rate of malignancy compared to placebo. The subcutaneous form of calcitonin is still available in some markets (e.g., Canada). Calcitonin is not a first-line treatment medication for osteoporosis and does not decrease the risk of hip or non-vertebral fractures [161].

Osteoanabolic Agents

PTH and PTHrP are encoded by related genes and bind to the same receptor, PTH 1 receptor (PTH1R) [162]. PTH (1–84) is an 84-amino acid polypeptide, and PTHrP (1–34) is a 34-amino acid polypeptide. PTH is secreted by the parathyroid gland and plays a fundamental role in calcium homeostasis. PTH increases serum calcium concentrations via promotion of osteoclast-mediated calcium release from bone, distal renal tubular calcium reabsorption, and intestinal calcium absorption. PTHrP is produced by many different tissues and exerts its effects via paracrine actions. Like PTH, PTHrP stimulates bone resorption and renal tubular calcium reabsorption, but in contrast to PTH, PTHrP plays a minor, if any, role in intestinal calcium absorption. PTHrP is additionally involved in fetal calcium regulation, placental calcium transfer, and lactation [163, 164].

Teriparatide and abaloparatide, like PTH and PTHrP, enact their effects via binding to PTH1R. Teriparatide, recombinant human PTH [PTH (1–34)], comprises the first 34 amino acids of the N-terminal end of PTH. Abaloparatide [PTHrP (1–34)] is a 34-amino acid synthetic analog of PTHrP that is identical to PTHrP at amino acids 1–22 but differs in amino acids 23–34. These differences were intentionally constructed to maximize the stability and anabolic activity of abaloparatide [12]. Abaloparatide shares 76% homology with PTHrP and 41% homology with PTH [165].

Whereas continuous exposure to PTH or PTHrP results in increased bone resorption, intermittent administration of PTH (1–34) or PTHrP (1–34) leads to an anabolic window and enhanced bone formation [166].

PTH increases bone formation through several actions, including increasing commitment of mesenchymal stem cells (MSCs) to the osteoblast lineage, increasing osteoblast maturation and possibly life span, and reducing the osteocyte production of sclerostin to further stimulate bone formation. PTH stimulation of osteoblastogenesis also increases RANKL production, which then stimulates osteoclast maturation and activity, increasing bone remodeling overall; however, the overall effect is a positive formation balance [167].

The anabolic effect of exogenous PTH was first reported in humans several years ago. Paired bone biopsies from a small group of patients receiving teriparatide by daily sc injections for 6–24 months demonstrated substantial increases in iliac trabecular bone volume, with evidence of new bone formation [168].

Teriparatide has shown vertebral and non-vertebral fracture reduction in postmenopausal women with osteoporosis [169]. In men with osteoporosis, those who received teriparatide and who may have received follow-up antiresorptive therapy had a decreased risk of moderate and severe vertebral fractures [170]. Teriparatide also has efficacy in glucocorticoid-induced osteoporosis. Compared with alendronate, teriparatide induced earlier and greater gains in BMD at the lumbar spine, and total hip and was more effective in preventing new vertebral fractures [171]. As for PTH(1–84) efficacy against vertebral fractures in postmenopausal women has been demonstrated [172].

Osteoporosis by Aiming at Bone Marrow Stromal Cells (BMSCs)

In old ages, BMSCs either differentiate into more adipocytes than osteoblasts or assume senescence, which ultimately results in senile osteoporosis. Therefore, in order to treat senile osteoporosis, it is required to use the strategies in what BMSCs can be stimulated either to differentiate into more osteoblasts than adipocytes or be eliminated their senescence. To date, numerous molecules including parathyroid hormone (PTH 1–84) or only its N-terminal fragment teriparatide (PTH 1–34), bisphosphonates, tetracycline, cationic peptides, and antibodies like denosumab and romosozumab have been used in the treatment of senile osteoporosis [20–24]. However, most of them are limited either, due to their severe side effects or inhibition of just bone resorption without decreasing bone regeneration. Therefore, in order to reduce such limitations, there is the need of using cell-based therapy strategy, for which BMSCs can act as an ideal cell source, due to their self-renewing and differentiation ability into various types of cells. In addition, easy isolation with high yields from different tissues and immunosuppressive and immune-privileged properties of BMSCs also make them the preferable cell source in cell-based therapies [173].

In order to treat senile osteoporosis, several researchers have reported the successful transplantation of BMSCs using animal models. Transplanted BMSCs serve in bone formation either by allocating damaged areas to differentiate into osteoblasts or assume paracrine mode, due to which they secrete specific growth factors to make a favorable environment for the nearby cells to repair the degenerative tissue [174]. Ichioka et al. injected normal allogeneic BMSCs intra-bone marrow into the senescence accelerated mouse prone 6 (SAMP6) mice, naturally prone to senile osteoporosis in their early lives. They demonstrated that the injected normal BMSCs were able to prevent the senile osteoporosis in SAMP6 mice with an increase in trabecular bone mass and decline in BMD loss [175]. Takada et al. also treated osteoporosis after it occurred in aged SAMP6 mice by injecting normal allogeneic BMSCs locally into their bone marrow. After the clinical examinations, no signs of senile osteoporosis were found, hence, succeeded in proving their hypothesis [176]. In another experimental procedure, when BMSCs isolated from healthy rats were injected into the

bone marrow of femurs of osteoporotic female ovariectomized rats, a quite increase in the bone mass of femur was observed after examination [177]. Similarly, Kiernan et al. also found an increase in bone formation when they injected systemically normal allogeneic BMSCs into the bone marrow of senile osteoporotic mouse model, giving a clue toward their applications against human senile osteoporosis [178].

Certain factors, microRNAs and long noncoding RNAs have also been recognized to play significant roles in treating senile osteoporosis by stimulating BMSCs to differentiate into more osteoblasts than adipocytes. Suppression of ectopic viral integration site-1 (Evi1) gene through RNA interference in rat BMSCs resulted in increased osteogenesis and decreased adipogenesis, suggesting Evi1 as a potent target for targeting osteoporosis [178]. Huan et al. have reported enhancer of zeste homology 2 (EZH2) factor as a competent therapeutic target for enhancing bone formation during osteoporosis as its suppression led to increased osteogenesis rather than adipogenesis [179]. Recently, Zhou et al. uncovered the role of orcinol glucoside (OG), a constituent of traditional Chinese medicine, in promoting bone formation. They reported that OG was able to revert the BMSCs differentiation fashion of more into adipocytes than osteoblasts in old ages through Wnt/catenin signaling pathway, thus may act as a novel therapeutic agent against senile osteoporosis [180]. Li et al. found the increased bone formation and decreased fat accumulation after injecting aptamer-antagomiR-188 into the bone marrow of osteoporotic aged mice. The aptamer-antagomiR-188 actually inhibited miR-188, whose overexpression is actually responsible for reducing osteogenesis and increasing adipogenesis [181]. Let-7, a miRNA family, has also been distinguished to promote osteogenesis and decline adipogenesis in BMSCs [182]. Very recently, Zhao et al. demonstrated that miR-21 possesses the ability to stimulate the osteogenic differentiation of BMSCs by finding the role of miR-21 inhibitor in inhibiting BMSCs differentiation into osteoblasts [183]. Recently, long noncoding RNA Bmncr was found as key regulator in promoting osteogenesis and inhibiting adipogenesis in mice during aging, suggesting it to be a therapeutic target against senile osteoporosis in future [184]. Chen et al. reported that overexpression of lncRNA XIST led to the inhibition of osteogenic differentiation of BMSCs in 3-week-old Sprague Dawley rats [185]; thus, its inhibition through specific inhibitor can revert the phenomenon and can treat the senile osteoporosis. Most recently, Zhu et al. have identified lncRNA HOXA-AS2 as a key positive regulator in causing osteogenesis in BMSCs through NF-κB signaling inactivation [186], which may act as a new therapeutic target against senile osteoporosis.

Different approaches have also been used to eliminate the senescence of BMSCs and, thus, treat senile osteoporosis. Elimination of senescent cells is of much importance regarding bone mass and strength. In order to uncover such importance, Farr et al. used some genetic and pharmacological procedures to eliminate the senescent cells. They found that activating INK-ATTAC caspase 8 in senescent cells or treating senescent cells with JAK inhibitor or senolytics increased bone mass and bone strength in mice with the bone loss [187]. A senolytic drug, ABT263, can also reduce senescence-associated factors and, hence, can act as a good therapeutic drug against senile osteoporosis [188]. Gao et al. delivered tetramethylpyrazine (TMP) locally into the bone marrow of aging mice with established senescent BMSCs' microenvironment; a significant reduction was found in senescent phenotype via modulating Ezh2-H3k27me3, suggesting TMP as a potent local eliminator of senescent BMSCs in age-related bone loss [189, 190]. Sun et al. suppressed the expression of NADPH oxidase, which is mainly involved in ROS formation in BMSCs; they found a significant increase in osteoblasts differentiation of BMSCs. Moreover, they also found an increase in bone formation after treating SAMP6 mice with apocynin for 3 months, hence, declared as a competent therapeutic agent against age-related bone loss. More recently, Zhou et al. demonstrated that resveratrol was able to attenuate senescence and promote osteogenic differentiation of BMSCs by

inhibiting AMPK activation/ROS inhibition signaling pathway in aged mouse, suggesting resveratrol as a novel therapy against senile osteoporosis, due to its inhibiting effects on ROS formation in BMSCs [191].

When to Repeat the BMD Testing

The response to therapy with any osteoporosis medication is often examined by repeating bone mineral density tests, although the bone density response may vary with different therapies. The optimal time to repeat bone density tests is 1–3 years initially. Ideally, testing should be performed at the same laboratory for each visit, to decrease variability between machines.

Once bone mineral density is stable, the testing interval can lengthen, allowing for 5–10 years for those who are low-risk and do not have a reason for potential fast bone loss.

The Onset of Anti-fracture Efficacy

Including women who have sustained an osteoporotic fracture, osteoporosis treatments have been frequently reported to be under-prescribed, one reason for this could be a reluctance of clinicians to prescribe treatment because of doubts they might have over the effectiveness of treatment in a short period of time [192]. However, as shown in Table 19.4, a number of RCTs have demonstrated clinically significant benefits in terms of fracture reduction within the first year of treatment. Thus, even in an oldest old patient population, it would seem that starting treatment with an anti-osteoporosis would, by and large, have time to exert a beneficial effect on bone.

Safety of Anti-osteoporotic Drugs

In general, the safety margins of anti-osteoporotic drugs are very good. Over the long term, osteoporosis treatments seem to maintain effectiveness and remain safe [202]. The guidelines recommend treatment re-evaluation every 3–5 years [203, 204]. For some patients, a "drug holiday" might be advocated [205]. The main issues concerning drug therapy in the oldest old include reduced intestinal absorption (thus lower bioavailability of oral treatments), metabolism (slower metabolic rate), excretion (impaired renal function), tissue sensitivity (skin effects), concomitant deficiencies (e.g., reduced endocrine responses to growth hormone (GH) and PTH), and concomitant treatments (invoking interactions for drug metabolism as well as target organ effects).

The large RCTs and meta-analyses have shown that under relatively stringent conditions, the adverse events tend to be mild to moderate and reversible. A few pharmacovigilance reports have associated some anti-osteoporotic agents with rare but severe events [206, 207].

Table 19.4 The beneficial effect after the first year of treatment with anti-osteoporotic treatment in older populations which is generally seen in the first year of treatment

Osteoporosis therapy	Type of vertebral fracture	% risk reduction	1-year fracture rates (treated vs placebo)	References
Alendronate	Symptomatic	59	NA	[193]
Risedronate	Symptomatic	69	NA	[194]
Risedronate	Morphometric	81	2.5 vs 10.9%	[192]
Zoledronate	Morphometric	60	1.5 vs 3.7%	[195]
Zoledronate (men)	Morphometric	68	0.9 vs 2.8%	[196]
Raloxifene	Symptomatic	68	0.3 vs 0.8%	[197, 198]
Denosumab	Morphometric	61	0.8 vs 2.2%	[199]
Parathyroid hormone	Morphometric	65	0.8 vs 4.2%	[200]
Romosozumab	Symptomatic	55	1.7 vs 3.7%	[201]

Gastrointestinal Effects

The problems of upper GI events with oral bisphosphonates, including irritation of the esophagus, difficulty swallowing, pain on swallowing, and heartburn, are well-known and have been reported and documented earlier [208]. The risk of upper GI events is lower when the instructions regarding how to take the medication are properly followed (including an appropriate quantity of water and post-dosing postural positioning) [209]. In placebo-controlled trials, the reported rates of upper GI events in the active and control arms are often very similar. For example, in the FIT trial, such an event was reported by 47.5% in the alendronate (10 mg/day) group and 46.2% of the placebo group [210]. In this trial and many others involving bisphosphonates, women with active ulcers or other GI symptoms requiring daily treatment were excluded, and it is likely that the dosing instructions were well explained. Patients with preexisting upper GI disorders, such as esophageal stricture, achalasia, or poorly controlled gastroesophageal reflux disease, should, preferably, not be treated with oral bisphosphonates.

Generic versions of bisphosphonates are associated with higher rates of GI events and greater risk of treatment discontinuation, and this is probably mainly due to their faster disintegration times [211]. Branded formulations allowing weekly or monthly dosing are associated with lower rates of upper GI effects than daily dosing for the same agent. Of potential interest for the oldest old is the development of an alendronate formulation in a gel form that is easier to swallow [212].

Acute upper gastrointestinal bleeding (UGIB) may be a problem in older patients, but it is not clear that this is exacerbated by bisphosphonates. In a Canadian population-based nested cohort study [213] in patients aged ≥65 years (n = 26,223), an incidence rate of 0.4% of acute UGIB within 120 days of treatment start was found, with 60% of cases being in patients aged over 80 years. Although relatively few of the affected older patients had a past history of gastric ulcers and serious GI bleeding or were concurrent NSAID users, it was concluded that the rate was concordant with the prevalence of UGIB (from any cause) in the general population. Indeed, advanced age has consistently been identified as a risk factor for UGIB and is likely related comorbidity and the use of multiple medications [213].

Diarrhea and nausea have been reported as common with strontium ranelate; nausea, vomiting, and gastroesophageal reflux disease are common with teriparatide.

Vascular Effects

Earlier reports have linked selective estrogen receptor modulators (SERMs), such as raloxifene or bazedoxifene, to sweating, leg cramps, as well as cutaneous flushing, particularly in the face and upper body ("hot flushes") [197, 198]. In the MORE study, the pivotal regulatory study of raloxifene—a postmenopausal osteoporosis population aged 31–80 years (mean age 65 years; 36 month of treatment)—"hot flushes" was the most frequently reported non-serious adverse event (almost 10%) [82]. The incidence of these events appears to be lower in women aged over 55 years, than in a younger age group [197].

Venous thromboembolic events (VTE) were reported to be the most well-known serious adverse drug reaction with SERMs. This includes both deep vein thrombophlebitis and pulmonary embolism. In MORE, the incidence rates of VTE were about 8–12/1000 in the treated arms (RR vs placebo: 3.1) [214]. A meta-analysis [215] has estimated a 62% increase in risk of VTE with raloxifene versus placebo. This effect of raloxifene is likely due to the estrogenic effects of on the blood clotting system.

Higher risk of VTE was also reported with strontium ranelate than in placebo, without clear explanation [124]. In an analysis of the UK General Practice Research Database (GPRD) database, Breart and colleagues [216] reported annualized VTE rates of 7/1000 for women (mean age 74 years) treated with strontium ranelate, at a similar rate as in patients receiving

alendronate. In that study and another large-scale population-based cohort study [125], the underlying condition itself (i.e., osteoporosis) appeared to be responsible for an increased risk of VTE (possibly due to comorbid conditions such as previous fracture or immobilization during hospitalization).

In the Breart et al. study, the untreated osteoporotic patients had a rate of VTE of 5.6/1000 and an age-matched non-osteoporotic cohort 3.2/1000. In the study carried out by Vestergaard and colleagues [217], data analysis revealed an increased risk of VTE with three different bisphosphonates compared to the general population and only a borderline effect for raloxifene. It is well established that the risk of VTE increases with age (along with surgery and trauma) [218, 219]. Therefore, in terms of VTE, the additional risk of an anti-osteoporosis treatment in the older adults is therefore very difficult to estimate.

Musculoskeletal Pain

Chronic musculoskeletal pains, whether affecting bone, joints, or muscle, have been frequently associated with bisphosphonates, both oral and IV (about 5–10% of patients), and also to some extent with raloxifene and teriparatide. Intravenous bisphosphonates are associated with the highest rates with some severe cases reported [220]. In 2008, the American Food and Drug Administration (FDA) issued an alert on cases of severe pain which can occur within days, months, or even years after starting bisphosphonates [221]. When initiating once-weekly dosage regimens of alendronate or risedronate, it has been suggested that starting with lower daily dosages for about 2 weeks before switching to the more convenient, once-weekly posology can avoid muscle pain [222]. Limb pain is a commonly reported adverse reaction with teriparatide and, to a slightly lesser extent, back and joint pain. In a placebo-controlled study in elderly women, however [223], the incidences of these events were not found greater in the active arm as compared to placebo.

Immune Reactions

Intravenous bisphosphonates have been associated with transient flu-like symptoms, myalgia, arthralgia, headache, and fever, collectively called an acute-phase reaction (APR). In a study with ibandronate, the incidence of APR with the IV form was 4.9 versus 1.1% for the oral form. Higher rates of fever have been reported postinjection with zoledronic acid (around 30%) [222]. The symptoms of APR, which seem to be attributed to the release of pro-inflammatory cytokines from circulating gamma-delta T-cells, generally appear 24–48 hours after administration and resolve, for some patients, within 48 hours. The likelihood of having an APR after an IV bisphosphonate, which is mostly observed after the first administration, may be reduced by administration of acetaminophen (paracetamol) prior to injection therapy.

Cutaneous hypersensitivity reactions have been also reported with several anti-osteoporotic medications [224] although these remain very rare. These events can be serious, with cases of Stevens-Johnson syndrome and toxic epidermal necrolysis reported for bisphosphonates and drug rash with eosinophilia and systemic symptoms (DRESS) in patients receiving strontium ranelate [224, 225]. These conditions require prompt and permanent drug withdrawal and treatment with steroids. The prognosis is good when treated rapidly.

Denosumab has been associated with higher rates of skin infections and eczema [226]. However, data from meta-analysis indicate that the increased risk is only borderline [226]. Denosumab (a human monoclonal antibody) neutralizes RANKL (receptor activator of nuclear factor-κB ligand), a signaling protein involved in osteoclast formation and function, but is also expressed by activated T lymphocytes, B cells, and dendritic cells. In the FREEDOM trial, the incidence of (serious) cellulitis (including erysipelas) was significantly higher in the active arm (0.3 versus <0.1%) [199]. The increase rates of eczema and allergic skin reactions, including dermatitis and rashes, reported in denosumab studies have been put down to "suboptimal tissue specificity" since

RANKL is also expressed in keratinocytes and Langerhans cells [226].

The summary of product characteristics for teriparatide notes that this agent is rarely associated with possible allergic events soon after injection but may include facial edema, generalized urticarial, and acute dyspnea.

Nervous System Effects

Headache is commonly reported with strontium ranelate. The event rate in the older adults (>80 years) was 3.3 versus 1.7% on placebo. For teriparatide the rate of headaches in older patients (>75 years) was 6 versus 5% on placebo (lower than in younger patients); the rate of dizziness was 9 versus 8% (the same as in younger patients) [223].

Rare cases of seizure have been reported in patients treated with zoledronic acid, and it has been hypothesized that the transient hypocalcemia sometimes caused by this bisphosphonate might alter the set point for seizure induction [227].

Teriparatide treatment has been associated with headache, vertigo, and depression (as reported in the summary of product characteristics).

Cancer

Rare cases of esophageal cancer have been reported in patients exposed to alendronate or other oral bisphosphonates, but the results from epidemiological studies on prescription databases have been conflicting. The FDA reports of esophageal cancer in patients who had received oral bisphosphonates were after relatively short treatment times (median time to diagnosis of 2.1 years), thus minimizing any probable causative effect. The most recent analysis performed on the UK GPRD [228] concluded that there was a small but significant increased risk of esophageal cancer in women. Of the 4442 annually reported cases of upper gastrointestinal cancer, 95 could be linked to bisphosphonate use (odds ratio of 1.34 for bisphosphonates). However, an analysis run by another group on the same database concluded there was no significant association [229].

Raloxifene is associated with significantly lower rates of breast cancer as compared to placebo or alendronate treated patients [230].

Teriparatide has been associated with osteosarcoma in experimental animals. However, there is no evidence of any causal association between teriparatide treatment and osteosarcoma in humans according to a long-term surveillance study in the USA [231].

Cardiac Effects

An increased risk of atrial fibrillation (AF) has been observed in the pivotal HORIZON study with zoledronic acid. In the active arm of zoledronate trial in postmenopausal osteoporosis, the incidence of AF was 1.3% versus 0.5% on placebo ($p < 0.001$) [195]. Post hoc analyses of other bisphosphonate trials and several large population-based studies have, however, been inconsistent in their findings, with no conclusive evidence that AF risk is increased. Screening for AF in the older patient may be however important since it is known that the prevalence of AF increases with age, roughly doubling every decade, so that in individuals aged over 85 years the rate is about 10% [232].

There was a signal of increased myocardial infarction incidence (1.7 versus 1.1% in placebo) reported in patients treated with strontium ranelate with a relative risk of 1.6. No increase in risk of cardiovascular mortality with use of bisphosphonates has been reported, and indeed a decrease in myocardial infarction has been associated with bisphosphonate use in patients with rheumatoid arthritis [233].

Impaired Fracture Healing and Induced Bone Weakening

Data from large clinical trials, regarding fracture healing, indicate that, with bisphosphonates, there is no evidence to support stopping therapy

while a fracture heals. On the other hand, rare cases of osteonecrosis of the jaw (ONJ) have been reported in the past years with antiresorptive therapy. These involve exposed bone in the maxillofacial region that show negligible healing of over a period of 8 weeks. In most of the cases (about 95%), ONJ has been mostly reported in cancer patients receiving high-dose of IV zoledronates for the prevention or treatment of cancer-related bone disease, and in those cases treatment should be stopped. No cases of ONJ have been prospectively identified the major RCTs of bisphosphonates (>60,000 patient-years of exposure) [234]. There have been a few reports of denosumab-related ONJ in the literature, but the incidence rates seem be similar or less than those of zoledronic acid [232].

Case reports of atypical subtrochanteric, low-trauma, femur fractures in bisphosphonate-treated patients have been published, and some have noted prodromal thigh pain in the preceding period. Although some epidemiological evidence suggests there may be an association between these events with duration of bisphosphonate use, such atypical fractures can occasionally be observed in untreated patients [232, 235, 236]. The duration of bisphosphonate exposure, particularly beyond 5 years, may constitute a risk factor [237].

Renal Safety

Renal insufficiency is a relatively common comorbidity in older adults and therefore may represent a concern for various drug treatments, including bisphosphonates, which are eliminated primarily through the kidney [238]. Therefore, as a precautionary measure, these products (both oral and IV forms) are not recommended in patients with severe renal impairment (creatinine clearance <30–35 mL/min). There have been rare reports of IV forms being associated with nephrotoxicity, but these have been in cancer patients with high treatment doses. Post hoc analyses of clinical trial data indicate however preserved anti-fracture efficacy and generally are associated with stable serum creatinine levels, suggesting that there is no evidence to advocate that the oral forms confer any increased risk in patients with chronic kidney disease (stage 1, 2 or 3) [238].

Optimizing Therapeutic Adherence in Osteoporosis

Nonadherence with drug therapy in chronic asymptomatic diseases is well reported [239] which is also the case for osteoporosis [240, 241]. While variable osteoporosis studies differ substantially in terms of methodology and patient demographics [240], the results revealed yearly persistence rates from 26% to 56% for daily anti-osteoporosis regimens and persistence rates from 36% to 70% for weekly regimens. Medication possession ratio (MPR), which represents an estimate of compliance, ranged from 46% to 64% and 58% to 76%, respectively, and thus also is influenced by the dosing interval. In an epidemiological study, carried out by Rabenda and co-workers [242], the authors noted that the MPR at 12 months was higher among patients receiving weekly as compared to daily alendronate (70.5 versus 58.6%; $p < 0.001$): similar results were found by Cramer and co-investigators [240]. It has been noted that compliance tends to diminish with increasing follow-up duration and the drop is particularly rapid over the first 2 years of treatment [240].

The clinical consequence of poor adherence is increased risk of fracture. Siris and colleagues [243] observed that in women aged ≥65 years (n = 175,022), the overall fracture rate declined with improved MPR: fracture rate was 5.1% in patients with MPR <50%, whereas it was 3.8% in those with MPR ≥80%. In a meta-analysis of six studies (171,063 patients), Imaz and co-workers [244] estimated that the increase in fracture risk for noncompliant patients (1–2.5 years of follow-up) was 28% for hip fractures and 43% for clinical vertebral fractures, whereas a further meta-analysis by Ross and colleagues (0.8–4.2 years of follow-up; n = 698,631) estimated the increase in fracture risk for noncompliance at 30% and for nonadherence at 30–40% [245].

Hiligsmann and colleagues, using a 3-year horizon (follow-up) modeled optimal adherence and "real-world adherence" [246]. In the real-world scenario, only 57% of fractures were prevented and the QALY (quality-adjusted life year) gain was only 56% of that expected with full adherence. The quality-adjusted life year or quality-adjusted life-year (QALY) is a generic measure of disease burden, including both the quality and the quantity of life lived. It is used in economic evaluation to assess the value of medical interventions. One QALY equates to 1 year in perfect health. The study authors concluded that an intervention could be an efficient use of resources if it improved adherence by 25% and cost less than 100 euros per patient-year.

Adherence to prescribed medication regimens is difficult for all patients and particularly challenging for the elderly. Older adults can be more forgetful; however, this can be counteracted by electronic and other reminders to prompt the patient or their carer. However, it appears that about 70% of nonadherence is intentional, i.e., an active decision by the patient. Many patients seem to perform an implicit risk/benefit analysis once given a prescription for a new treatment and during their treatment, which determines their subsequent behavior [247–249]. Furthermore, nonadherers are frequently "selectively nonadherent," i.e., while they might receive several different treatments for different illnesses, they might be compliant for some treatments, but not for others. As older patients are more likely to have a number of comorbid conditions, this selective nonadherence is particularly apparent in this age group.

A study which included a large cohort of US adults was carried out to assess the reasons for not initiating treatment and poor medication persistence [249]. The main reason underlying nonadherence was the financial hardship of paying for the treatment (about 50% of respondents), followed by fear or experience of side effects (about 40%), concerns about pharmacological treatments in general (about 28%) and lack of perceived need for the treatment (about 24%); with other possible reasons playing more minor roles. The lack of a perceived need for treatment in many patients arises from the fact that they may not experience any symptoms directly from their osteoporosis. Moreover, given the rather wide range of side effects outlined earlier, many patients are likely to believe that the negative effects of anti-osteoporosis medication outweigh any possible benefits.

Predictors of Nonadherence

In older adults (without cognitive dysfunction), the main medication difficulties, which give rise to nonadherence, appear to center around misunderstandings about their disease and health in general, worries concerning adverse effects and polypharmacy, and factors surrounding the patient provider relationship (and, in some cases, logistical barriers to obtaining medications) [250]. Challenges can be tackled through implementing patient-centered care and shared decision-making [251].

The beliefs and misunderstandings about osteoporosis are quite variable. In patients with fragility fractures, it has been reported that there may be failure to appreciate or even possible denial of the idea that their facture was related to bone health. Such patients seem to reject the term "fragility" fracture as not being strong enough to reflect their trauma [252] and that the fall was just tripping. In addition, while patients may have a good understanding of what osteoporosis is, they may not always understand how their treatment can help [253].

The challenge is, therefore, to understand and anticipate these motivations by identifying potential "nonadherers" in the clinic. Predictors of medication nonadherence include specific disease states, such as cardiovascular diseases and depression [254]. A variety of interventions designed to improve treatment compliance have been tested in the clinic, which have been the subject of Cochrane reviews [255, 256], and a further systematic review assessed osteoporosis medications in particular [257]. In general, the

periodic follow-up visits between patients and health professionals are beneficial, but few intervention strategies were clearly efficacious. Patient coaching (e.g., a discussion with a nurse just before the consultation that encourages the patient to ask questions), as opposed to the distribution of written material, seems to produce an increase in patient satisfaction with only a small increase in consultation length. Since nonadherence is due to a range of intentional (e.g., negative beliefs) and unintentional (e.g., forgetting) factors, a simple "one-size-fits-all" approach to improving adherence is no longer tenable. Targeted treatment approach tailored to the patient's needs and associated comorbidities is a good tactic to handle this challenge. Many current adherence programs lack assessment and personalization around intentional and nonintentional adherence factors, which limits their effectiveness.

During follow-up visits, patients should be questioned as to their adherence, but not by using a closed-ended interrogative approach. Instead, patients should be asked to describe how they take their medicines in a nonthreatening manner avoiding any notion of judgment [254]. Assessment tools for older adults may help for these interviews [258–261].

In conclusion, age-related bone loss is a complex and heterogeneous disease. A combination of genetic, hormonal, biochemical, and environmental factors underlie its pathophysiology. The result is a decline in bone quantity and quality that increases fracture risk in a progressive manner. There is a growing understanding, based directly on studies in humans, of the pathogenesis of age-related bone loss. Clearly, optimizing peak bone mass during growth is critical for minimizing fracture risk late in life. Sex steroids, particularly estrogen, play a key role in regulating bone metabolism and age-related bone loss in both women and men. Understanding of the factors controlling the aging of the cell in general and the aging of osteoblasts, osteocytes, and osteoclasts in particular is pinpointing the pathways that could be targeted to delay these age-dependent changes.

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Bone Healing and Osteoporosis

20

Yasser El Miedany

Introduction

The major characteristic of osteoporosis is a decrease in bone mass and quality [1], rendering people prone to osteoporotic fracture (fragility fracture) caused by low-energy trauma [2]. Osteoporosis-associated fragility fractures may occur in almost all skeletal segments, but the preferential locations are the vertebral column, the proximal ends of the femur and humerus, and the distal end of the radius (Colles' fracture). Trauma due to a fall is by far the most frequent cause of fractures affecting long bones (femur, humerus, and radius), while it is more difficult to determine the cause and the exact time of fragility fractures of the vertebral body, which often go undiagnosed [3].

While surgery is the primary treatment strategy for osteoporotic fracture, poor prognoses are often encountered attributed to a combination of biological and surgical factors [4]. The common sites of osteoporotic bones are usually compromised and comminuted, which makes it hard to achieve an optimum reduction and stable fixation [5]. Osteoporotic fractures occur mostly in elderly patients, who exhibit underlying, unfavorable systemic conditions which are prone to complications [6] (Fig. 20.1). The abnormal remodeling status of bone with osteoporosis would deteriorate after bed braking. This poses a disadvantage with respect to fracture healing and bone callus strength. Furthermore, the refracture risk following surgery increases significantly [7]. In terms of the complexity of treatment and poor prognosis, the annual facility-related hospital cost of osteoporotic fractures is the highest (up to $5.1 billion), followed by that of myocardial infarction and stroke [8].

Earlier studies reported decreased callus area (20–40%) and bone mineral density (BMD) occur in the fracture sites of elderly osteoporotic patients. Studies have indicated that the delayed or nonunion of osteoporotic fractures is implicated in the scarce capacity of bone regeneration with aging [9, 10]. Additionally, the bone properties of such patients are quite different from those of normal individuals and are manifested in the decrease of bone mechanics and mechanosensation, as well as the abnormal bone metabolism caused by immune disorders [11]. Knowledge of the various factors involved in this process is essential for understanding the pathophysiology of fracture healing, its management, and the influence of osteoporosis and aging on the duration and efficacy of the repairing process. This chapter will highlight the molecular basis of osteoimmunology and the biology of bone healing. It will expand to discuss the effects of aging on fracture healing, inflamm-aging, and immunosenescence as well as implications of osteopo-

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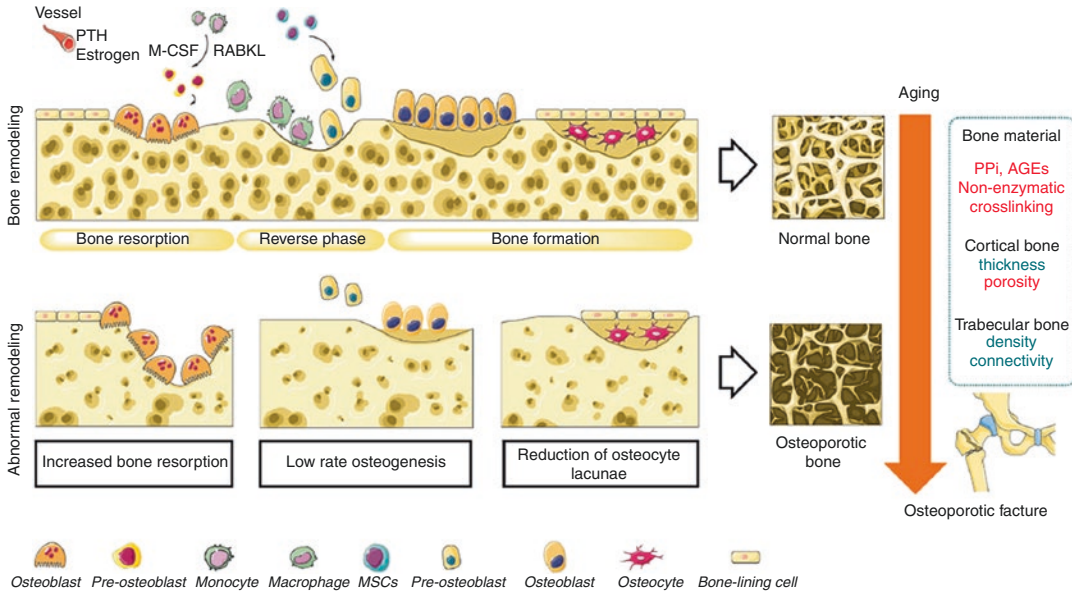

Fig. 20.1 Static and dynamic changes in osteoporotic bone. An osteoporotic fracture is the macroscopic result of microstructural alterations that change the response of bone to the applied load. The aging process in osteoporotic bone would lead to overaccumulation of PPi, AGEs, and nonenzymatic cross-linking of collagen, which disturb the normal organization of bone material. With the increase of bone resorption and low rate osteogenesis, the osteocyte lacunae reduction leads to decreased trabecular thickness and more porous cortical bone. PTH parathyroid hormone, M-CSF macrophage colony-stimulating factor, RANKL receptor activator of nuclear factor kappa-B ligand, PPi inorganic pyrophosphate, AGEs advanced glycation end products, MSCs mesenchymal stem cells. "Red" refers to upregulation; "green" refers to downregulation. (Quoted from [6] under open access scheme and a Creative Commons Attribution 4.0 International License)

rosis treatment for fracture healing. This includes the two main categories of drugs which affect bone remodeling, namely, the anabolic and anti-catabolic medications. It will conclude by discussing the management of atypical femoral fractures.

Pathophysiology of Fractured Bone Healing

Bone healing throughout fracture repair is a repairing process that follows a well-defined spatial and temporal order. Two distinct phases can be recognized: an anabolic phase, characterized by tissue formation, and a catabolic phase, characterized by remodeling of woven bone into trabecular and cortical bone. Anabolic and catabolic phases follow each other and overlap in the repairing process. Fracture healing is temporally defined process (Fig. 20.2) [13]. The initial trauma disrupts the bone as well as the periosteum and provokes an inflammatory response, which represents the first step of the anabolic phase. This involves the release of a variety of substances including fibronectin, growth factors, fibroblasts, endothelial cells, and osteoblasts, which act to fill the fracture gap with granulomatous tissue. The inflammatory process is followed by the reparative phase which involves a periosteal response with angiogenesis and formation of connective tissue and soft callus, that is gradually replaced by immature woven bone via intramembranous or endochondral bone formation. In the final remodeling phase (catabolic phase), the woven bone callus is gradually replaced by lamellar bone.

Injuries to the appendicular skeleton heal through two distinct processes: direct (primary) and indirect (secondary) healing. Primary healing involves a direct transition of mesenchymal cells to bone-forming osteoblasts (intramembranous

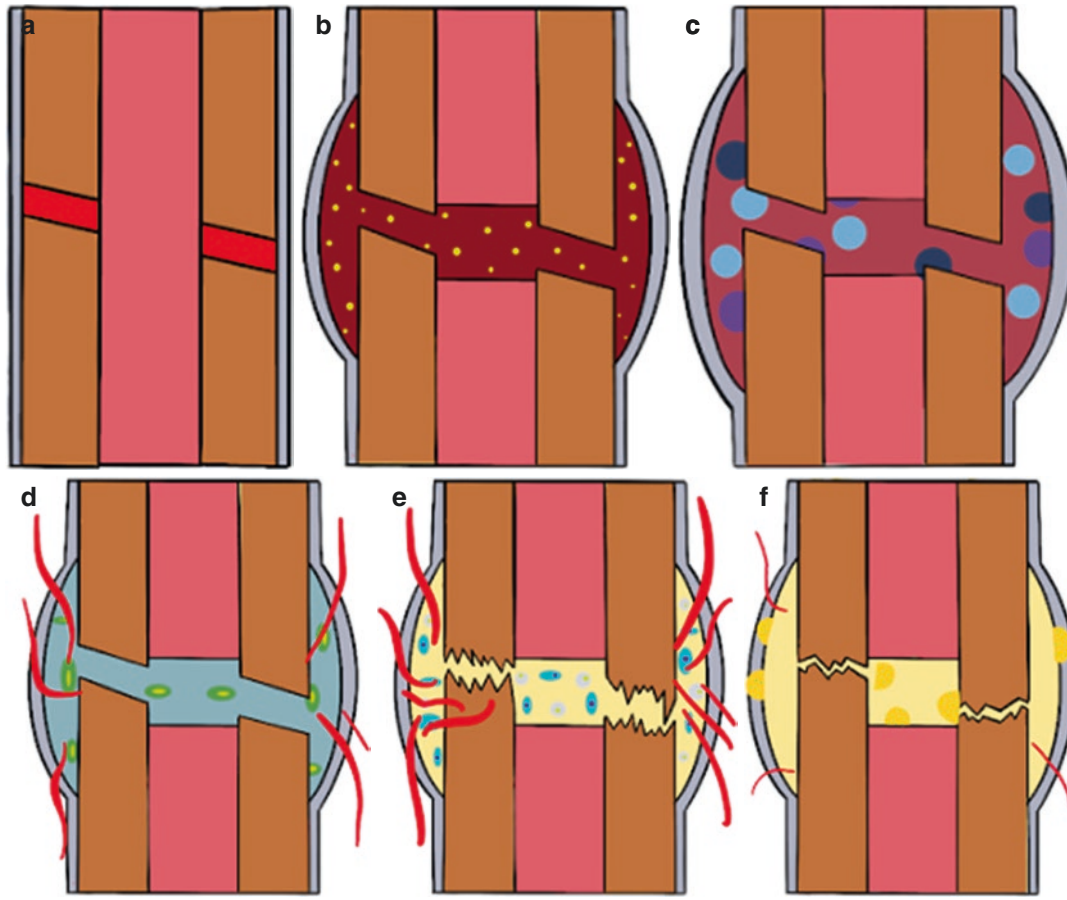

Fig. 20.2 Fracture healing is temporally defined process. (**a**) At injury there is disruption of periosteum and bone. (**b**) A clot forms immediately providing a provisional matrix. Platelet degranulation releases chemokines to recruit inflammation. (**c**) Inflammatory phase leads to a period of (**d**) mesenchymal expansion and migration from the periosteum and endosteum and angiogenesis. (**e**) Bone is formed via both endochondral (blue large oval cells) and intramembranous ossification (smaller grey cells). (**f**) Osteoclasts (multinucleated cells) resorb primary bone and the process of remodeling restores bone shape and structure. (Quoted from [13] under open access scheme and a Creative Commons Attribution 4.0 International License. *Dr. Kurt Hankenson:* kdhank@umich.edu)

ossification). Secondary healing progresses through a cartilage intermediate before bone is formed by osteoblasts (endochondral ossification). Secondary fracture healing occurs after a fracture without rigid fixation. Under the influence of active loading, an external callus is initiated to bridge the fracture gap in a three-stage process consisting of inflammation, repair, and remodeling [14, 15]. The first two of these partially overlapping phases restore bone structure and continuity over a period of 3 months to allow full weight bearing. The last phase involves gradual remodeling of bone to withstand the usual strains of daily life [16]. In contrast, primary fracture healing without formation of a periosteal callus usually requires direct contact of compact bone or rigid surgical intervention that makes the fracture gap <200 μm. However, elderly osteoporotic bones, such as metaphyseal sites, which are highly susceptible to bone degradation, make it difficult to maintain anatomical reduction and rigid fixation using traditional screws due to inadequate insertional torque. In this situation, the healing process will be more like indirect bony union with the response of loading and inflammation, forming a periosteal callus bridging the fracture gap [17].

The cellular and molecular factors that coordinate fracture callus formation and resolution are complex and highly orchestrated; therefore, the three main phases of bone repair will be discussed in more details.

The Inflammatory Phase

The acute pro-inflammatory response is vital for initiating the fracture healing process. As a result of the fracture, bone architecture and vascular supply are disrupted (Fig. 20.2). This results in a loss of mechanical stability, a decrease in tissue oxygenation and nutrient supply, and the release of bioactive factors at the site of injury [18]. Within the first minutes of fracture, a fibrin-rich blood clot forms to achieve hemostasis [19, 20]. The role of this fibrin-rich clot during fracture healing has been examined in mice lacking the key enzyme for fibrin degradation, plasminogen. While fibrin is not required for bone healing, repair does not properly progress without fibrinolysis. Specifically, the absence of plasminogen results in ectopic ossification and poor healing [21].

The inflammatory cells themselves, along with the cytokines and extracellular matrix they produce, appear essential in facilitating normal healing, as mice deficient in innate and adaptive immunity have significantly impaired endochondral bone repair [20]. Cytokines released by the clot (particularly during platelet degranulation) recruit inflammatory cells including lymphocytes, macrophages, eosinophils, and neutrophils [16, 18–22]. As one example, C-C motif chemokine ligand 2 (also known as monocyte chemoattractant protein 1) (CCL2 or MCP1) and its receptor chemokine receptor type II (CCR2) stimulate monocyte chemotaxis in the inflammatory response [23]. CCL2is expressed from days 1–3 in the fracture site [24]. When subject to fracture, Ccl2-null and Ccr2-null mice both exhibit delayed fracture healing and decreased callus volume as a result of diminished mesenchymal cell infiltration and impaired vascularization [25]. Inflammatory cells are deposited throughout the clot during hemorrhage and migrate to the injury site from local sources. While, the contribution of inflammatory cells derived from circulation versus those that are locally derived is not fully understood, tissue resident macrophages, called ostealmacs, are necessary for fracture healing. One role of inflammatory cells, particularly neutrophils and macrophages, is debridement of injured and devitalized tissue. Inflammatory cells also produce cytokines that positively and negatively influence healing [26–28]. Some of these cytokines are detected at the fracture site within the first 24 hour post-injury and are important for the expansion of the inflammatory response by acting on cells in the bone marrow, periosteum, and hematoma [25, 29].

This chapter will highlight the molecular basis of osteoimmunology and bone mechanosensation in different healing phases of elderly osteoporotic fractures.

Osteoimmunology in Older Adults

As bone fracture induces immediate inflammation and bleeding around the fractured bone extremities and within the medulla, with the formation of a hematoma as a template, is formed for callus formation, inflammatory cells, such as macrophages/monocytes or B/T cells, are activated to release inflammatory cytokines, including tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) into the systemic circulation [30]. These cytokines are responsible for the initiation of immune and inflammatory responses [31], including enhancement of blood flow and vessel permeability, as well as the recruitment of immune cells for pathogen clearance [32]. This limited inflammatory response is required to initiate the repair cascade and mobilize all the required factors involved in the early bridging of the fracture gap, especially in indirect bony unions without rigid fixation [33]. The role of osteoimmunology in hematoma and inflammatory phase of fracture healing was reviewed recently in an article by Xie and colleagues [6].

The interactions between the skeletal system and immune function, comprising *osteoimmunology*, in osteoporotic fractures are altered with age

[34]. It has been reported that an age-associated decline in the absolute numbers of human B-cell precursors in bone marrow leads to a significant decrease in the number of mature human B cells [35–37]. Compared with young adults, the B-cell repertoire is less diverse in elderly individuals [38]. As to T cells, studies exhibit reductions of proliferation and function in the helper CD4+ T cells that recruit neutrophils and macrophages to infected sites of elderly individuals [39]. Consistent with this finding, the impaired neutrophil/monocyte-mediated phagocytosis also showed an age-dependent reduction [40–42]. In contrast, the expression of Toll-like receptors (TLRs), a group of pattern recognition receptors (PRRs) that trigger pro-inflammatory responses [43], is increased in monocytes and dendritic cells in elderly people, accompanied by increased production of IL-1 and TNF-α [44]. In vitro and in vivo studies have shown that persistent tumor necrosis factor (TNF) expression impairs cell-mediated immune responses and Th2 differentiation from naïve T cells [45–47].

Moreover, constant stimulation by TNF-α elevates the threshold for T-cell activation via the T-cell receptor (TCR), attenuating T-cell responses to antigen [48], and negatively affecting angiogenesis during fracture healing [49]. Thus, the early immune responses and pathogen clearance of aged patients with osteoporotic fractures would be impaired or delayed due to the insufficient acquired immunity and dysfunction of the innate immune system [50]. Furthermore, pathogen infections induce host inflammation and contribute to local bone loss. The most frequent pathogen identified in bone infection is *Staphylococcus* [51]. *Staphylococcus aureus* protein A induces the production of inflammatory cytokines, such as TNF-α, [52] IL-6, interleukin-1 alpha (IL-1α), interleukin-1 beta (IL-1β), and neutrophil-attracting chemokines in local tissues [53]. On the one hand, short-term (24- hour) upregulated cytokines, such as TNF-α, are essential for local recruitment of neutrophils [30], macrophages, and T cells for pathogen clearance [54, 55]. However, the long-term presence of these cytokines, especially TNF-α, IL-1, and IL-6, activates CD4+ T cells, promoting RANKL expression by osteoblasts [56] and synergizing directly with RANK to amplify osteoclastogenesis [57] and bone resorption [58].

In general, high levels of pro-inflammatory cytokines, either in the circulation or local tissues, are found in the aged population [59]. Serum IL-1, IL-6, and/or TNF-α levels have been shown to be upregulated in elderly patients with bone loss,70 supporting the hypothesis of increased inflammation with aging [60]. In fact, TNF-α promotes bone resorption by both directly inducing osteoclast differentiation [61] and inhibiting osteoblast differentiation and function [62, 63]. IL-1 drives osteoclast differentiation via a RANKL-/RANK-independent mechanism [64]. IL-6 indirectly plays a positive role in osteoclast differentiation by binding IL-6 receptors expressed on osteoblastic cells to induce RANKL expression [65]. Neutrophils stimulate osteoclastogenesis by upregulating cell surface RANKL expression under TLR stimulation [66] or by inducing osteoblast retraction [67]. Interferon gamma (IFN-γ), secreted by anti-inflammatory macrophages (M2), inhibits osteoclast differentiation via rapid degradation of TRAF6 [68]. However, macrophage polarization shows a shift toward macrophages (M1) that promote inflammatory cytokines as a consequence of aging [69].

On another front, mature B cells are important regulators of a decoy receptor for RANKL, osteoprotegerin (OPG). In total, 40% of the OPG in bone marrow is produced by mature B cells alone [70]. The increased bone resorption and low levels of bone marrow OPG were demonstrated in B cell-deficient mice; this defect can be normalized by the transplantation of B cells. As a result of the decreased number of mature human B cells, the supply of OPG is low in patients with osteoporosis. Thus, current evidence supports that the high RANKL/OPG ratio caused by aging-related inflammation and the lack of mature B cells is associated with the hyperactivation of osteoclastogenesis and aggravation of bone resorption in elderly patients with bone loss, which increases the incidence of further intraoperative or postoperative fractures (Fig. 20.3). Moreover, Yonou et al. concluded that overactivation of osteoclasts

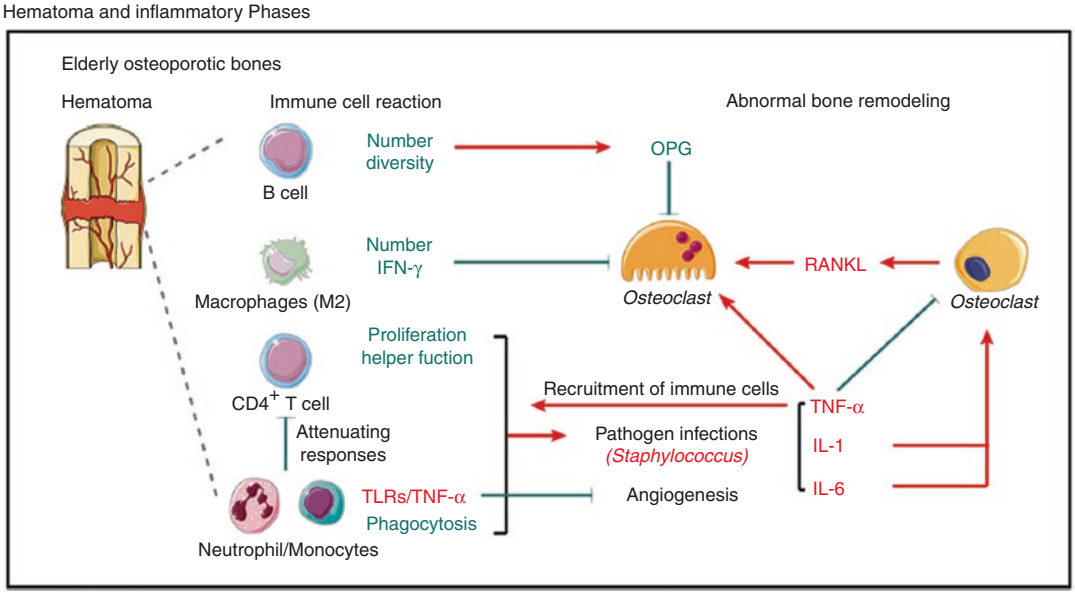

Fig. 20.3 Osteoimmunology in elderly osteoporotic bones. Hematoma and inflammatory phases are the immediate reactions to a fracture. The limited inflammatory response at the fracture site is essential to initiate repair processes and mobilize all the required factors involved in the early bridging of the fracture gap, especially in indirect bony unions without rigid fixation. The high RANKL/OPG ratio caused by aging-related inflammation and the lack of mature B cells is associated with the hyperactivation of osteoclastogenesis and aggravation of bone resorption in elderly patients with bone loss, which increases the incidence of intra- or postoperative further fractures. OPG osteoprotegerin, IFN-γ interferon gamma, RANKL receptor activator of nuclear factor kappa-B ligand, TLRs toll-like receptors, TNF-α tumor necrosis factor alpha, IL-1 interleukin-1, IL-6 interleukin-6. "Red" refers to upregulation; "green" refers to downregulation. (Quoted from [6] under open access scheme and a Creative Commons Attribution 4.0 International License)

plays an important role in chronic pain after osteoporotic fracture by creating acidosis [71]. Hyper-osteoclast activity may lead to pathological modifications of bone sensory nerve fibers, with an overexpression of acid-sensitive pain receptors, which contributes to generating and maintaining pain in osteoporosis [72].

The Repair Phase

Following inflammation, the angio-mesenchymal phase of repair begins. This phase has been termed the "fibrovascular phase" and is defined by vascular remodeling (angiogenesis and neovascularization) and recruitment of mesenchymal progenitor cells, sometimes referred to as mesenchymal stem cells (MSCs), that will ultimately differentiate into chondrocytes and osteoblasts to regenerate the fractured bone.

Revascularization During the initial fracture trauma, the periosteal, cortical, and medullary vascular supplies are disrupted leading to acute cellular necrosis and acidosis. The lack of vascularization causes local hypoxia, in which oxygen tension is lowered to 0.1–2% [73–75] from 5%. Revascularization is required for perfusion of the callus with oxygen, nutrients, inflammatory and progenitor cells to facilitate repair, and the egress of waste products. In most cases, vascular supply is re-established rapidly through the development of a new vascular network [76]. Formation of the network occurs by two distinct processes: angiogenesis and vasculogenesis. Angiogenesis is the process by which new blood vessels are formed by sprouting from existing vasculature. Vasculogenesis is de novo formation of blood vessels from in situ endothelial progenitor cells (EPCs) within the callus. Endothelial cells in forming callus vasculature can develop from a

variety of sources, including existing vessels of the periosteum and the intramedullary vasculature [77], circulating EPCs [78] that are increased during fracture repair [79], or the bone marrow [80]. Circulating EPCs are not only increased in rodent models but are significantly increased in human patients at day three postfracture [81]. Vascular endothelial growth factor (VEGF) is a well-characterized driver of angiogenesis and vasculogenesis [82]. VEGF is produced by a variety of cells in the fracture callus, including inflammatory cells and mesenchyme, but also osteoblasts and hypertrophic chondrocytes. VEGF binds the VEGF family of receptors VEGFR1 (FLT1) and VEGFR2 (FLK1) activating signaling cascades that lead to increased proliferation and sprouting of endothelial cells and recruitment of EPCs to the fracture.

As the angiogenic response is a required event in fracture healing, deficiencies in angiogenesis result in delayed or insufficient fracture repair. Clinically, the non- or delayed-union rate increases from a basal level of 10–20% in the normal fracture population to 46% when there is concomitant damage to the vasculature [83]. Comorbidities such as aging, diabetes, and smoking are also associated with delayed fracture healing, likely due to underlying vascular defects. Elderly and middle-aged mice exhibit a decreased callus volume formation coupled with inhibited angiogenesis and reduced expression of VEGF and MMP9 relative to juvenile fractures [84]. In an obesity-induced model of type II diabetes mellitus, neovascularization of the fracture callus is inhibited resulting in decreased formation of woven bone [85]. In distraction osteogenesis, cigarette smoking inhibits neovascularization and delayed tibial lengthening [86]. Taken together, identifying clinically relevant conditions that affect angiogenesis is required to improve outcomes in fracture healing.

Bone Formation Phase

Osteoblasts and Chondrocytes Following the fibrovascular phase of healing, many of the MSCs that formed the fibrovascular callus undergo differentiation to either osteoblasts or chondrocytes to initiate the bone formation phase of healing [87]. Factors regulating the decision of progenitor cells toward the chondrogenic or osteogenic fate are multifactorial, integrated, and still being defined. Extrinsically, mechanical factors and oxygen tension are undoubtedly important variables regulating fate decision [87, 88]. These microenvironmental cell-extrinsic factors then lead to very specific cell-intrinsic regulation of chondrogenesis and osteoblastogenesis.

Increased motion has been shown to induce the formation of more chondrocytes and in turn increases endochondral ossification [89, 90], while stabilization results in the generation of more osteoblasts and direct bone repair via intramembranous formation [89]. Another putative environmental signal that may regulate the fate decision of MSC is oxygen tension. The relationship between oxygen tension and MSC differentiation in vitro has been extensively investigated, and the preponderance of evidence suggests that hypoxia promotes a chondrogenic phenotype, whereas higher levels of oxygen promote osteoblast differentiation. Secreted growth factors also have a direct effect on MSC differentiation. Bone morphogenetic proteins (BMPs) are the classic osteogenic molecule associated with bone formation (reviewed in further details in Reference [13]). Another secreted growth factor family that could play a role in regulating MSC fate determination in bone healing is the Wnt family. In nonfracture environments, inhibiting beta-catenin activity in the osteoblast lineages leads to decreased bone mass and increased chondrogenesis [91–93], while ablation of Wnt inhibitors, sclerostin, increases bone formation and bone mass [94].

Osteoblasts (Intramembranous Ossification) Direct differentiation of mesenchymal progenitors to osteoblasts is the exclusive mechanism of bone repair in fully stabilized defects (intramembranous ossification) but also occurs along the periosteal and endosteal surfaces of the bone in less stabilized fractures. Periosteal progenitor

cells appear to have a bi-potent osteochondral potential, with differentiation linked to the mechanical microenvironment, as detailed previously. Osteogenic differentiation of the periosteal MSC gives rise to intramembranous bone locally along the bone surfaces adjacent to the fracture; while these same periosteal progenitor cells migrate into the fracture gap to undergo chondrogenesis. In contrast, endosteal stem cells exhibit unipotent osteogenic potential. Intramembranous bone formation from these endosteal stem cells is thus responsible for rapidly bridging across the marrow cavity [95].

Chondrocytes (Endochondral Bone Formation) Conversion of the cartilage callus to bone occurs following a highly regulated maturation of chondrocytes from a proliferative through a hypertrophic state. Hypertrophic maturation is distinguished morphologically by a dramatic increase in cell volume. Chondrocyte hypertrophy represents a pivotal state during endochondral ossification [13]. Hypertrophic chondrocytes are highly angiogenic and facilitate a second phase of vascular invasion into the cartilage callus by synthesizing VEGF [96–98], PDGF (platelet-derived growth factor) [99], and PlGF (placental growth factor) [100]. Subsequently, hypertrophic chondrocytes begin to express canonical markers of bone, including, alkaline phosphatase, osterix, osteopontin, and osteocalcin [101]. Together, activation of osteogenic programs and angiogenesis result in calcification of the cartilage matrix [102]. From a functional perspective, this calcification provides additional rigidity to the fracture.

The mechanism by which chondrocytes transform into osteocytes remains poorly defined, but a few possibilities have been proposed. The osteocyte could just be the terminal fate of the chondrocyte, representing the natural phenotypic progression of these cells during maturation; or the chondrocyte could dedifferentiate to a progenitor-like state prior to activating the osteoblast programs and then becoming an osteoblast [103, 104]. Another proposed mechanism is that the hypertrophic chondrocytes undergo an asymmetric cell division, at which point one of the daughter cells becomes an osteoblast/osteocyte and the other undergoes apoptosis [105–107].

Callus Remodeling and Osteoclasts Remodeling of the bony callus is traditionally considered the last stage of fracture repair. Remodeling must occur to degrade the provisional bone that is first produced, referred to as woven bone, and replace it with mature lamellar bone. A key component of callus remodeling is bone degradation by osteoclasts [108]. Osteoclast-mediated degradation of the bone liberates bone-sequestered factors, such as TGF-beta as well as factors produced by the osteoclast itself, such as complement 3a, Wnt10b, BMP6, and SLIT3 [109, 110] which are hypothesized to be critical in the subsequent stimulation of osteogenesis [111, 112]. Resorption is concluded with the apoptotic death of the osteoclast, an event that can be stimulated by the hormone calcitonin or 17-beta-estradiol-enhanced Fas ligand expression [113].

Effects of Aging on Fracture Healing

Age-Related Changes in Bone Metabolism in postmenopausal women or in elderly people, could negatively affect fracture repair, leading to a "physiologically impaired fracture healing." The real pathway by which these alterations influence bone-healing progression remains still unclear. Animal study on ovariectomized fractured mice showed how estrogen deficiency negatively affects all stages of fracture healing, particularly the mineralization and remodeling phases, as it promotes osteoclastic activity. These results suggest that estrogen deficiency in postmenopausal women could be an important factor in the development of nonunions and delayed fracture healing. Elderly mice with iatrogenic fracture showed delayed periosteal reaction, cell differentiation, cartilage vascularization, and endochondral ossification [114].

Cellular Alterations in osteoporotic conditions, these include decreased number of MSCs (mesenchymal stem cells) with consequent gradual replacement of red marrow by adipose tissue, impaired ability of MSC response to humoral stimuli (with diminished proliferation capacity and reduced osteogenic differentiation), and reduced osteoblastic response to mechanical stimuli (lower production of TGF-β, resulting in reduced fibroblast, chondroblast, and osteoblast proliferation). Moreover, in senile osteoporosis, it has been established that mesenchymal stem cells tend to differentiate toward adipose tissue, with consequent reduction in osteogenesis [115].

Inflamm-Aging and Immunosenescence The term "inflamm-aging" has been used to describe a chronic increased pro-inflammatory status in the elderly [116]. Elderly people are found to have higher levels of circulating pro-inflammatory cytokines, even in healthy individuals. It appears that the increased pro-inflammatory status in the elderly predisposes them to the range of systemic diseases including osteoporosis, Alzheimer's disease, type II diabetes, atherosclerosis, and Parkinson's disease [117–119]. Currently, it is unclear what drives this increased inflammation. Inflamm-aging has been suggested to be the result of a defect in the proper resolution of the normal inflammatory response, or the result of an unknown chronic mechanism that signals and prolongs the inflammatory response [120, 121]. As the inflammatory response is a critical step in proper fracture healing, any disruption of the inflammatory response could negatively affect fracture healing.

Inflamm-aging may also be a result of age-related changes to the immune response. Aging of the adaptive immune response has been described as immunosenescence [123]. Immunosenescence describes a loss of immune function that is associated with a predisposition to infection and disease in the elderly [124]. Increased age is associated with changes in T- and B-cell production and maturation. With increasing age, the source of T-cell progenitors, the hematopoietic compartment decreases in size and is associated with a decrease in T-cell progenitor quantity and proliferation potential [125].

Associated Comorbidities Pathological conditions, which are relatively common in older adults, may have negative impact on bone health and impair fracture healing. Frequently, comorbidities or drug therapies in patients who sustain a fragility fracture may influence the fracture healing process at different levels. The most common comorbidities are diabetes and hypertension. Diabetes mellitus, in particular, type 1 diabetes (T1DM), has been associated with impaired osseous wound healing properties. The currently available evidence shows that the main mechanisms underlying diabetic bone pathophysiology may be hyperglycemia and/or hypoinsulinemia, in the case of T1DM. Insulin plays a critical role in directly promoting the fracture healing potential, and impaired diabetic osseous healing may be associated with reduced local insulin levels, as a result of decreased systemic insulin levels in the diabetic state. The accumulation of advanced glycation end products (AGEs) in bone as a result of nonenzymatic glycosylation has been implicated in the pathogenesis of diminished bone formation, in a fracture healing model with experimental diabetes [126].

Clinical and experimental studies have demonstrated some negative effect of hypertension on bone mineral density. Earlier studies support the clinical investigations documenting an association between low bone mineral density (BMD) and high blood pressure. Angiotensin II is the major mediator of the maintenance of extracellular fluid volume and blood pressure. Although the effect of angiotensin II on osteoblastic cells is still controversial and predominantly based on in vitro studies, there is some evidence to suggest that this mediator is a potent suppressor of the differentiation of osteoblastic cells and, consequently, of bone formation. Individuals with essential hypertension could be a risk group for bone disorders [127].

Many drugs could impair fracture healing. The most common drugs involved in delayed fracture repair are antineoplastic agents, corticosteroids,

antibiotics, NSAIDs, and anticoagulants. They all compromise chondroblastic and osteoblastic proliferation, thus impairing bone callus formation and mineralization [128].

Implications of Osteoporosis Treatment for Fracture Healing

Many drugs affect the processes of bone repair [129, 130]. Some have a negative effect, such as glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAIDs), which act on the vascular supply during the inflammatory phase. The delay in fracture healing under NSAIDs is mostly based on numerous animal experiments and retrospective studies in humans, but randomized controlled trials (RCTs) have failed to confirm this effect up to now [131]. A number of drugs have been surmised to have positive effects, such as growth factors and prostaglandins; but there is currently no evidence supporting their clinical application. Osteoporosis drugs would be expected to affect the remodeling phase of bone repair but not the inflammatory and reparative phases. This is an important field of research since patients with osteoporosis are likely to be receiving an osteoporosis drug at the time of fracture or to be prescribed one shortly after the event. This section will discuss the impact of different osteoporosis therapeutic agent on bone healing, which has been summarized in Fig. 20.4.

Anti-catabolic Medications

Bisphosphonates

All bisphosphonates (BPs) are analogues of inorganic pyrophosphate, wherein a carbon, in place of the natural oxygen, connects the two phosphates. As a result, BPs have two side chains that can be modified to modulate their pharmacological properties. Clinically used BPs can be divided into non-nitrogen-containing compounds such as etidronate, clodronate, tiludronate, and nitrogen-containing BPs such as pamidronate, alendronate, ibandronate, risedronate, and zoledronate. All BPs have a high affinity for calcium, and in the body, they concentrate in the skeleton at sites of active bone remodeling. Both classes of BPs become embedded in new bone during the anabolic phase of remodeling by binding to the hydroxyapatite of bone, where they remain inert. When bone containing a BP is resorbed, the BPs are released in the acidic lacuna created by the osteoclast and are taken up by these cells. The

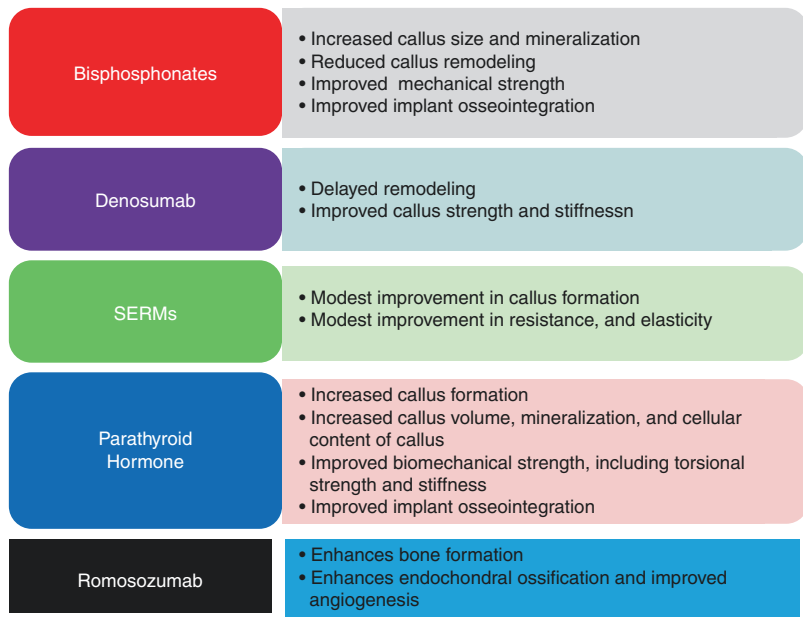

Fig. 20.4 Effect of the variable available osteoporosis treatments on fracture healing and bone repair

non-nitrogen-containing BPs induce apoptosis in the osteoclast by incorporating into ATP and thereby reduce resorption by decreasing the number of active osteoclast cells on the bone surface. The more widely used nitrogen-containing BPs inhibit farnesyl pyrophosphate synthase (FPPS), a key enzyme in the mevalonate pathway. This results in cytoskeletal changes in the osteoclast, which inhibit the activity of the osteoclast and or may induce apoptosis of these cells [132]. Similar to the non-nitrogen-containing BPs, the net result is a decrease in osteoclastic bone resorption. Because these compounds become entombed in the bone, they reside in the body long after treatment cessation, and, indeed, the calculated half-life of elimination of BPs from the skeleton is up to 10 years (reviewed in [133]). This is substantiated by the observation of detectable levels of pamidronate in the urine of patients 8 years after they had ceased treatment [134]. Given that resorption of bone by the osteoclast is a key component of fracture repair, concerns have been raised regarding BP-associated inhibition of the repair process.

Van der Poest [135] evaluated whether alendronate prevented bone loss in distal radius after Colles' fractures. The BMD of distal radius increased significantly at 3 and 6 months compared with that of the control group. There were no significant differences of anatomic and functional outcomes between the alendronate group and control group after 1-year follow-up. In a high tibial osteotomy study, Harding et al. [136] found that infusion of zoledronic acid increased the pin fixation of external fixation but did not affect the bone healing. Bisphosphonates reduced osteoclast activity, but further clinical results showed that they did not have advert effects on bone healing.

The timing of bisphosphonates infusion was a controversy. In an animal study, Amanat et al. [137] found that delayed infusion of zoledronic acid increased more callus volume compared to both saline and infusion of zoledronic acid immediately at the time of the fracture. However, a meta-analysis reported that the timing of infusion bisphosphonate did not affect fracture healing [138]. This was consistent with Colon-Emeric's report [139]. One possible reason may be that both included studies involved cancellous bone fractures. The spacious environment for cancellous new bone formation is large enough, so the bone remodeling process which suppressed by a reduction in the resorption process by bisphosphonate was not so important [140]. But the compact bones are different. Fracture bone debris needs to be absorbed to allow space for new bone formation [141]. Another reason may be that the dose of bisphosphonates for treating osteoporosis is sufficient for affecting bone healing in animal but insufficient for human. Conversely, fracture healing in patients already on BP at the time of fracture was reported to be slightly delayed, and a delay in bony union was observed an estimated 26% of the time; but there was no difference in nonunion incidence [132].

The clinical effect of oral bisphosphonate on osseointegration has been explored in trials in postmenopausal women with osteoporosis [142], in which patients with internal fixation of a pertrochanteric fracture were randomly allocated to alendronate 70 mg/week orally or control. The removal torque for the screws was two times higher in the treatment group, indicating improved osseointegration. Other studies with ibandronate and clodronate have shown that both systemic and local perioperative treatment with bisphosphonate can improve the fixation of total knee prostheses [143, 144].

Local Application of Bisphosphonates and Its Effect on Bone Repair

Bisphosphonates have an anabolic effect on osteoblasts, improving proliferation and maturation inhibiting apoptosis. In the meantime, it decreases both the activity and number of osteoclasts, as well as indirectly inhibits the activity of osteoclasts by altering the signals sent by osteoblasts to osteoclasts. Considering these actions, it results in increased bone formation [145, 146].

Earlier studies have shown that locally delivered alendronate has an effect on increased bone repair in a critical-sized calvarial defect [147] and peri-implant bone formation [148] and is associated with bone allografts [149]. Moreover, alendronate enhances alkaline phosphatase

(ALP) activity and bone neoformation [147]. In a study done by Ozer and colleagues [150] to evaluate the effects of alendronate sodium administered locally in mandibular bone defects created in rabbits, results revealed that the use of alendronate sodium in conjunction with autogenous bone grafting improves the osteoconductive properties of the graft, enhances graft retention in the defect, and improves ossification. In another study carried out by Limirio and co-workers [151] to investigate the local effect of 10% doxycycline and 1% alendronate combined with poly(lactic-co-glycolic acid) (PLGA) on bone repair in rats, results revealed that the association of 10% doxycycline and 1% alendronate with PLGA-accelerated bone repair.

In conclusion, there is RCT evidence that bisphosphonate treatment after the fracture does not delay fracture healing, even following hip fracture surgery or when the drug is administered in the immediate postoperative period. Local or systemic application of bisphosphonate may improve osseointegration. In patients already on long-term BP therapy who sustain an atypical femoral fracture (a clinically rare event), a delay in bony union was observed in nearly one-quarter of the cases.

Denosumab

There has been one experimental study in animals of the impact of denosumab, the fully human monoclonal antibody against the RANK ligand (RANKL), on fracture healing [19]. Denosumab is a potent inhibitor of osteoclast-mediated bone resorption and would, therefore, be expected to have similar properties to the bisphosphonates. The effects of denosumab were therefore compared with those of alendronate in male huRANKL knock-in mice [152]. In a mouse model, unilateral transverse femoral fractures were induced, and animals were treated with denosumab (10 mg/kg) or alendronate (0.1 mg/kg) biweekly for 42 days. Both groups showed increased callus and increased amounts of mineralized cartilage in the callus, but remodeling and organization of the callus was delayed. However, despite the delay in healing, the strength at the fracture site was still improved compared with controls as callus strength and stiffness were greater in treated animals than in controls. The authors concluded that neither intervention had negative implications for short-term repair of fracture. To our knowledge, there are no studies on denosumab and osseointegration.

In another work, carried out by Adami and colleagues [153], the effect of denosumab on fracture healing was assessed in the FREEDOM trial, in the subset of 199 patients with incident non-vertebral fractures [34]. In this double-blind, placebo-controlled analysis, the use of denosumab was not associated with delayed healing or with any complications following fracture or surgical management, providing further support to the concept that even potent antiresorptive treatment does not interfere with fracture healing.

Selective Estrogen Receptor Modulators: Raloxifene

The effects of selective estrogen receptor modulators (SERMs) on bone repair, fracture healing, and osseointegration remain unclear. One experimental animal study in ovariectomized rats showed that raloxifene did not have an impact on progression of fracture repair [154], with similar radiographic assessments and biomechanical properties to sham-operated animals. Similar properties were found for estrogen. In another study [155] carried out to determine, whether systemic application of the selective estrogen receptor modulator raloxifene promotes fracture healing compared to untreated control-, estrogen-deficient-, as well as estrogen-treated mice using a standardized femoral osteotomy model ($n = 60$ mice). Ten days after surgery, contact radiography and undecalcified histomorphometric analysis revealed that raloxifene administration significantly improved the early stage of fracture healing compared to all other groups. At day 20, raloxifene and estrogen treatment led to a significant increase in callus mineralization and trabecular thickness compared to control mice. μCT analyses revealed no evidence of complete bony bridging of the fracture site in any control- nor estrogen-deficient mouse after 20 days, while all femoral fractures in the raloxifene and estrogen

group already healed adequately at this time. These data indicate that raloxifene treatment significantly improves all phases of fracture healing at least in mice. Animal studies also revealed better callus formation, resistance, and elasticity with raloxifene and estrogen therapy [156]. Therefore, raloxifene could be a possible pharmaceutical to enhance fracture healing in women, without the known side effects of estrogen.

On the basis of the limited nonclinical data available, it can be concluded that raloxifene (like estrogen) has a modest, if any, effect on fracture healing. So far, there is no clinical evidence for an impact of SERMs on bone repair.

Anabolic Medications

Parathyroid Hormone

Parathyroid hormone (PTH) is the first bone anabolic drug approved for the treatment of osteoporosis, and, intriguingly, a number of animal studies prove the ability of PTH to induce fracture healing. PTH may therefore parathyroid hormone therapy has been considered a potential novel treatment option in humans with impaired healing. Teriparatide has different effects on trabecular and cortical bone. Because of the high degree of remodeling and apoptosis of trabecular bone osteoblasts, teriparatide has a more profound activity on trabecular as compared to cortical bone, which has a lower degree of osteoblastic apoptosis.

The existing basic science data suggest a role for PTH signaling in the regulation of chondrogenesis and osteogenesis. Investigations in humans have confirmed an anabolic role for PTH (1–34) in enhancing bone density and reducing fracture risk. Animal studies on fracture healing suggest that PTH signaling improves the biomechanical properties of fracture callus and accelerates callus formation, endochondral ossification, and bone remodeling [157].

Assessing for the clinical evidence revealed that there are a growing number of case reports on the effects of teriparatide on fracture healing [158–160]. These reported positive effects of teriparatide on healing in patients with hip fracture [160] or delayed union of a fracture of the spine or extremities [159]. There is also a report from an observational cohort of 145 patients with complicated fractures in a number of different anatomical sites (including spine and extremities) [161]. Treatment with 20 ug/day teriparatide was associated with resolution of pain or evidence of at least partial fusion within 12 weeks in 141 patients (97%). A recent meta-analysis [162] revealed that parathyroid hormone treatment in patients with fracture was better than a placebo or no treatment based on the time for fracture healing, the degree of fracture pain, and the functional outcomes. There is great clinical value in healing fractures over a shorter time, with reductions in pain and with functional improvements [163]. Therefore, these results showed the effectiveness of PTH in fracture healing. The meta-analysis revealed that parathyroid hormone treatment accelerated fracture healing, which allows patients to return to normal life sooner and reduces the medical consumption and chronic morbidity associated with long-term treatment. Furthermore, parathyroid hormone can be applied to any type of fracture, commenced at any time, and applied throughout the entire healing period. As a result, it was postulated that parathyroid hormone therapy may be useful in the course of implant fixation and in the established nonunion fracture. Some studies have started to explore related issues [164–169], but the number of these studies is still limited, and most of them are small sample size.

In conclusion, the effectiveness and safety of PTH in fracture healing is reasonably well-established and credible. There is clinical evidence for an effect of teriparatide in fracture healing. Anecdotal case reports cannot be considered as clinical proof, and interpretation of the RCT is hampered by the absence of an effect of the higher dose. However, the evidence is consistent with a positive impact of 20 ug/day teriparatide on clinical fracture healing and fracture nonunion, and this is supported by the preclinical investigations which suggest a faster healing process with this agent. More high-quality RCTs are needed to verify the differential effects of PTH on fracture healing in different populations.

Romosozumab

The effects of sclerostin antibodies (Scl-Ab) treatment on fracture healing have been investigated in various animal models. Scl-Ab treatment increases bone mass and strength at the fracture site in rats using either a closed femoral fracture model [170] or a femoral osteotomy fracture model [130, 171]. More bony tissue and less cartilage tissue have been observed at the fracture site in the rat femoral osteotomy fracture model [171, 172] and cynomolgus monkey bilateral fibular osteotomy model [170], indicating that Scl-Ab treatment is able to enhance endochondral ossification during fracture healing. Similarly, the bone mass and strength is increased during fracture healing in SOST-KO mice, in both a femoral closed fracture model [173] and a tibial closed fracture model with external fixation [132]. In both models, the endochondral ossification is hastened as evidenced by increased cartilage removal [173, 174]. These studies indicate that down regulation of sclerostin expression enhanced fracture healing through faster endochondral ossification. As the downstream target of sclerostin, the Wnt/β-catenin signaling pathway is well-known to be an important factor to facilitate proper fracture healing [175]. Beta-catenin signaling is activated in the fracture callus throughout the entire period of fracture healing [176], and precise regulation of β-catenin expression in the fracture site is required for fracture healing. Condition knock down of the β-catenin gene expression in the fracture callus impairs fracture healing [176]. The β-catenin level has also been shown to elevate during the femoral bone defect healing in SOST-KO mice [167], as well as open tibial fracture healing in mice treated with DKK1-Ab treatment [177], indicating that the inhibition of sclerostin or DKK1 promotes bone healing though activating the Wnt/β-catenin signaling pathway. Although no investigations have been reported that Scl-Ab treatment will activate the Wnt/β-catenin signaling during fracture healing, results from these two related studies [177, 178] support that Scl-Ab treatment shall also act through the same signaling pathway to promote fracture healing.

Scl-Ab treatment also enhances bone repair in osteoporotic condition. In a tibial drill-hole defect model in OVX rat, Scl-Ab treatment accelerates the intramembranous bone repair in both the trabecular bone and cortical bone of the defect region. This indicates that Scl-Ab treatment also enhances bone formation and bone healing in OVX conditions. In addition, in rat femoral osteotomy healing, Scl-Ab treatment has proven to enhance fracture healing through the hastened endochondral ossification and improved angiogenesis [171]. Angiogenesis is essential for bone healing, in both normal and osteoporotic fracture healing [179, 180]. Given that Scl-Ab improves fracture healing in a rat long bone closed fracture model [170], rat femoral osteotomy, or cynomolgus monkey bilateral fibular osteotomy model [170], Scl-Ab is also expected to be able to improve osteoporotic fracture healing. Clinical trials are essential to support the potential routine applications of Scl-Ab for fracture healing enhancement in osteoporotic patients, apart from the known effects of Scl-Ab in the prevention of secondary osteoporosis in this high-risk group.

Management of Atypical Femoral Fractures

In 2005, the first cases of atypical femoral fractures (AFF), occurring in the shaft of the femur, were reported. Since then, more cases have been documented, leading to great concern among patients and a consequent dramatic decrease in bisphosphonate prescribing was noted. In the first ASBMR task force report [181], a provisional definition of AFF was published, with a subsequent update in 2014 [182], and the fracture must have four of five of the major features, and minor features may or may not be present. Table 20.1 shows the major and minor features included in the definitions of atypical femoral fractures.

Typically, patients are referred to osteoporosis specialists or primary care clinicians after surgery for the AFF. In most cases, a medullary nail is placed to provide fixation of the fracture and allow healing. For patients with bowed femurs, an alternative nail entry site may be necessary [183], and lateral fixation has been suggested as an alternative [184]. In any event, surgery

Table 20.1 major features included in the definitions of atypical femoral fractures according to the updated ASBMR definition [182]

Updated ASBMR definition of atypical femoral fractures
Major features
Associated with minimal trauma at most
Starts at lateral cortex and is mostly transverse, although it may become oblique
No or minimal comminution
Complete AFF produce a medial spike, incomplete affect lateral cortex only
Lateral cortex has localized reaction resulting in breaking or flaring
Minor features
Bilateral fractures (may be complete or incomplete)
Prodrome of groin or thigh pain
Increased femoral shaft cortex
Delayed fracture healing

followed by a rehabilitation program is necessary for those who have had a complete fracture; it is possible that the surgical technique will be refined over time. Medical management [181, 182] has been suggested as follows: discontinuation of antiresorptive treatment, adequate dietary calcium, vitamin D supplementation if needed, and consideration of teriparatide, particularly for patients with incomplete AFF who have not undergone surgery. The response to teriparatide has been variable [185]. In a recent open label study, Watts and co-workers [186] performed iliac crest bone biopsies and clinical assessment in 14 patients treated with teriparatide for 2 years. Five had incomplete fractures (two bilateral), six had unilateral complete fractures, one had bilateral complete fractures, and two presented with complete unilateral fracture but developed a contralateral fracture during teriparatide therapy. Spine BMD was increased in most patients and stable in the remainder. In the hip, bone density remained stable throughout the teriparatide treatment.

In conclusion, drugs and bioactive substances will probably have a role in the future management of fractures. The evidence for the effects of osteoporosis drugs on bone repair and fracture healing is overall positive. Experimental studies indicate that teriparatide may have a favorable impact on fracture repair, and there are signs that these effects may potentially translate into therapeutic applications. There is no evidence that short-term treatment with the antiresorptive agents (bisphosphonates, SERMs, and denosumab) is detrimental to fracture repair, though the impact of long-term therapy is unknown. There is high demand for accurate epidemiological study of fracture, osteoporotic or otherwise, which is difficult due to widely differing coding systems between hospitals and variations in the criteria for good functional outcome [71]. Delayed union appears to be likely in 5–10% of cases. The risk of nonunion is increased by local factors, such as poor contact, biomechanical instability, and the magnitude of the injury, as well as a number of systemic conditions (e.g., osteoporosis, diabetes, or NSAID use). Further research is therefore needed to provide more accurate data on epidemiology as well as the natural course of the disease.

Finally, surgical decisions and expertise could markedly change the impact of pharmacological treatment, particularly if the treatments affect both fracture healing and orthopedic fixation with screws. This issue is closely tied to the quantitative evaluation of fracture healing in RCTs. A related problem is difference in the impact on bone repair for differing fracture sites (e.g., radius, tibia, or hip) or bone types (cortical or cancellous bone). There are currently no guidelines on whether results at one site can be extended to all others. This is an important point given the relative difficulties in recruiting patients with very serious fracture into RCTs.

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Part V

Towards Optimized Practice

Osteoporosis Management: Gaps in Patients' Care and Treatment

21

Yasser El Miedany

Introduction

Osteoporosis is a major public health threat in the United States and around the globe. As of 2010, 10.2 million adults have osteoporosis and another 43.4 million have low bone mass, a figure expected to rise nearly 30% by the year 2030 (Fig. 21.1). Osteoporosis is the major cause of fragility fractures, which are from low trauma not likely to occur in healthy bone, in the population age 50 and above. Taking the American population as an example, as osteoporosis prevalence increases parallel with aging, the number of fragility fractures may increase from two million in 2005 to three million in 2025 [1, 2]. Patients who sustain fragility fractures will, most likely, experience the morbidity/comorbidity consequent upon fracturing. Furthermore, fragility fractures cause substantial pain and severe disability, often leading to a reduced quality of life. In addition, hip and vertebral fractures are associated with decreased life expectancy. Patients who have had any one fracture have an increased risk of subsequent fractures. The US Preventive Services Task Force recommends osteoporosis screening and treatment after a first fracture due to increased risk of future fractures, including a 20-fold greater risk for a clinically serious hip or spine fracture [3, 4]. The National Osteoporosis Foundation considers all postmenopausal women and men older than 50 years with prior hip or vertebral fracture as candidates for osteoporosis treatment [5].

Fortunately, osteoporosis is a preventable disease that can be diagnosed and managed before any fracture occurs. Previous studies suggest that sex, age, race, education level, insurance type, baseline calcium use, fracture site, prior osteoporosis diagnosis, previous fracture, chronic comorbidities, and history of cigarette smoking are predictors of the use of osteoporosis medication for secondary prevention of further fractures [6–11]. In patients who have already experienced a fracture, the appropriate use of available therapies can effectively decrease the risk of future fractures by up to 50%. Yet osteoporosis is underdiagnosed and undertreated worldwide, and secondary fracture risk is poorly addressed in patients who have sustained a first fracture [12–21].

This chapter will start by discussing the need to treat in osteoporosis, followed by highlighting the gaps in osteoporotic patients' care as well as treatment. The chapter will expand to analyse and describe approaches to close these gaps and lastly and present the most recent guidelines for the management of osteoporosis.

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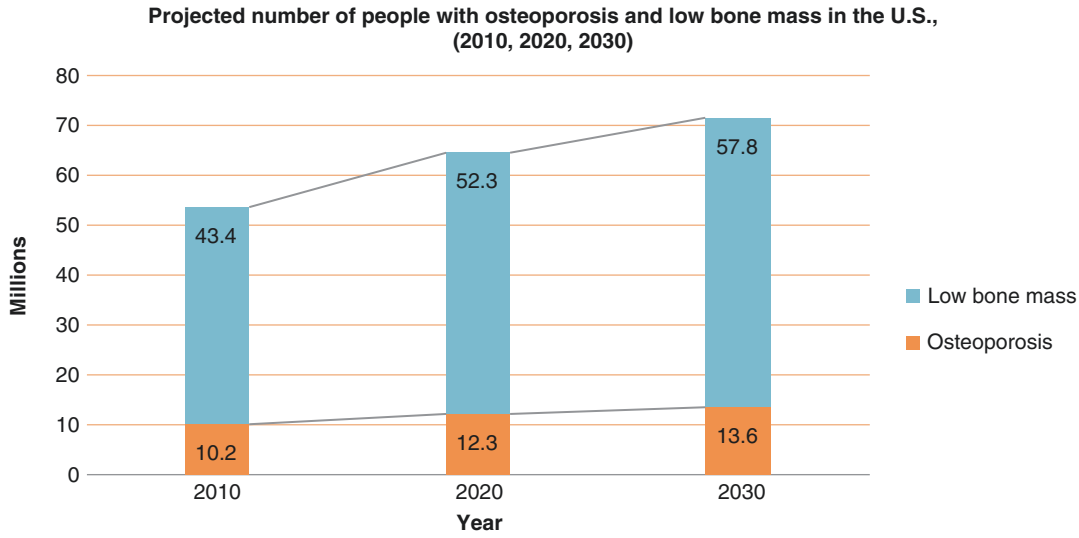

Fig. 21.1 Projected number of people with osteoporosis and low bone mass in the United States (2010, 2020, 2030)

Osteoporosis: The Need to Treat

Many guidelines for the assessment and treatment of osteoporosis recommend that intervention be considered in men and women who have sustained a fragility fracture [22]. Guidelines in North America [23, 24] specifically refer to a prior hip fracture, as well as spine fracture, as mandatory indication for treatment because of the marked effect of fractures at these sites on both morbidity and mortality. In addition, hip fractures have large economic consequences. For example, hip fractures account for 17% of all osteoporotic fractures in Europe but comprise 54% of the direct cost of fractures [22]. The need for treatment arises because of the increased risk of a second fracture [25], which is particularly acute in the immediate post-fracture period when fracture rates are substantially increased [26–28].

Despite a number of advances, particularly in the diagnosis of osteoporosis, the assessment of fracture risk, the development of interventions that reduce the risk of fractures, and the production of practice guidelines, many surveys indicate that a minority of men and women at high fracture risk actually receive treatment [29–35]. According to the 2008 Joint Commission Report, Improving and Measuring Osteoporosis Management, only 20% of patients with low-impact fractures in the general population are ever tested or treated for osteoporosis or receive therapies to reduce the risk of future fracture within the year following the fracture [13, 36–39].

In another large observational cohort study, only 6.6% of hip fracture patients received calcium and vitamin D after surgery [12]. Paradoxically, the therapeutic care gap may be particularly wide in the elderly in whom the importance and impact of treatment is high; studies have shown that as few as 10% of older women with fragility fractures receive any osteoporosis therapy (oestrogens not considered) [40, 41]. Furthermore, treatment rates following a fracture are lower for those individuals who reside in long-term care [33]. This contrasts with the situation following myocardial infarction, for which condition a significant care gap has been overcome in the past 15 years: 75% of such individuals now receive beta blockers to help prevent recurrent myocardial infarction [42].

Osteoporosis is a silent disease that progresses without the evidence of symptoms until a fracture occurs. Fragility fractures are responsible for considerable pain and suffering, severe disability, reduced quality of life, and use of long-term care and rehabilitation resources [43]. The leading

cause of the loss of independence in men or women 70 years of age and older are fragility fractures due to falls at home [44]. Most patients do not regain their pre-fracture functionality or independence and many are permanently limited in mobility, ability to fulfil social roles, and performance of activities of daily living and self-care [45]. Psychological consequences have also been noted, such as loss of self-efficacy, depression, and anxiety [46].

The economic burden due to osteoporotic fractures is high and will escalate as the population ages. Overall, the medical cost of osteoporosis and related fractures is estimated to be $20 billion per year. The annual cost in the United States of caring for osteoporotic-related fractures alone parallels or exceeds the annual cost for myocardial infarction, breast cancer, and/or cerebrovascular accidents [47]. Direct costs are predicted to escalate to $25 billion by 2025 and $50 billion by 2050 due to the increase in the incidence of osteoporotic fractures [48].

In the United States, two million osteoporotic fractures occur every year. One of two women and one of five men will sustain an osteoporotic fracture in their lifetime [49]. For women over 50 years, the lifetime risk of a fracture is higher than the combined risk of developing cervical, uterine or breast cancer, while men over 50 it is higher than risk of developing prostate cancer [50].The incidence rates of fragility fracture due to osteoporosis at all skeletal sites increase with advancing age in both women and men, with those 85 years and older at highest risk [51].

Furthermore, an initial fragility fracture increases the absolute risk of sustaining future fractures for both men and women [52]. An individual who sustains a fracture is 86% more likely to sustain a fracture of another type [53]. For men, although their risk for an initial fracture is lower than that of women, once they sustain an initial fracture, their risk for additional fractures escalates to the same level of risk for subsequent fracture as women in their age group. For women, an initial fracture increases their risk for subsequent fraction as high as or higher than the initial fracture risk carried by women in the 10-year age group above theirs. Research has demonstrated increased risk for future fracture applies to virtually all clinical fracture sites, is highest immediately after the initial event, and persists for up to 10 years [54].

Premature mortality associated with fracture, particularly following hip and vertebral fractures, is well documented [55, 56], and evidence of elevated mortality risk following other types of osteoporotic fractures is mounting [55]. Risk of death is most pronounced in the first three to 6 months after sustaining a fracture and the risk increases substantially with subsequent fractures [57]. The cumulative incidence of adverse outcomes following all low-trauma fractures leads to the death in 39% women and 51% men within 5 years and excess mortality related to fracture can extend up to 10 year. These mortality rates far exceed that expected for an age- and sex-matched population (24% in women and 27% in men) [58].

Osteoporosis: Gaps in Care

Osteoporosis is a preventable disease that physicians can diagnose and manage in the early stages of low bone mass. For reducing morbidity and mortality associated with osteoporosis-related fractures, it is imperative to recognize individuals at risk for osteoporosis. Yet, contrary to recommendations for universal screening and treatment, osteoporosis is vastly underdiagnosed and undertreated worldwide. Considering the reasons linked to such paradox, three gaps in patient care could be identified challenges facing healthcare professionals and policymakers responsible for providing care to populations in relation to bone health.

Gap 1: Failure to Follow Guidelines for Screening for Osteoporosis

Based on the analysis of medical claims data collected from a large American cohort between 2008 and 2014, screening rates among privately insured women ages 50+ were persistently low. Only 26.5% women in the age group

65–79 and 12.8% women 80 years and older had measurement for their bone mass. Even lower utilization rates were seen among non-Hispanic black women and women of low socioeconomic status [59].

There is also evidence that physicians who do screen may not be following recommended diagnostic guidelines and may be making the treatment decisions based on incorrect assumptions. The analysis of 5 years of electronic health and radiological records at a regional health care system in United States revealed two-thirds of women receiving new medication prescriptions for osteoporosis therapy did not need treatment. In fact, one half of the women being treated may not have qualified for screening at all, because they were of younger age and had no risk factors for osteoporosis [60]. Another study found that family physicians order bone densitometry and try to manage osteoporosis appropriately but lack a rationale for testing [61]. Surveys on physicians' learning needs indicate the majority (66.8–83.2%) want to be informed about criteria for ordering and the interpretation of densitometry reports and T-scores and the frequency of testing [62, 63].

In conclusion, the first gap in the patients' care lies in the hands of the physicians who need information regarding who and when to test, guideline-based diagnostic criteria and indications for testing, and information on how to interpret tests.

Gap 2: Failure of Secondary Fracture Prevention

Secondary fracture prevention is an obvious first step in the development of a systematic approach to prevention of all fragility fractures caused by osteoporosis. Early aggressive treatment intervention after a first low-trauma fracture, especially in those with low bone density, can reduce the risk of additional fractures and associated premature mortality. Since the 1980s, it has been reported that up to one half of hip fracture patients have already sustained a previous fracture [64–67]. Meta-analyses have shown that individuals who have sustained a fracture are at approximately double the risk of sustaining subsequent fractures, as compared to their fracture-free peers [68, 69]. However, data show that the percentage of patients receiving a treatment for osteoporosis, even after sustaining a hip fracture, has declined in the United States from 41% in 2001 to 21% in 2011. These numbers demonstrate a low participation of physicians in their patients' secondary fracture prevention.

The effectiveness of the broad range of currently available osteoporosis treatments has been comprehensively reviewed [70]. Cochrane Collaboration systematic reviews have evaluated most of the anti-osteoporotic medications for secondary fracture prevention. The outcomes documented the effectiveness of the available osteoporosis treatments to reduce future fracture risk. Therefore, it is of great concern that a pervasive and persistent secondary prevention care gap is evident throughout the world. The International Osteoporosis Foundation (IOF) Capture the Fracture® program website provides an up-to-date bibliography of all PubMed cited secondary prevention audits and surveys, undertaken internationally, nationally, regionally, and locally [71].

In response to this widely documented care gap, models of care have been developed in many countries to ensure that fragility fracture patients receive secondary preventive care – which includes both osteoporosis management and intervention to prevent falls – in a consistent and reliable fashion. The most common models are referred to as orthogeriatrics services and fracture liaison services (FLS) [72].

In conclusion, physicians need information regarding the range of anti-osteoporotic agents available for treatment and how to select the appropriate one for each patient, drug safety profiles, dosing instructions, timing of initiation of medication, and how to treat patients at moderate risk for fracture. The implementation of services such as orthogeriatrics and fracture liaison service does help in secondary fracture prevention.

Gap 3: Patient-Physician Communication Failure

This lack of patient awareness and action is coupled with a lack of healthcare professional (HCP) awareness and intervention. Multiple studies demonstrate that patients diagnosed to have osteoporosis tend to underestimate their risk of becoming osteoporotic and are less concerned about the consequences of osteoporosis than other diseases. Earlier studies assessing osteoporotic patients who have multiple FRAX risk factors, one-third did not believe they were at an increased risk for future fracture [73, 74]. Even when patients have had fragility fractures, more than half do not link their fractures with osteoporosis even when told they have the disease, nor do they appear to understand they are at increased risk for future fracture [75].

Patient education on low bone mass and osteoporosis is imperative for long-term management of osteoporosis and fracture prevention. Therefore, it is crucial for physicians to communicate to patients that a diagnosis of osteoporosis, increasing age, or a fragility fracture increases the risk of future fracture. However, surveys and focus groups indicate primary care physicians feel there are barriers to communicating with elderly patients about the complexity of osteoporosis risk and fracture prevention, which include time constraints, the complexity of their other health problems, and their reluctance to add new medications to long lists of prescribed therapies [61, 63].

In conclusion, better approaches to deliver the message such as informative video clips, adverts, or information leaflets to highlight the magnitude of the issue to the patients, educate and empower them to actively participate in shared decision-making, and support self-care and medication adherence as well as persistence. Physicians need training to enable them to provide clear physician-patient communication and patient education that can help patients understand their risk and agree to adhere to a management pathway.

Osteoporosis: Mind the Treatment Gap

Despite the increasing number of effective drugs to treat osteoporosis, discouraging evidence suggests that there is a growing gap in treatment options. This has been evidenced by the finding that many patients who should receive pharmacological treatment are either not being offered these drugs or, when prescribed, not taking them [76]. This has also been reported in patients recovering from hip fracture, for whom there is universal agreement of the importance of pharmacological therapy [77]. Although many reasons exist for this gap in osteoporosis treatment, perhaps the two most important reasons are fear of rare side effects and concerns regarding long-term efficacy.

Fear of Rare Side Effects

In an article published earlier in the New York Times Gina Kolata [78], patient concerns with side effects, particularly atypical femur fractures, were highlighted as an important contributor to the lack of appropriate treatment for osteoporosis. Although these side effects have only been clearly associated with bisphosphonates, patient perceptions about these risks are extending to all osteoporosis drugs, which is particularly concerning because atypical femur fractures are extremely rare. So although the relative risk of atypical femur fractures in patients taking bisphosphonates is increased, the absolute risk ranges from 3.2 to 50 cases per 100,000 person-years [79]. When used in patients who are at high risk of fracture, these drugs are estimated to prevent 80–5000 fragility fractures for each atypical femur fracture possibly induced by treatment [80]. Several steps can be taken to address this problem [81], such as improved patient and doctor education regarding both the risk-benefit ratio of these drugs and the prodromal symptoms (e.g., groin or hip pain) of atypical femur fractures; potential use of dual x-ray energy absorptiometry to monitor patients on therapy specifically for

features of atypical femur fractures [82]; identification of high-risk patients using femur geometrical characteristics and other risk factors for atypical femur fractures [83]; and the development of pharmacogenomic markers identifying patients at increased risk of atypical femur fractures.

A second rare side effect of bisphosphonate use is osteonecrosis of the jaw, which was initially described in the setting of high-dose bisphosphonate use in patients with metastatic cancer. This side effect is extremely rare in patients treated at doses recommended for osteoporosis, with an estimated incidence of 0.001–0.01% [84]. Again, better education of patients, doctors, and dental practitioners, along with maintenance of good oral hygiene and dental health, are key to overcoming this barrier to treatment.

Concerns Regarding Long-Term Efficacy

As highlighted by a position statement from the FDA [85], data regarding the anti-fracture efficacy of bisphosphonates after 5 years of use is scarce and perhaps conflicting. This assessment, combined with the observation that the risk of the rare side effects of atypical femur fractures and osteonecrosis of the jaw increases with duration of therapy [79, 84], has led to legitimate concerns about the long-term (>5 years) treatment of patients with bisphosphonates or other anti-resorptive agents, such as denosumab. However, data from the Fracture Intervention Trial Long-term Extension (FLEX) [86] showed that postmenopausal women with low hip T scores (−2.0 to −2.5) who continued treatment with alendronate for 10 years had fewer clinical vertebral fractures than women receiving placebo after 5 years had. Similarly, in the HORIZON extension study of zoledronic acid [87], women with T scores less than −2.5 had fewer morphometric vertebral fractures after six annual infusions than women who received only 3 years of treatment had. On the basis of these studies, current recommendations are to treat patients who warrant therapy with a bisphosphonate for 5 years and then reassess, basing subsequent treatment on the level of fracture risk and potentially considering a so-called drug holiday for a variable period of time, albeit in the absence of data showing the efficacy of this approach [88]. Long-term treatment (up to 10 years) with denosumab in an open-label extension of the FREEDOM trial has been shown to have a persistent benefit by reducing non-vertebral fractures [89].

Osteoporosis: Closing the Gaps

Osteoporosis is a preventable disease that physicians can diagnose and manage in the early stages of low bone mass. Recognition and management of individuals at risk for osteoporosis is imperative for reducing morbidity and mortality associated with osteoporosis-related fractures. This part of the chapter will provide a comprehensive overview of the state of osteoporosis care for individuals at high risk of suffering fragility fractures and how to close the gaps in both the patients' care and treatment. The different 'gaps' identified are listed in Table 21.1; to facilitate their discussion and approach to handling, they have been clustered into four major themes. Given current projections indicating that the burden of fragility fracture is heavy and expected to grow over the coming few decades, it is imperative that governments, key opinion leaders, and national patient societies work together now to ensure that epidemiological data are available to inform policy development. There is much to be done. Therefore, the task now is to ensure the dissemination and adoption of these best practice examples, adapted for local considerations, in order to tackle the current, and future, burden of fragility fractures worldwide.

Closing Gap 1: Secondary Fracture Prevention

In 2012, the IOF issued a report on the World Osteoporosis Day devoted to the global Capture the Fracture® Campaign [64, 90]. Approximately

Table 21.1 Gaps in care and treatment of patients diagnosed to have osteoporosis

Theme	Gaps in care and treatment
Case finding and management	Gap 1: Secondary fracture prevention Gap 2: Osteoporosis induced by medicines Gap 3: Diseases associated with osteoporosis Gap 4: Primary fracture prevention for individuals at high risk of fracture
Public awareness	Gap 5: The importance of staying on treatment Gap 6: Public awareness of osteoporosis and fracture risk Gap 7: Public awareness of benefits versus risks of osteoporosis treatment
Government and health system issues	Gap 8: Access and reimbursement for osteoporosis assessment and treatment Gap 9: Prioritization of fragility fracture prevention in national policy
Lack of data	Gap 10: The burden of osteoporosis in the developing world

half of the patients admitted with hip fracture suffered a prior fragility fracture in the months or few years before breaking their hip [64, 65, 67, 91], representing an obvious opportunity and, indeed, imperative for assessment and intervention to be carried out to prevent future fractures. The report also cited numerous audits undertaken across the world to establish what proportion of fracture patients received the osteoporosis care that they needed: in the absence of a systematic approach, less than a fifth received such care. Whilst some exciting progress has been made to close this care gap, many publications and initiatives since 2012 highlight that there is still a huge amount of work to be done throughout the world. This was reviewed in a dedicated publication by the international osteoporosis foundation [92]. Clinically effective models of care, namely, orthogeriatrics and fracture liaison services, have been developed in many countries to close the secondary prevention care gap in a highly cost-effective manner.

Models of Care: Orthogeriatrics Services and Fracture Liaison Services

In response to the well-documented secondary fracture prevention care gap, innovators throughout the world have developed models of care designed to ensure that health systems respond to the first fracture to prevent second and subsequent fractures.

- *Orthogeriatrics services* (OGS): The need for effective orthopaedic–geriatric co-care of patients admitted to hospital with hip fractures is well recognised in professional guidance [93–95]. Such models of care focus on expediting surgery, ensuring optimal management of the acute phase through adherence to a care plan overseen by senior orthopaedic and geriatrician/internal medicine personnel, and delivery of secondary fracture prevention through osteoporosis management and falls prevention.
- *Fracture liaison services* (FLS): The fracture liaison service (FLS) model of care has also been adopted in many countries. The purpose of an FLS is to ensure that all patients aged 50 years or over, who present to urgent care services with a fragility fracture, undergo fracture risk assessment and receive treatment in accordance with prevailing national clinical guidelines for osteoporosis. The FLS also ensures that falls risk is addressed among older patients through referral to appropriate local falls prevention services.

These two service models are entirely complementary. As the adoption of orthogeriatrics services for hip fracture sufferers becomes more widespread, orthogeriatrics services are increasingly likely to deliver secondary preventive care for these patients. As hip fractures constitute approximately 20% of all clinically apparent fragility fractures, in health systems which have implemented orthogeriatrics services, FLS will provide secondary preventive care for the other 80% of fragility fracture sufferers who have experienced fractures of the wrist, humerus,

spine, pelvis, and other sites. This 'division of labour' is illustrated in the falls and fractures pyramid in Fig. 21.2, which was first presented in policy developed by the Department of Health for England in 2009 [96]. A similar approach has been advocated in Australia [97], Canada [98], New Zealand [99], and the United States [100, 101].

For the vital role of secondary fracture prevention, as well as both orthogeriatrics services and FLS as a reliable means to deliver this care to fracture patients, this has been addressed and featured in a growing number of clinical guidelines and government policies.

Closing Gap 2: Medication-Induced Osteoporosis

Many widely used medicines have been associated with decreases in bone mineral density and/or increased fracture incidence, although these links have not been proven as causal in every case. A 2014 review described the potential pathogenesis of bone loss associated with all of these classes of medicines [102, 103]. Table 21.2 shows a list of these medications. This section will focus on three very commonly used agents: glucocorticoids for a range of conditions, androgen deprivation therapy for treatment of prostate cancer in men, and aromatase inhibitors for the treatment of hormone receptor-positive breast cancer in women.

Steroids-Induced Osteoporosis

Steroids are very commonly used to control inflammation in the setting of a broad range of conditions including autoimmune dermatological and respiratory diseases, as well as malignancies and organ transplants. Estimates suggest that 1 in 13 adults aged 18 years and over have been prescribed oral steroids at some stage of their life [103]. Up to 30–50% of patients receiving chronic glucocorticoid therapy experience clinically apparent fragility fractures and/or asymptomatic vertebral fractures, making steroid-induced osteoporosis the leading cause of secondary osteoporo-

Table 21.2 Osteoporosis induced by medicines

Medications most commonly associated with osteoporosis
Glucocorticoids
Proton pump inhibitors
Selective serotonin reuptake inhibitors
Thiazolidinediones
Anticonvulsants
Medroxyprogesterone acetate
Hormone deprivation therapy
Calcineurin inhibitors
Chemotherapies
Anticoagulants

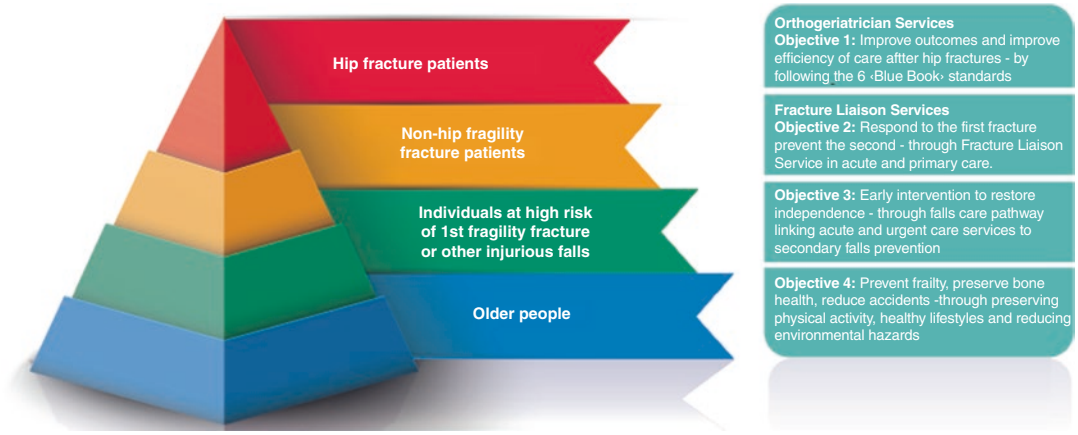

Fig. 21.2 Orthogeriatrics services and fracture liaison services as components of a systematic approach. (Quoted from reference [96] under open access scheme)

sis [104]. Meta-analysis has shown previous steroid use to be associated with a relative risk of 2 for any fracture at the age of 50 years and 1.7 at the age of 85 years [105]. For osteoporotic fracture, the range of relative risk is 2.6 and 1.7; and for hip fracture 4.4 and 2.5 for the same age groups.

Steroids have a direct impact on the bones as it affects both the function and numbers of the three major types of bone cells [106–110] (Fig. 21.3):

- Osteoclasts: Stimulation by steroids results in prolonged survival of osteoclasts, leading to excessive bone resorption, particularly in trabecular bone in the spine.
- Osteoblasts: By reducing the recruitment of the precursors to osteoblasts, the number of mature osteoblasts is reduced, resulting in decreased bone formation.
- Osteocytes: Osteocyte apoptosis (cell death) is triggered by steroids and may contribute to an increase in fracture risk prior to a reduction in bone mineral density (BMD).

Steroids' indirect effects on bone: Other mechanisms that may contribute to glucocorticoid-induced bone loss through indirect effects on bone include hypogonadism, reduced physical activity, increased renal and intestinal losses of calcium, and reduced production of growth hormone, insulin-like growth factor 1 (IGF1), and IGF1 binding protein (IGF-BP) [111]. In addition, the underlying diseases for which glucocorticoid therapy is administered are often associated with increased inflammation, which contributes to bone loss through increased production of pro-inflammatory, pro-resorptive cytokines. Whilst glucocorticoids suppress inflammation and hence should mitigate the adverse effects of inflammation, disease relapse despite therapy is associated with episodes of increased bone resorption. Finally, glucocorticoid excess has adverse effects on muscle mass and function, leading to myopathy and increased risk of falls [112, 113].

To close this gap, clinical guidelines for the prevention and treatment of glucocorticoid-induced

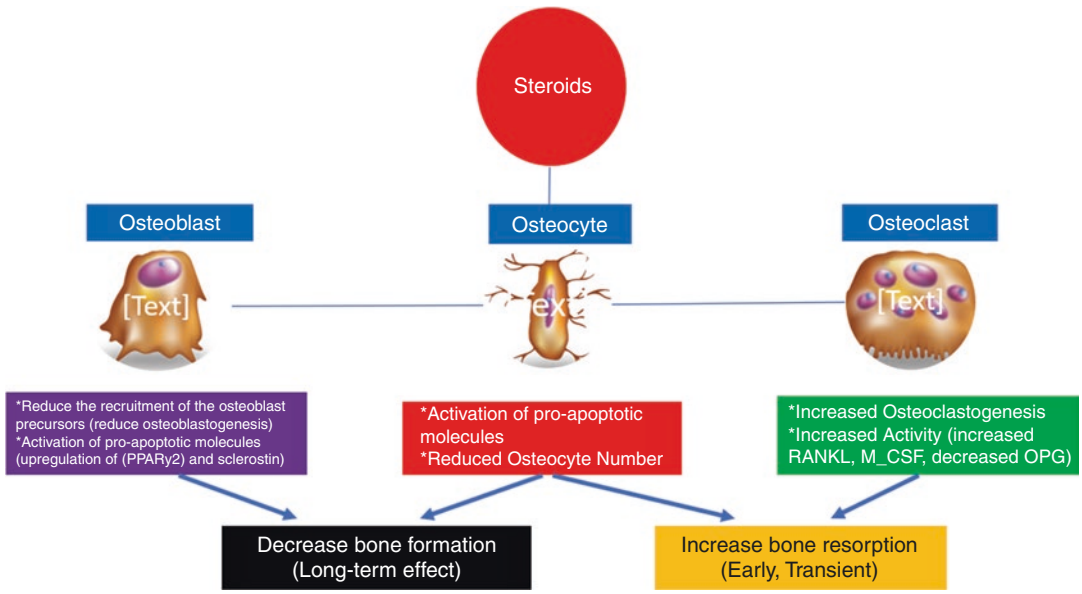

Fig. 21.3 Direct effects of glucocorticoids on bone. PPARγ2: Peroxisome proliferator-activated receptor gamma receptor 2 (favoring the differentiation of pluripotent precursor cells to adipocytes in preference to osteoblasts). Sclerostin: It binds to the co-receptors for frizzled, Lrp4 and Lrp5, resulting in the inhibition of Wnt sigaling, leading to reduced differentiation of osteoblast precursors to mature osteoblasts and increased osteoblast and osteocyte apoptosis. M-CSF macrophage colony stimulating factor, RANKL receptor activator of nuclear factor-κB ligand, OPG osteoprotegerin. (Increased M-CSF and RANKL and decreasing production of OPG by osteoblastic cells and osteocytes result in an increase in both the number and activity of osteoclasts. This effect diminishes with time, possibly as a result of the reduction in number of osteoblasts and osteocytes)

osteoporosis are already available in several countries. The European League Against Rheumatism (EULAR) [114] and a Joint Guideline Working Group of IOF and the European Calcified Tissue Society (ECTS) [115] have produced internationally relevant guidance. Whilst the detail of individual guidelines varies somewhat, the common theme is that individuals receiving chronic steroids therapy are at increased risk of fracture on account of taking steroids, and, in a significant proportion, the risk is great enough to warrant the offer of preventive treatment. An organized programme of care – GIOP (Glucocorticoid-Induced Osteoporosis Program) – has been implemented in the United States in order to improve preventive care for members [116]. The programme goals are to identify patients at risk of fracture, provide education, redesign and implement new pathways of care, and monitor outcomes.

Androgen Deprivation Therapy-Induced Osteoporosis

Pathogenesis: Androgen deprivation therapy (ADT), in the form of gonadotropin-releasing hormone agonists (GnRHs), limits the production of testosterone and estradiol, leading to chemical castration [102]. GnRHs elicit this effect by reducing the secretion of luteinizing hormone and follicle-stimulating hormone. This is a consequence of GnRHs binding to GnRH receptors in the pituitary gland and downregulating the gonadotropin producing cells.

The beneficial clinical effects of ADT in men with symptomatic metastatic prostate cancer are rapid and dramatic [117]. ADT is universally accepted as the first-line treatment of symptomatic metastatic prostate cancer [118]. Prostate cancer is the most common non-cutaneous malignancy in men, with 1 in 6 men being diagnosed during their lifetime [119]. Approximately half of men diagnosed with prostate cancer will receive ADT at some stage after diagnosis [120]. A meta-analysis of relevant studies reported that between 9% and 53% of survivors had osteoporosis166. A rapid decline in BMD is observed during the first year of ADT treatment [121]. A cohort study based on medical claims data from Medicare beneficiaries in the United States compared fracture rates for men with non-metastatic prostate cancer who initiated GnRH agonist treatment against a comparison group who did not receive GnRH agonist treatment [122]. The men treated with GnRHs had statistically significantly higher rates of any clinical fracture (relative risk [RR]: 1.2), vertebral fractures (RR: 1.5), and hip/femur fractures (RR: 1.3). Longer duration of treatment also conferred greater fracture risk.

To close this gap, clinical guidelines relating to the prevention and treatment of ADT-induced osteoporosis have been published in several countries. Local clinical leaders in osteoporosis care should explore opportunities for collaboration with colleagues in urology departments to establish what proportion of ADT treated patients have undergone osteoporosis assessment and received guideline-based care.

Aromatase Inhibitor-Induced Osteoporosis

Pathogenesis: Aromatase inhibitors (AIs) reduce oestrogen levels by the inhibition of the peripheral conversion of androgens to oestrogens. This results in lower oestrogen levels with a consequent increase in bone turnover and bone loss.

Aromatase inhibitor use and fracture incidence: Breast cancer is the most common neoplasm and primary cause of cancer-related mortality in women, affecting 1 in 8 women worldwide. Aromatase Inhibitors currently represent the gold standard adjuvant treatment for postmenopausal women with hormone receptor-positive breast cancer [123]. The annual rate of bone loss observed for women taking Aromatase Inhibitors of around 2.5%. This figure is elevated compared to healthy postmenopausal women who lose about 1–2% per year [124].

The analysis of the Women's Health Initiative Observational Study compared fracture rates among breast cancer survivors with women with no history of breast cancer at baseline [125]. After adjustment for factors related to hormone levels, risk of falls, prior fracture history, medica-

tion use, comorbidity, and lifestyle, the increased risk for all fractures studied among survivors was 15%. Studies comparing two commonly used aromatase inhibitors, anastrozole [126] and letrozole [127], with tamoxifen have reported significant increases in fracture risk for the aromatase inhibitor–treated patients. A comparative study of anastrozole with exemestane showed similar fracture rates [128]. A position paper from the European Society from Clinical and Economical Aspects of Osteoporosis (ESCEO) has comprehensively documented studies on the skeletal effects of aromatase inhibitors [124].

The care gap for aromatase inhibitor–induced osteoporosis has not been documented as comprehensively as the secondary fracture prevention and steroid-induced osteoporosis care gaps have been discussed. Clinical guidelines relating to the prevention and treatment of aromatase inhibitor–induced osteoporosis are available in several countries. Local clinical leaders in osteoporosis care should explore opportunities for collaboration with colleagues in oncology departments to establish what proportion of aromatase inhibitor–treated patients have undergone osteoporosis assessment and received guideline-based care.

Closing Gap 3: Diseases Associated with Osteoporosis

There are many health problems which can increase an individual's risk of developing osteoporosis and suffering fragility fractures [129]. These include a broad array of disorders: autoimmune, digestive and gastrointestinal, endocrine and hormonal, hematologic, neurological, mental illness, cancer, and AIDS/HIV. These include also malabsorption, anorexia nervosa, primary or secondary hypogonadism, dementia, and diabetes.

In many of these conditions, there is lack of specific guidelines for management of osteoporosis, whereas clinical guidelines relating to the prevention and treatment of associated osteoporosis is available in some countries for some of these conditions. Working Group comprised of clinical experts in the field of COPD and fracture prevention published a 5-step approach which includes case finding, risk evaluation, differential diagnosis, therapy, and follow-up [130]. Clinical guidelines relating to the prevention and treatment of osteoporosis in celiac disease are available. Similarly, guidelines relating to the prevention and treatment of osteoporosis in inflammatory bowel disease (IBD) have been published [92].

The estimated number of people living with dementia in 2013 was estimated to be 44.4 million, a figure set to increase to 75.6 million and 135.5 million by 2030 and 2050, respectively. The largest increases in the projected number of dementia sufferers will be in East Asia and Sub-Saharan African regions. By 2050, the proportion living in what are currently low- and middle-income countries will increase to 71%, compared to 62% in 2013. In 2010, the global societal cost of dementia was US$604 billion, representing 1% of global GDP [131], and 486,000 people died as a result of dementia worldwide [132].

A significant overlap exists between sufferers of dementia and older people at high risk of injurious falls and fractures; this is particular evident amongst patients presenting with hip fracture. A UK study published in 2009 found that during a 12-month period, 66% of participants with dementia had a fall compared with 36% of age-matched controls [133]. Furthermore, the incidence of falls in dementia was nine times higher than that observed among a control group. The incidence of hip fracture among patients with Alzheimer's disease has been reported to be almost three times higher than amongst cognitively healthy peers [134]. In a meta-analysis, the prevalence of dementia amongst older hip fracture patients was estimated to be 19% [135]. The prevalence of cognitive impairment was estimated at 42%. In 2007, the Scottish Hip Fracture Audit reported on the prevalence of dementia amongst hip fracture patients [136]. Over a quarter (28%) of patients had a documented past medical history of dementia, which the authors indicated was likely to be a significant underestimate of actual prevalence on account of the poor diagnosis rates for dementia documented at that time.

In 2011, a monograph on the subject of dementia, falls, and fractures summarised the current evidence [137]:

- Persons with dementia suffer more falls, more fractures, and higher post-fracture mortality than those without dementia, yet they are under-assessed for falls risk factors and are less likely to receive treatment for osteoporosis.
- Falls and fracture patients have a high prevalence of dementia and cognitive impairment, yet do not routinely receive cognitive assessment and, consequently, frequently miss an opportunity for a diagnosis of dementia to be made.

Subsequent studies from Canada [138], Finland [139], the United Kingdom [121], and the United States have added to the evidence that osteoporosis is infrequently diagnosed and treated in people living with dementia.

As the population of dementia sufferers is set to grow spectacularly in the coming decades, evidence-based guidelines for the management of osteoporosis – and falls risk – in dementia must be drafted and implemented as soon as possible.

Closing Gap 4: Primary Fracture Prevention

Whilst the prevention of secondary fractures remains a priority, in the long term, the ultimate goal would be the prevention of the first fracture. Advances in the fracture risk assessment during the last decade provide a platform for development of clinically effective and, crucially, cost-effective approaches for the identification of those individuals at high risk of a primary fracture. In order to ensure that a primary fracture prevention programme has the potential to be cost effective, consideration must be given to which first fragility fracture is to be prevented. Primary prevention of hip fracture is likely to be more cost-effective than primary prevention of wrist fracture, because hip fractures cost considerably more to manage than wrist fractures. In this regard, consideration must be given to what proportion of all hip fractures occur as an individual's first fragility fracture at any skeletal site [93].

Whilst definitive data are not available to give an accurate estimate of the primary hip fracture incidence, the following illustration is consistent with the current evidence-base:

- Approximately 50% of hip fracture patients have suffered clinically apparent fragility fracture(s) prior to breaking their hip, which was usually a non-vertebral fracture [64, 65, 67, 91].
- Conservative interpretation of studies from Spain and Japan suggests that a further 10% [140] to 25% [141] of hip fracture patients may have suffered previous vertebral fractures – the majority of which are not recognised or diagnosed as such [142] – but have not suffered clinically apparent non-vertebral fractures.
- Therefore, 25–40% of hip fracture patients may have suffered the hip fracture as their first overt fragility fracture at any skeletal site.

This analysis highlights the challenge faced by efforts to proactively case-find the relatively small proportion of individuals who are likely to suffer a hip fracture as their first fragility fracture. It should also be noted that fragility fractures at sites other than the hip impose a significant burden on older people.

Vertebral fractures lead to many adverse consequences for sufferers, including [143]:

- Back pain, loss of height, deformity, immobility and increased number of hospital bed days [144, 145]
- Reduced quality of life resulting from the loss of self-esteem, distorted body image, and depression [146–149]
- A significant negative impact on activities of daily living [150, 151]

Studies from Australia [152], Canada [153], and the international Global Longitudinal Study of Osteoporosis in Women (GLOW) [154] have all reported significant reductions in health-related quality of life among individuals who have suffered fragility fractures at all skeletal sites. Accordingly, a robust clinical case exists for primary prevention of all major osteoporosis fractures, defined as hip, clinical vertebral, wrist or proximal humerus fractures.

To close this gap, pragmatic approaches to case-finding individuals at high risk of suffering these fractures as their first fracture should be adopted, these include:

- Gap 2: Osteoporosis induced by medicines: systematic case finding of individuals at high fracture risk in this group
- Gap 3: Diseases associated with osteoporosis: systematic case finding of individuals at high fracture risk in this group
- Absolute fracture risk calculation: systematic application of tools such as FRAX® to risk stratify the older population

This is supported by most clinical guidelines which cover both secondary and primary fracture prevention

Closing Gap 5: Adherence to Therapy

Similar to other chronic, asymptomatic diseases, adherence to osteoporosis therapies is poor. The reasons for suboptimal adherence are multiple but include fear of possible side effects, dosing requirements, and an unwillingness to take a medication for a "silent" disease. Two measures of adherence to treatment are commonly used in studies:

- Persistence: Defined as either the time to treatment discontinuation or as the proportion of patients that at a certain time point still fill prescriptions without a gap in refills longer than an allowed period of time (e.g., 30, 60 or 90 days).
- Compliance: Defined as the ability of a patient to adhere to the dosing, timing, and conditions described by the prescriber or in accordance with the medicine's patient information leaflet. One measure of compliance is the medication possession ratio (MPR). MPR is usually defined as the number of days of medication available to the patient, divided by the number of days of observation.

In routine clinical practice, both persistence and compliance with osteoporosis treatment are sub-optimal, a phenomenon previously reported for other classes of widely used medicines including antihypertensives [155] and statins [156]. Approximately half of patients initiated on osteoporosis treatment do not follow their prescribed treatment regimen and/or discontinue treatment within a year [157]. This is particularly notable on account of the flexibility of dosing options of widely available osteoporosis treatments, which can be taken as daily, weekly, or monthly tablets, or as daily, quarterly, six-monthly, or annual injections. Intravenous or sub-cutaneous routes of administration provide a means to ensure 100% adherence with treatment, as long as a robust system is in place to administer the initial injection and reliably arrange follow-up injections at appropriate intervals. It has been estimated that improved adherence in the United States would reduce fracture rates by 25%, equating to approximately 300,000 fewer fractures per year and generate savings of US$3 billion [158].

In a trial to close the gap, in 2013, the Medication Adherence and Persistence Special Interest Group of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) undertook a systematic literature review of interventions to improve osteoporosis medication adherence [159]. Interventions identified which may improve adherence were:

- Simplification of dosing regimens
- Electronic prescriptions
- Patients' decision aids
- Patient education

Patients were most persistent with medications which had the least frequent dosing regimens [160–162]. The use of electronic prescriptions in combination with verbal counselling was associated with a 2.6-fold improvement in short-term compliance compared to verbal counselling alone [163]. A study from the United States evaluated the use of a patient decision aid in combination with usual primary care practice compared to usual primary care practice alone [164]. While adherence at 6 months was similar for both groups, the proportion with more than 80% adherence was significantly higher with the decision

aid. With regard to the impact of patient education, it should be noted that the largest and least biased studies reviewed showed only marginal improvement in adherence [165–168].

The impact of FLS on adherence has been evaluated in several studies [169–173]. Among patients managed by an FLS after fracture, between 74% and 88% remained on treatment at 12 months, and between 64% and 75% at 24 months. These data reinforce the notion that a 'teachable moment' exists after individuals have suffered a fragility fracture which can be capitalized upon by an FLS to improve adherence to treatment.

Closing Gap 6: Public Awareness of Osteoporosis and Fracture Risk

Over the past 2 decades, a number of studies have been undertaken to characterise the awareness of osteoporosis and fracture risk among older people. In 2008, investigators from a non-profit Health Maintenance Organization (HMO) in the Northwest United States sought to evaluate key stakeholder perspectives on osteoporosis care after a fracture [174]. These stakeholders included fracture patients, quality and other healthcare managers, primary care physicians, and orthopaedic clinicians as well as staff. Both patients and primary care physicians commented that confusion of osteoporosis with osteoarthritis was common. Furthermore, this confusion led to the perception that osteoporosis is a benign consequence of ageing.

In 2010, Canadian investigators evaluated osteoporosis knowledge among older fracture patients who were treated by orthopaedic surgeons at two major teaching hospitals in Ontario [175]. Fractured patients were asked two questions:

1. Do you know what osteoporosis is?
2. If yes, what do you think it is?

The overwhelming majority of respondents (91%, 115/127) said they knew what osteoporosis was. Among these individuals, 75% gave responses that were considered to be correct. Almost 40% of the interview participants completed a 'Facts on Osteoporosis Quiz'. Notably, less than half (41%) of those who took the quiz knew that a person who had suffered a spine fracture was at increased risk of suffering a fracture in the future as compared to a fracture-free individual.

The international GLOW study compared self-perception of fracture risk with actual risk among more than 60,000 postmenopausal women in 10 countries in Europe, North America, and Australia [176]. Key findings included:

- Among women reporting a diagnosis of osteopenia or osteoporosis, only 25% and 43%, respectively, thought their risk was increased.
- Among women whose actual risk was increased based on the presence of any one of seven fracture risk factors, the proportion who recognized their increased risk ranged from 19% for smokers to 39% for current users of glucocorticoid medication.
- Only 33% of those with at least 2 risk factors perceived themselves as being at higher risk.

To close the gap, efforts to improve awareness need to provide clear, evidence-based messages.

Disease awareness campaigns (DACs) such as 2Million2Many from the NBHA in the United States provided an innovative example of implementing this approach [177]. The key messages for 2Million2Many are very simple and compelling:

- Every year, there are two million bone breaks that are no accident (in the USA).
- They are the signs of osteoporosis in people as young as 50.
- But only 2 out of 10 get a simple follow-up assessment.
- Together we can break osteoporosis before it breaks us. But we must speak up. Remember: Break a bone, request a test.

The main target of the disease awareness campaigns is to drive awareness throughout the population of the world that fracture begets fracture. If all individuals aged 50 years or over know that suffering a first fragility fracture significantly increases their risk of suffering second and subsequent fractures, up to one half of all people who will suffer hip fractures in the future could be aware of that risk, and be proactive in taking steps to lower it.

Closing Gap 7: Public Awareness of Benefits Versus Risks of Osteoporosis Treatment

Numerous RCTs and Cochrane Collaboration systematic reviews have demonstrated the efficacy and safety of treatments for osteoporosis. However, in the last decade use of these treatments among individuals at high risk of fracture has been significantly impacted by reports relating to rare side effects, including osteonecrosis of the jaw (ONJ), atrial fibrillation (AF), and atypical femur fracture (AFF).

Earlier studies documented that the risk-benefit calculation for the treatment of osteoporosis among individuals who are at high risk of suffering fragility fractures, including life-changing and life-threatening hip fractures, significantly favours treatment [80, 178, 179]. Patients at risk of osteoporotic fractures should not be discouraged from initiating bisphosphonates, because clinical trials have documented that these medicines can substantially reduce the incidence of typical hip fractures. The increased risk of atypical fractures should be taken into consideration when continuing bisphosphonates beyond 5 years [180].

To close the gap, public awareness of osteoporosis must be increased dramatically throughout the world. Effective disease awareness campaigns are needed to ensure that when an older person sustains a fragility fracture, their first thought – and that of their family and friends – is: 'Did that bone break because of osteoporosis?' Health professionals and their organisations, national patient societies, health system leaders, and regulatory agencies must work together to craft clear, balanced communications concerning the benefits and risks of treatments. In concordance, both clinicians and patients need to be able to objectively discuss and evaluate the risk-benefit calculation for the patient's individual circumstances when making collaborative treatment decisions. Having ready access to absolute fracture risk calculation tools such as FRAX® can make such discussions far more tailored – and meaningful – to individual patients. It requires all those involved in the care of osteoporosis patients to ensure clear, balanced communication of these issues – to – individual patients and more widely when opportunities arise.

Closing the Gap 8: Access and Reimbursement for Osteoporosis Assessment and Treatment

During the last decade, IOF has undertaken a series of regional audits throughout the world [181–186]. These audits have evaluated epidemiology, costs, and the burden of osteoporosis in the regions, and have included an overview of access and reimbursement to treatment. Some countries had a very good reimbursement policy for diagnostic tools and therapies, while in other countries there was absolutely no reimbursement available and patients had to pay for all diagnostic tests and treatment.

In the United States reimbursement for treatment varies greatly depending on each patient's health plan. Health care reform is evolving from fee for service to supporting improved quality, prevention, and care coordination with financial incentives (or penalties) to encourage healthcare professionals and health systems to report on and improve patient outcomes. There are a number of quality measures focused on osteoporosis and post-fracture care but performance around these measures remains low compared to other major chronic diseases. Further, a major drop in reimbursement for DXAs performed in the office setting has led to a drop in the number of providers and more than one million less DXAs performed [93].

Closing the Gap 9: Prioritization of Fragility Fracture Prevention in National Policy

The IOF regional audits provide comprehensive information on the level of priority afforded to fragility fracture prevention by governments throughout the world [181–186].

Osteoporosis guidelines have been endorsed by several governments all over the world; however, there has been quite variation regarding the designation of osteoporosis as a national health priority. The majority of EU states (18/27), as well as most of the developing world, did not recognize osteoporosis or musculoskeletal diseases as a national health priority (NHP).

In the United States, despite a landmark report by the Surgeon General in 2004 and the specific

recommendations from key national and scientific societies intended to prioritize and improve osteoporosis and fracture prevention [187–189], implementation has been poor. Many patients are not given the necessary information about prevention and are not receiving appropriate testing to diagnose osteoporosis or establish osteoporosis risk. Most importantly, a majority of patients who have osteoporosis-related fractures are not being diagnosed with osteoporosis and are not receiving any of the Food and Drug Administration (FDA)–approved, effective therapies.

To close this gap, the provision of robust epidemiological estimates of fracture incidence throughout Asia-Pacific, Central Asia, Latin America, the Middle East, and Africa will be a critical step towards supporting development of fracture prevention policies for these rapidly aging populations.

Closing the Gap 10: The Burden of Osteoporosis in the Developing World

The developing world is set to bear the brunt of the burden of osteoporosis as the world's population rapidly ages during the first half of this century. Accordingly, it is ironic that few data on fracture rates exist in many developing countries. The IOF regional audits provide valuable insights in this regard [181–186].

In Asia, there is an urgent need at the national level to accurately quantify osteoporosis and fracture prevalence in many countries of this region. In eastern Europe and central Asia the lack of solid epidemiological and economic data on the costs and burden of the disease has been linked to the under recognition of osteoporosis status on the side of both the governments and healthcare professionals. Similarly, in Latin America, regional Audit identified a major lack of data on fracture incidence in the region. In the middle east and Africa, The IOF Middle East and Africa Regional Audit identified a major lack of data on fracture incidence in the region in 2011 [186]. Only 6 of the 17 countries in the audit had published hip fracture incidence data. Further, prevalence rates for vertebral fractures were available for only 3 countries.

To close this gap, all governments need to establish osteoporosis as a national health priority, with commensurate human and financial resources to ensure that best practice is delivered for all.

patients in their jurisdictions. Where the current disease burden is not known, studies to close such evidence gaps must be commissioned forthwith.

Guidelines

There has been significant development in the guidelines published for the management of osteoporosis. In general, guideline provides recommendations based on current evidence for best practice in the management of osteoporosis and prevention of fractures. It addresses risk factors for fracture, commonly used tools for fracture risk assessment, approaches to targeting therapy, pharmacological, and non-pharmacological treatments to reduce fracture risk in different patient groups, treatment of painful vertebral fractures and systems of care. Sometimes, the assessment and prevention of falls and surgical management of fractures is included.

The most recent guidelines published is the guideline update of the pharmacological management of osteoporosis in postmenopausal women published by the Endocrine Society, USA [190]. The Guideline Update is a document that permits rapid and focused communication to guideline stakeholders in response to new developments that substantially impact the recommendations of an existing clinical practice guideline (e.g., important new drug approval or withdrawal, important new risks or harms). This Guideline Update is published in response to the recent approval of romosozumab by the United States Food and Drug Administration (FDA), the European Medicines Agency, Health Canada, and other agencies; and it represents a formal amendment to the Endocrine Society's recently published clinical practice guideline regarding the pharmacological management of postmenopausal osteoporosis [191].

The guideline for the management of postmenopausal osteoporosis is designed to provide

the clinician with an evidence-based approach to the management of this condition. The guidelines (Fig. 21.4) stratify the patients according to their risk of fracture, using that FRAX algorithm, into four risk categories:

1. *Low risk:* It includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above −1.0, a 10-year hip fracture risk <3%, and 10-year risk of major osteoporotic fractures <20%.
2. *Moderate risk:* It includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above −2.5, and 10-year hip fracture risk <3% or risk of major osteoporotic fractures <20%.
3. *High risk:* It includes a prior spine or hip fracture, or a BMD T-score at the hip or spine of −2.5 or below, or 10-year hip fracture risk ≥3%, or risk of major osteoporotic fracture risk ≥20%.
4. *Very high risk:* It includes multiple spine fractures and a BMD T-score at the hip or spine of −2.5 or below.

NOGG (UK) provided another approach to stratification of osteoporotic fracture risk combining FRAX risk assessment and BMD measurement (Fig. 21.5). The intervention threshold is set at a risk equivalent to that associated with a prior fracture. Two bounds around the intervention threshold where the assessment of BMD will help to determine whether the individual close to the threshold either exceeds that bound or lies below the intervention threshold. These are called assessment threshold for bones. Very high risk is identified as the risk lying above the upper assessment threshold, whereas high risk lies between the intervention threshold and the upper assessment threshold. On the other hand, low risk is reported when the risk lies below the intervention threshold. Figure 21.6 shows a suggested algo-

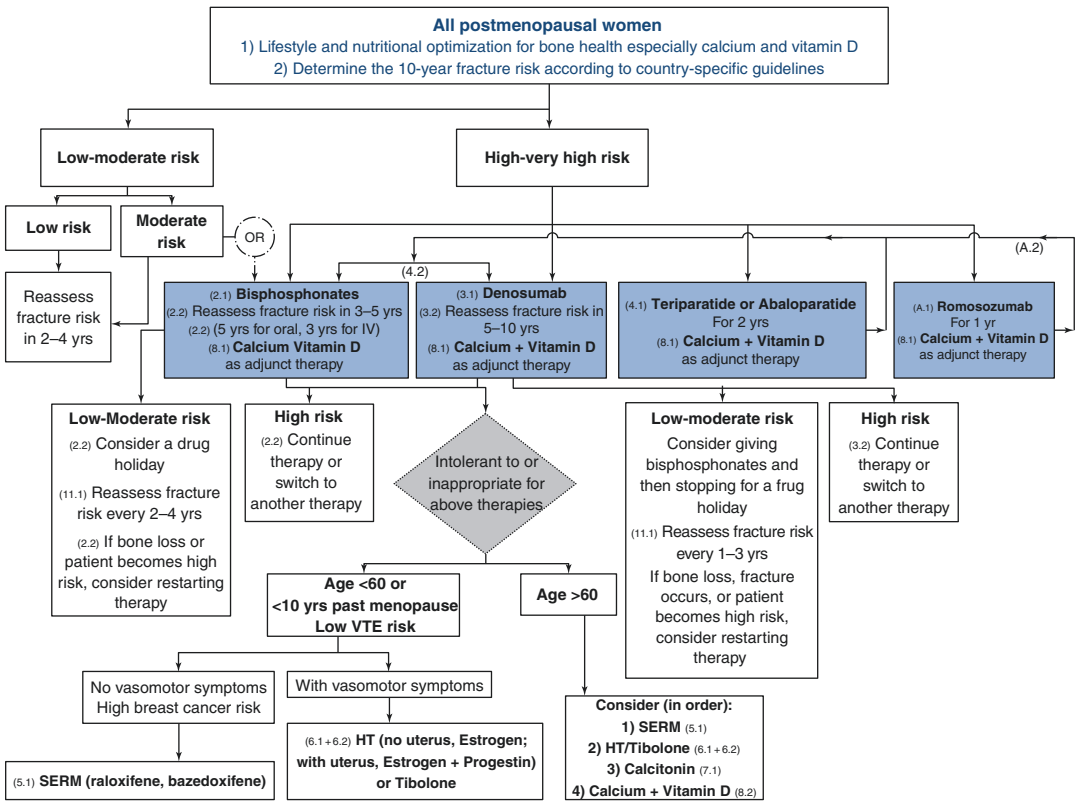

Fig. 21.4 Updated algorithm for the management of postmenopausal osteoporosis. (Quoted with permission from the American endocrine society update [190])

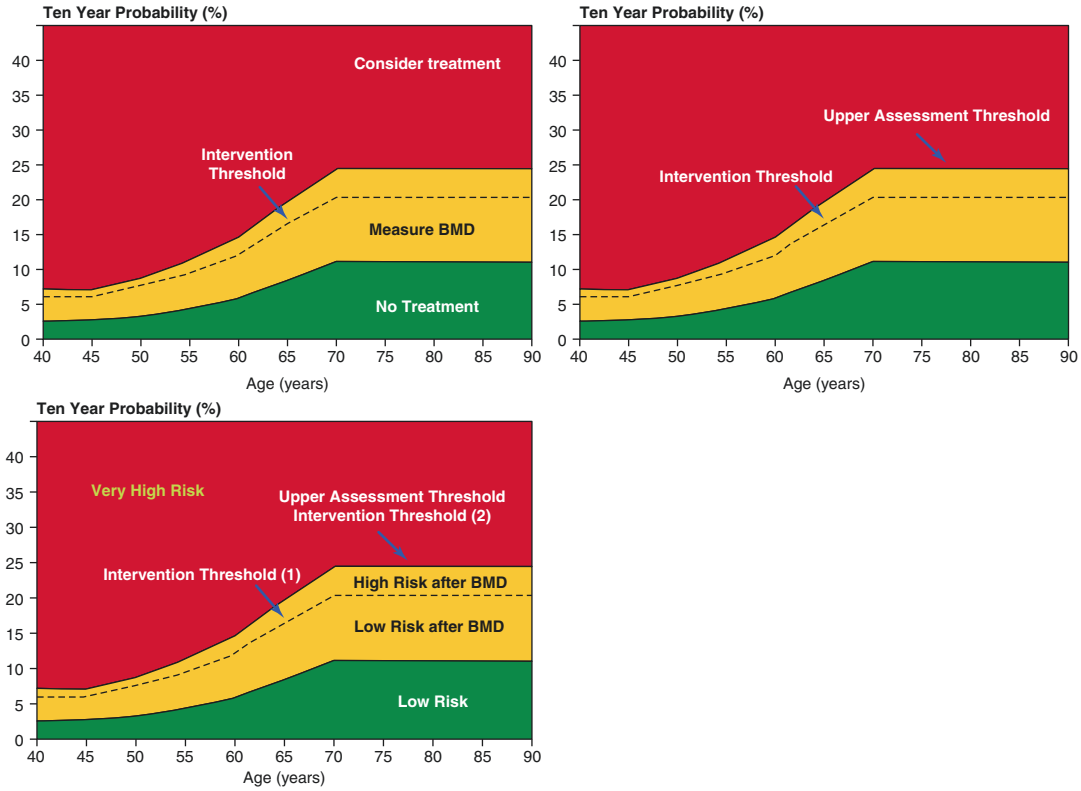

Fig. 21.5 Infographic outlining of the characterisation of fracture risk by FRAX major osteoporotic fracture probability in postmenopausal women. FRAX probability in the intermediate (orange) zone should be followed by BMD assessment and recalculation of FRAX probability including femoral neck BMD. After recalculation, risk located in the red zone, above the intervention threshold (2), is identified as "very high risk", orange zone above the intervention threshold (1) is identified as "high risk," whereas risk below the intervention threshold (1) or in the green zone is identified as "low risk"

rithm for the management of postmenopausal women adopting the recent recommendations. Recommendation regarding drug holiday and further assessment including repeat FRAX measurement has also been outlined in the guidelines.

In conclusion, this chapter has outlined a stepwise approach to case finding individuals who are at high risk of sustaining fragility fractures. By first closing the secondary fracture prevention care gap, up to half of individuals who would otherwise fracture their hip could be treated to prevent this debilitating and costly injury. Integration of bone health and falls risk assessments into the management of individuals who take medicines which have adverse effects on bone must become standard practice. Similarly, individuals who are diagnosed with diseases which feature osteoporosis as a common comorbidity need to receive care that will minimise their fracture risk. When the needs of these obviously high-risk groups have been addressed, we must turn our attention to the development of cost-effective strategies to prevent the first major osteoporotic fracture.

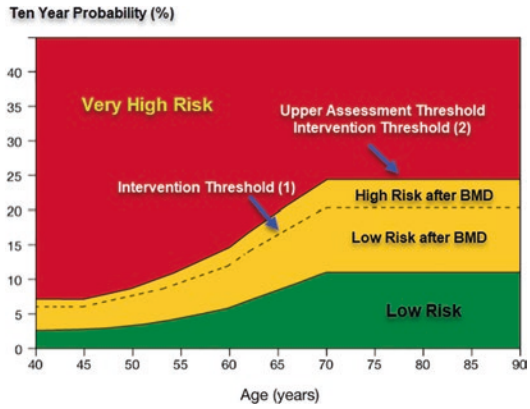

Fig. 21.6 Case finding and treatment pathways according to the categorisation of fracture risk: updated algorithm for the management of postmenopausal osteoporosis. The determination of fracture risk was carried out based on fracture risk score calculation (e.g., FRAX) and the measurement of lumbar spine and hip BMD. *Stratification of osteoporotic fracture risk can be based on NOGG (UK) as shown in the figures. The intervention threshold is set at a risk equivalent to that associated with a prior fracture. Two intervention thresholds are identified based on FRAX calculation based on BMD assessment. The treatment modality is suggested based on whether the individual either exceeds the intervention threshold or lies below it. Alternatively, using FRAX score alone, the fracture risks can be defined as follows: (1) low risk includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above −1.0, a 10-year hip fracture risk <3%, and 10-year risk of major osteoporotic fractures <20%; (2) moderate risk includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above −2.5, and 10-year hip fracture risk <3% or risk of major osteoporotic fractures <20%; (3) high risk includes a prior spine or hip fracture, or a BMD T-score at the hip or spine of −2.5 or below, or 10-year hip fracture risk ≥3%, or risk of major osteoporotic fracture risk ≥20%; and (4) very high risk includes multiple spine fractures and a BMD T-score at the hip or spine of −2.5 or below [190]. **Continue treatment up to 3 years (IV zoledronate) or 5 years (oral bisphosphonate / denosumab), reassess fracture risk: 1. if low or low-moderate risk, consider drug holiday. Reassess fracture risk every 2–4 years; if bone loss, fracture occurs or patient becomes high risk consider restarting therapy. 2. If high risk, continue therapy after checking for adherence or switch to another therapy. ***After the completion of the anabolic therapy course, consider giving bisphosphonate, then stopping for a drug holiday. Reassess fracture risk every 1–3 years. If bone loss, fracture occurs, or patient becomes high risk, consider restarting therapy

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22

Precision Medicine: Pharmacogenetics and Pharmacogenomics of Osteoporosis

Yasser El Miedany

Introduction

One challenge of clinical medicine is that patients vary in their response to pharmacologic agents. Such significant interindividual variability in the response to medications would explain why doses effective in some subjects are ineffective or cause adverse drug reactions in others (Fig. 22.1) [1]. Plasma drug levels can vary more than 1000-fold when the same drug dose is administered to two individuals having approximately the same weight [2]. Drug–drug interactions, drug–food interactions, sex, age, systemic/organ state (particularly renal and hepatic function), and pregnancy can all influence variability in drug responses between patients. Adverse drug reactions have been implicated as an important cause of hospital admissions, in one series accounting for 6·5% of all hospitalisations in two large UK hospitals [3]. In the 1990s, a large survey suggested that adverse drug reactions occurring in hospitals were the fourth to sixth leading cause of in-hospital mortality in the USA [4], and a follow-up survey in 2010 showed no improvement [5].

Genetic factors are likely to play a major role, given the fact that the individual response to a given pharmacologic agent is highly reproducible [6, 7]. In theory, the identification of genetic factors that influence drug absorption, metabolism, and action at the receptor level should facilitate for personalized therapy; could optimize drug efficacy and minimize toxicity profiles in a given population [8–11]. The potential for cost savings (through increased drug efficacy) and for decreased morbidity and mortality (through increased drug safety and fewer adverse drug reactions) is immense [12–16]. Although many adverse drug reactions are preventable and attributed in many cases to human error, others appear idiosyncratic, and potentially influenced by genetic factors. In one study of 2227 adverse drug reactions identified in a large teaching hospital, fewer than 50 percent had readily identified causes and thus might have been due to pharmacogenetic variability [17].

By itself, osteoporosis is a complex disease. Its complexity is not just characterized by the multiplicity of clinical aspects, risk factors or variability in the response to therapy; but also numerous other determinants. Similar to several other multifactorial disorders, osteoporosis is determined by environmental factors (such as dietary intakes, physical activities, falling and education), as well as genetic susceptibility; and likely by the interaction between these factors. It is not necessary to suggest that genetic variations do cause osteoporosis or fracture, but they can affect a subject's susceptibility to specific environmental factors and consequently modify the disease risk. This implies that each subject in the

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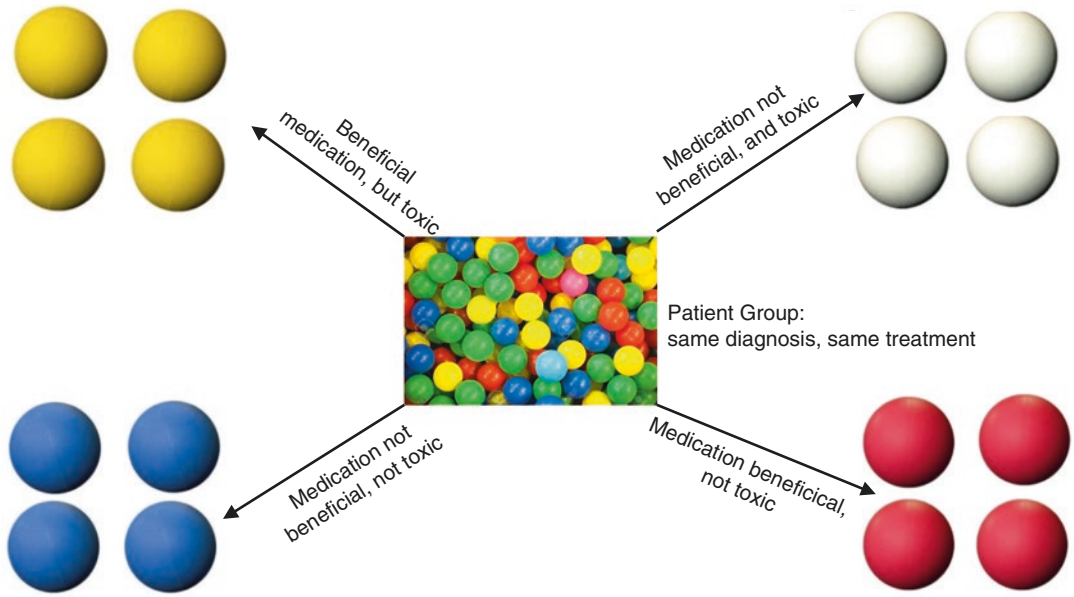

Fig. 22.1 Conventional treatment in standard practice: one size fits all. Interindividual variability in the response to medications would explain why doses effective in some subjects, are ineffective or cause adverse drug reactions in others

population has a unique risk profile that is amenable to change with time. Therefore, population data can be only cautiously extrapolated to the individual subject. Yet, at present, decisions about diagnosis and treatment of osteoporosis are still based on statistical data of the subjects' general population [18].

Clearly, attributed to the individual genetic and environmental risk profile, the standard generalized management protocols are suboptimal compared to personalized approach. Osteoporosis presents an ideal case for such an approach, because of its strong genetic precipitation and high variability in the susceptibility of fracture risk among individuals. In this framework, the principles of pharmacogenomics, which seek to correlate phenotypes and biomarkers by taking advantage of genomic technology, could be applied to identify the actual genetic basis of inter-individual variation in drug efficacy.

This chapter will take you on a journey starting with human genetics and genomics to and pharmacogenetics as well as pharmacogenomics of osteoporosis. It will discuss the already available data and conclude with future directions in this field.

Terminology

The term 'pharmacogenetics' was coined in the 1950s and captures the idea that large effect size DNA variants contribute importantly to variable drug actions in an individual [19]. Later, the International Conference on Harmonisation, a worldwide consortium of regulatory agencies, has put definitions for both pharmacogenomics as well as pharmacogenetics [20]. Gradually, the field started to adopt a standard set of definitions of other related terminologies and nomenclatures. For the reader we include the most important terminologies related to this field in this section.

Pharmacogenomics

Pharmacogenomics has been defined as the study of variations of **DNA and RNA characteristics** as related to drug response [20]. Therefore, it refers to the role of various components of the genome on response to a drug. Among the most commonly studied are genetic sequence variants, structural changes in chromosomes (e.g. translocations), epigenetic variants (e.g. changes in gene methylation), and variation in the expres-

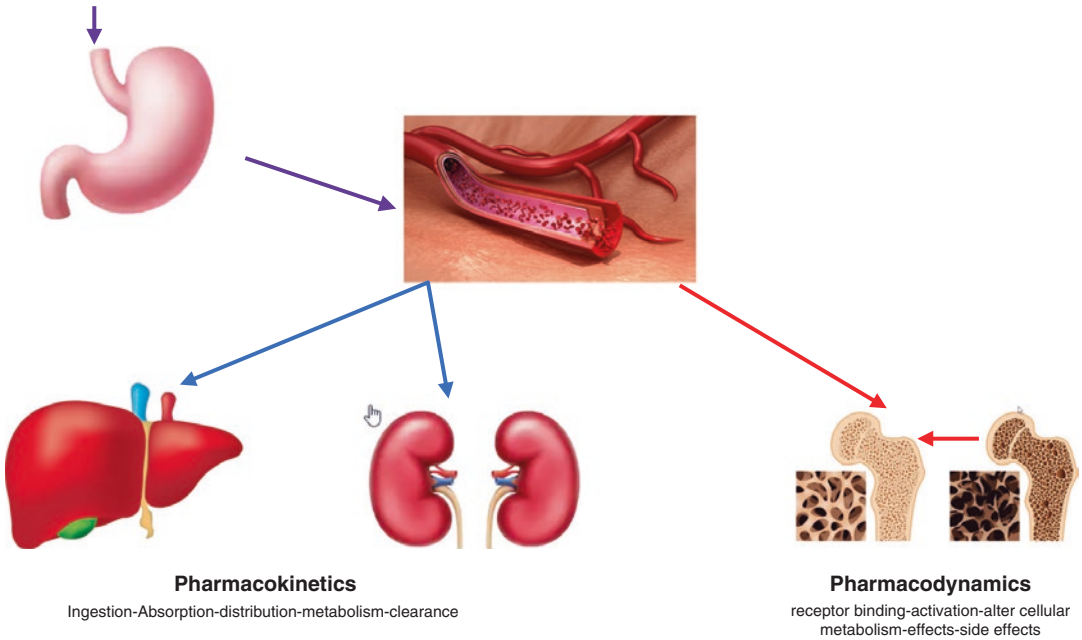

Fig. 22.2 Pharmacokinetics Vs Pharmacodynamics of a medication: Pharmacokinetics refers to how a drug moves through an individual's body. A drug's pharmacokinetics includes its absorption, distribution, metabolism, and elimination, all of which affect the drug's effect by altering the drug's concentration at its site of action. Pharmacodynamics refers to an individual's body's therapeutic response to a drug. A drug's pharmacokinetics includes medication receptor binding, post-receptor activation, alteration in the cellular metabolism, drug efficacy and side effects

sion profile of genes (changes in messenger RNA [mRNA] levels) or noncoding RNA (e.g. changes in microRNA). The genetic variation can be inherited through the germline or acquired (e.g. somatic mutation in a tumour). The availability of high-throughput techniques to interrogate the entire genome has facilitated many pharmacogenomic studies [19]. High-throughput screening (HTS) is a method of scientific experimentation that comprises the screening of large compound libraries for activity against biological targets through the use of automation, miniaturized assays, and large-scale data analysis.

Pharmacogenetics

Pharmacogenetics has been defined as the study of variations in **DNA sequence** as related to drug response [20]. Therefore, it is considered a subcategory of pharmacogenomics that refers to the role of genetic variation on response to a drug. Pharmacogenetics is generally used to refer to a specific DNA polymorphism or coding variant rather than epigenetic or transcriptomic changes across the genome. Pharmacogeneticists adopted a star nomenclature (e.g. CYP2C19*2) to describe variants in genes (sometimes termed pharmacogenes) underlying variability in drug response. In practice, pharmacogenetics and pharmacogenomics are often used interchangeably [19].

Pharmacokinetics

Pharmacokinetics (PK) refers to how a drug moves through an individual's body [21]. A drug's pharmacokinetics includes its absorption, distribution, metabolism, and elimination, all of which affect the drug's effect by altering the drug's concentration at its site of action.

Pharmacodynamics

Pharmacodynamics (PD) refers to an individual's body's therapeutic response to a drug [21]. This is generally determined by the drug's affinity and activity at its site of action, which is often a receptor (Fig. 22.2).

Genotyping
Genotyping refers to determining the combination of alleles (variants) at a specific location in the genome. The alleles can be single base changes, insertions, deletions, or tandem repeats.

Genetic Variation
Genetic variation refers to differences in genetic sequences among individuals in a population. Single nucleotide polymorphisms (SNPs) refer to variation at a single base pair, typically with a population frequency of at least 1%. Other forms of variation include insertions, deletions, copy number variants and short tandem repeats (short tandem repeats (STRs) are accordion-like regions of the human genome that vary in length (through expansion or contraction) between people based on a repeated DNA sequence). Variants that are seen at much lower prevalence than 1% of the population are often referred to as mutations, although this term may also be used to distinguish between variation that is inherited versus variation that arises de novo. All forms of variation have the potential to impact phenotype, regardless of their frequency, but the impact depends on a number of factors including the location of the variation within the genome and the functional consequences of the variation [19].

Epigenetic Changes
Epigenetic changes are those that affect genes without altering the gene sequence. This may occur via changes in gene methylation or histone modification (methylation, acetylation), either of which can influence the rate of transcription or silencing of gene expression. Other epigenetic changes include the alterations in noncoding RNAs and telomere length. These epigenetic changes can be passed on from parents to offspring but can also result from environmental influences on the epigenome. An example of an epigenetic change that affects drug metabolism is reduced sensitivity of a tumour to a chemotherapeutic drug due to gene methylation [22].

Linkage
Linkage is a powerful approach for identifying mutations causing classical Mendelian, monogenic disorders (i.e. changes in a single gene are implicated in the disease process and usually exhibit characteristic inheritance patterns, i.e. additive, dominant, or recessive genetic models). Generally speaking, mutations causing Mendelian disease are both rare in the general population and highly penetrant, with an obvious effect upon phenotype. Linkage of a locus with disease is evident when genetic markers at or near that locus are inherited together (co-segregate) with disease phenotype within families. Linkage analysis was very successful in identifying the causative gene for many monogenic diseases.

In contrast to the success in mapping monogenic disease, linkage was not so successful in mapping polygenic diseases such as osteoporosis [23]. There are many reasons for this, including the lack of power – a huge number of families would be needed for adequate power to detect the likely small effects of each individual quantitative locus affecting BMD [24]. Furthermore, for an age-related disease such as osteoporosis, the penetrance of genetic risk factors may only become evident with age.

Both candidate gene and whole-genome linkage scans were undertaken in osteoporosis, primarily focussing on BMD although some included femoral neck geometry, ultrasound properties of bone and bone loss (full review in Reference [25]). However, even the largest study, a meta-analysis involving 11,842 individuals, failed to demonstrate linkage with BMD at any locus at a genome-wide level of significance [26].

Genome-Wide Association Studies (GWAS)
In 1996, a prophetic paper was published, entitled ‘The future of genetic studies of complex human diseases’ [27]. The authors argued – incontrovertibly – that linkage was underpowered to identify the small-to-moderate genetic effects likely to be acting in common complex diseases (such as osteoporosis), and that a more

powerful approach would be linkage disequilibrium mapping to perform large-scale genome-wide association studies (GWAS). Linkage disequilibrium is the non-random association of alleles at different loci in a given population. Loci are said to be in linkage disequilibrium when the frequency of association of their different alleles is higher or lower than what would be expected if the loci were independent and associated randomly [28]. A major advantage was that such an approach did not require families but instead could use unrelated cases and controls. They also suggested that the appropriate level for statistical significance for a study of a million polymorphic markers would be $P < 5 \times 10^{-8}$.

At the time, such a study was, to a large extent, a theoretical experiment only. But in the following decade, advances in high-throughput genotyping technology (including optics and chemistry), study design and improved statistical analysis led to the development of GWAS and a revolution in modern disease genetics. Briefly, the technological advances mean that hundreds of thousands of variants (single nucleotide polymorphisms 'SNPs') dispersed throughout the genome can be genotyped simultaneously. SNPs are the most common type of genetic variation among people. Each SNP represents a difference in a single DNA building block, called a nucleotide. For example, a SNP may replace the nucleotide cytosine (C) with the nucleotide thymine (T) in a certain stretch of DNA. Genotyping is undertaken in both cases and controls and the results analysed for the evidence of association.

The proof that this approach could work was provided by the landmark GWAS paper published by the Wellcome Trust Case Control Consortium [29]. Suddenly, 24 loci were identified with association for seven major diseases, at a genome-wide level of significance, with further 58 probable loci (most of which were subsequently verified). The use of GWAS has meant that there is now robust evidence of association for a vast range of common complex diseases, with over 2000 loci identified for human diseases at P-value of $<5 \times 10^{-8}$. This has had an enormous impact upon our understanding of pathogenesis for almost all common human diseases, which may lead to the development of novel risk prediction and diagnostic strategies, and highlight potential therapeutic developments.

GWAS exploit linkage disequilibrium (LD) – where SNPs are inherited together more often than they should be by chance (i.e. 50% of the time, as predicted to Mendel's law of random assortment). This occurs because SNPs lying physically close to each other on a chromosomal strand are unlikely to be separated at meiosis: instead, they are inherited together on that chromosomal strand (known as a haplotype. A haplotype is a set of genetic determinants located on a single chromosome inherited from one parent). The extent of linkage disequilibrium and hence haplotypic structure in the genome has been determined through large mapping projects such as the HapMap. The immediate applicability of knowing the haplotypic structure is that one can infer the genotypes of all SNPs on a shared haplotype block through genotyping of only a single SNP – this SNP effectively 'tags' the entire haplotype block. Thus, by genotyping only a relatively small number of SNPs, one can impute the genotype of a much greater number of variants, all of which can then be assessed for association in the trait under question. This approach has allowed meta-analysis of studies genotyped by different platforms – even if only a small fraction of SNPs are genotyped by both studies, the genotypes of many other SNPs can be imputed allowing for a much larger group of overlapping SNPs for association analysis [30].

Several large GWAS have been undertaken in the field of osteoporosis genetics, resulting in an explosion of BMD-associated genes [31–33]. More recently several meta-analyses have been employed combining data from previously published smaller studies to enhance sample size, with consequent increase in statistical power and new gene discovery. The largest osteoporosis meta-analysis included data from collaborators from 17 GWAS encompassing 33,000

individuals of European and East Asian ancestry, with replication in over 100,000 independent subjects. This study confirmed the association of 24 pre-existing genetic loci and identified a further 32 novel associated loci with BMD; 14 loci were also associated with fracture risk [34].

GWAS results can be further explored using advanced data mining algorithms. For example, the Gene Relationships Across Implicated Loci (GRAIL) algorithm can elucidate further genes associated with known biological pathways and identify new connections.26 GRAIL analysis in the GWAS meta-analysis published by Estrada et al. [34] showed that the identified genes cluster in pathways: WNT/β-Catenin; RANK-RANKL-OPG and endochondral ossification. These pathways were not novel discoveries heralded by GWAS results; however, their identification validates GWAS as a means of identifying pathways of relevance to the biological system under examination. Further, several of these pathways are already exploited as therapeutic targets in osteoporosis (e.g. the use of denosumab, targeting the RANK-RANKL-OPG pathway and romosozumab targeting the WNT/β-Catenin pathway). This suggests that exploiting the therapeutic potential of other pathways identified through GWAS of BMD and osteoporosis will similarly lead to effective new agents for fracture prevention.

Elucidating Pharmacogenomic Mechanisms

Currently, most pharmacogenomic studies depend on comparing expression profiles at the mRNA (genomics) or protein (proteomics) level for a given tissue or cell type after a relevant stimulus. Comparison of expression profiles at the mRNA level is attractive, particularly with the advent facilitating the availability of microarrays allowing concurrent analyses of tens of thousands of genes. This technology can help to, rapidly, genotype individuals to provide information on polymorphic drug metabolism genes, and also identify genes differentially expressed in response to a drug. In fact, one gene chip, CYP2C6/CYP2C19, is already available for identifying potential poor drug metabolizers. On the other hand, this genomics-based technology might also help to understand the biological drug responses and to interpret therapeutic trials [35].

Comparing mRNA expression profiles can be used to explore which genes are up-regulated or down-regulated in osteoporosis treatment by comparing the expression profiles in tissue taken from affected and unaffected individuals. The potential difficulty with this approach is that small variations in the cellular constituents of the tissue might produce large fluctuations in mRNA and/or protein, giving rise to false positive (or negative) results. Another potential problem is that the logistical difficulties of dealing with data on thousands of gene products (which by definition may have no known function) are considerable. These problems can be avoided to some extent by simplifying the experimental design. For example, one approach is to use cultured human bone cells from a single individual and then to compare expression profiles after treatment with, for example, bisphosphonates [36].

Apart from the logistical difficulties in sampling from bone and obtaining comparable bone tissue, study design will also be a major issue. As with genetic linkage studies, a major challenge for pharmacogenomics of osteoporosis lies in the design of meaningful studies for the use of these technologies. In any mRNA-level study, a reasonable number of paired replicates must be performed and relevant time points examined. In practice, it may be possible to reduce this to a baseline and two different time points for this kind of experiment. However, even then, with an appropriate number of replicates, the number of samples to be processed and the logistics of multiple samples, at least in humans, remain daunting if not ethically impossible.

On the other hand, large epidemiological studies are required to identify associations between specific gene polymorphisms and predisposition to osteoporosis before these could

be useful in clinical settings. At present, large-scale SNP-based association studies in osteoporosis are feasibly prevented by limitations in genotyping resources and biostatistical models. Large-scale association studies involving SNPs will be more practical when high-throughput and affordable SNP scoring methods are available [37]. The progress has, nevertheless, been impressive: to date, the Human Genome Project has provided more than two million SNPs as genetic markers [38]. Within the next few years, SNPs located every 3–50 kb will likely be characterized; it will be possible to perform genome-wide association studies to obtain information about major genes that contribute to the disease or pharmacological differences, as well as secondary, modifier, genes that also affect the disease. The development of a single mouthwash method for obtaining genomic DNA clinical studies may be suitable for large community-based studies in which samples can be collected by the participants themselves [39].

The advance of genomic research gives rise to several ethical issues that need to be resolved. While information such as race and ethnicity have long been used in predicting therapeutic response, a growing number of critics view the use of this information as potentially prejudicial [40]. Collecting and storing genetic information from individuals raise questions of privacy as well as security and ethical dilemmas, since the information also provides information about potentially non-censored relatives. Thus, guidelines need to be developed to protect the privacy and confidentiality of participants and their family members. A critical component of any such study will be to ensure that the ethical principle of beneficence is fulfilled. The analysis of DNA samples, including those from large population-based studies, in research is very important for understanding the genetic influences of disease susceptibility, but the benefit must be weighed against risk to persons, including the potential for discrimination and invasion of privacy. Although these issues are difficult, it has been suggested that treating participants as limited partners in genetic research can provide a framework for addressing many of these concerns [41].

Bone Mass Pharmacogenetics

Osteoporosis has a strong genetic component and between 50 and 80% of the variability of bone mineral density (BMD) may be explained by hereditary factors [42, 43]. Currently, over 60 genes have been identified to be associated with BMD at genome-wide significance [reviewed in References [44, 45]. Many of them are related to oestrogen, Wnt and RANKL (RANK ligand) pathways, which confirms the important role of these pathways in skeletal homeostasis. Other genes not previously suspected to be involved in bone metabolism have been associated with the skeletal phenotype in several GWAS.

Richards et al. [46] assessed 36,000 single-nucleotide polymorphisms (SNPs) in 150 candidate genes chosen based on at least one previous study of this gene in osteoporosis. Only nine genes (ESR1, LRP4, ITGA1, LRP5, SOST, SPP1, TNFRSF11A, TNFRSF11B and TNFSF11) showed robust evidence of association with BMD at either femoral neck or lumbar spine; and further four genes (SPP1, SOST, LRP5 and TNFRSF11A) were associated with fracture risk, although this was independent of BMD (at least in part) only at SPP1 and SOST.

Oestrogen receptor: Given the important role of gonadal hormones in bone health, both in accrual and maintenance of bone mass, it is not surprising that ESR1 (encoding the oestrogen receptor α) was also studied extensively in the pre-GWAS era – with conflicting results. Several GWAS have shown the association of the region containing ESR1 with BMD, although the exact variant responsible for the association signal may not ultimately be attributable to ESR1 and it is possible that more than one association signal is present as associated SNPs from different GWAS are not in linkage disequilibrium with each other [47, 48].

Vitamin D receptor: Vitamin D receptor gene (VDR), as undoubtedly expected, has been the most studied gene in osteoporosis. The first published association study of variants in VDR and BMD suggested that 80% of variability in BMD was due to variants in this gene – a result that was not really biologically plausible based on

the observed inheritance of osteoporosis. However, this publication literally launched a thousand further such studies. To date, a definitive association of VDR with BMD or fracture has not been established robustly at genome-wide significance [49].

WNT/β-catenin pathway: Genes in this pathway were among the first to be identified in osteoporosis GWAS, starting with LRP5, [50] with multiple other genes also identified at genome-wide significance [AXIN1, CTNNB1, DKK1, GPR177, JAG1, LRP4, LRP5, MEF2C, RSPO3, SFRP4, SNT16, SOST, WNT4, WNT5B and WNT16 (reviewed in Ref. [26]). LRP5 is one of very few genes showing association in candidate gene association studies [51, 52] subsequently validated in the GWAS era. LRP5 mutations have been identified as the cause of both low bone mass and high bone mass skeletal dysplasias, respectively, osteoporosis pseudoglioma syndrome (MIM 259770) and a high bone mass phenotype (MIM: 601884). Mutations in SOST cause a high bone mass phenotype of van Buchem's diseases (MIM: 607636) and sclerosteosis (MIM: 269500). Romosozumab, anti-sclerostin antibody, is currently available for osteoporosis therapy.

RANK-RANKL-OPG pathway: This pathway was also one of the earliest to be associated with BMD and fracture risk in the population, with OPG, RANKL and RANK all detected in the first two comprehensive GWAS published in osteoporosis [47, 50] and subsequently confirmed by many independent GWAS and meta-analyses. Mutations in TNFRSF11 (RANKL), TNFRSF11A (RANK) and TNFRSF11B (OPG) genes also have been identified in several skeletal dysplasias, including early onset Paget's disease (MIM 602080) and familial expansile osteolysis (MIM 174810), demonstrating their importance in bone physiology. Denosumab, a monoclonal antibody against RANKL, inhibits RANKL signalling through RANK and subsequent osteoclast stimulation and is currently widely used in osteoporosis treatment [48].

Osteoporosis Pharmacogenomics and Fracture Prediction

One of the main objectives of osteoporosis genetics is to identify a set of variants that can be measured to allow the identification of groups at high risk for future fracture. This is of particular relevance to osteoporosis as safe interventions exist for osteoporosis, and such preventive therapy, years before disease onset, could decrease the population health burden of the disease.

Because many genome-wide-significant alleles have been identified, a weighted allele score can be implemented, which simply counts the number of deleterious alleles per person, weighting each allele by the effect size that is attributed to this allele in an independent population cohort. Individuals with more deleterious alleles would therefore have a higher risk score. Indeed, using 15 genome-wide-significant SNPs for lumbar spine BMD in the GEFOS-1 GWAS, this consortium was able to show a difference between the highest risk group and lowest risk group of approximately 0.7 standard deviations [53]. Increasing the number of SNPs by including those identified in the larger GEFOS-2 effort to 63 autosomal SNPs increased this gradation of effect to approximately 0.86 standard deviations [54]. Comparing these two findings suggests that a substantial increase in the number of risk alleles (of decreasing effect size) does not dramatically improve the ability of a weighted allelic risk score to partition individuals.

More clinically relevant, however, was the demonstration of the effect of this allelic risk score on the receiver operating characteristic (ROC) curve for fracture risk. A considerable body of work has already gone into understanding the relevance of clinical risk factors (such as age, sex and weight) and BMD in risk stratification for fracture. Using only well-validated clinical risk factors, irrespective of genotype, the area under the ROC curve for osteoporotic hip fracture is 0.83 [55].

However, the area under the ROC curve for fracture risk using the allelic risk score without any clinical information was marginally better than chance alone and had a value of 0.57 (95% confidence interval: 0.55–0.59). Similarly, the allelic risk score for a diagnosis of osteoporosis (BMD T score ≤ -2.5) had an area under the curve of 0.59 (95% confidence interval: 0.56–0.61), which was again worse than a risk score including just age and weight (0.75 (95% confidence interval: 0.73–0.77)) and improved only marginally when adding the allelic risk score to age and weight (0.76 (95% confidence interval: 0.74–0.78).

Some observers have suggested that to predict risk of a disease, 150 genes with odds ratios of 1.5 or 250 genes with odds ratios of 1.25 will be needed [56]. Data that show the combined effect of many common variants on the explanation of trait variance may improve our ability to prognosticate osteoporosis. However, the published data from the field of osteoporosis suggest that simple clinical risk factors, such as age, weight and height, outperform an allelic risk score that is comprised of susceptibility alleles [57].

These findings may be improved in the future by identifying a set of alleles that influence risk of fracture independently of BMD or by identifying less common variants that have a large effect on the risk of fracture and/or BMD. However, the highly polygenic allelic architecture of BMD and the low variance explained of this trait suggest, at present, that the reliable prediction of individuals at risk for fracture or osteoporosis using genetic information is not feasible [58].

Pharmacogenomics of Osteoporosis Therapy

The optimal dose of a drug is a balance between efficacy and side effects and may vary significantly among individuals due to genetic differences. Examples from standard clinical practice is warfarin, which is used worldwide to prevent blood thrombosis; however, it may cause excess bleeding in subgroups of patients. Through pharmacogenetic studies it has been possible to identify two genes that affect what is the optimal dose and thereby facilitated a personalized adjustment of warfarin treatment. Similar studies on drugs to treat, e.g., Alzheimer's disease and schizophrenia are ongoing aiming at identifying the genetic markers which can be employed to optimize the dosage for individual patients.

In osteoporosis therapy, some drugs, e.g., bisphosphonates, are not subject to metabolism, but many others are metabolized to active components or as part of their elimination pathway. Despite the evidence of genetic effects on the variation in efficacy and safety of pharmacological agents in other diseases, these are still largely untested in the treatment of osteoporosis, but their potential is underlined by their rapid adoption in disciplines such as obesity and hypertension.

Nevertheless, some evidence has been published suggesting that genetic factors may mediate the response to drug treatment [59] and modify the dynamic association between bone turnover markers and bone density. A series of studies by Palomba and colleagues [60–62] suggested that among postmenopausal women who were on alendronate and hormone replacement therapy (HRT) treatments, the b allele of the VDR's Bsm-I polymorphisms was associated with a greater increase in BMD than those carriers of the B allele. However, interestingly, among patients on raloxifene the B allele carriers were associated with a greater increase in BMD than the b allele carriers. As a result of the opposite effects, among those on combined alendronate and raloxifene, there was no significant association between VDR polymorphisms and BMD change. These results clearly illustrate the interaction between VDR polymorphisms and various anti-resorptive drug therapies in BMD change.

Osteoporosis Pharmacogenomics: Recent Insights and Future Perspectives

Besides these three genes, few studies on other candidate genes have been published in the last years. Polymorphisms in the FDPS gene, a critical enzyme in the mevalonate pathway and the major target of nitrogen-containing bisphosphonates were shown to influence the change in either bone turnover markers or BMD in two studies on Caucasian osteoporotic women treated with bisphosphonates. The association was not replicated in a study of Korean ostoporotic women, where a polymorphism in GGPS1, another enzyme in the mevalonate pathway, was shown to influence drug efficacy [63, 64]. Furthermore, three studies searched for genes involved in raloxifene metabolism and disposition and showed the involvement of UGT1A1, SLCO1B1 and ABCB1 polymorphisms in the pharmacokinetics and pharmacodynamics of this drug [65–67]. Positive association was demonstrated also for polymorphisms in the osteoblast-secreted anti-osteclastogenic protein OPG and efficacy of bisphosphonates. On the other hand, the association of polymorphisms in LRP5, which is involved in the Wnt signalling pathway, was demonstrated for the efficacy of HRT, but not of bisphosphonates [63, 64].

So far, studies have focused mainly on postmenopausal osteoporosis, using changes in BMD or biochemical markers of bone turnover and not antifracture efficacy as primary outcomes. Contradictory results in different reports might be partly due to small samples, ethnic differences in genotype distributions, and calcium and vitamin D status [68]. In addition to postmenopausal osteoporosis, pharmacogenomics might also play a role in secondary osteoporosis, which develops as a consequence of another disease or treatment. While there is some evidence for the genetic contribution to the susceptibility of secondary osteoporosis, like glucocorticoid-induced osteoporosis, genetic contribution to treatment efficacy has not been studied. Similarly, male osteoporosis remains largely unexplored [69].

Pharmacogenomics of Adverse Drug Reactions

All anti-osteoporotic drugs have the potential for different adverse reactions that may affect adherence and raise concerns about the safety of their long-term use [16, 17]. Bisphosphonates, for example, can provoke oesophageal irritation, musculoskeletal pain, acute -phase reactions and, very rarely, atrial fibrillation, hypersensitivity reactions, renal impairment, atypical femoral fracture and osteonecrosis of the jaw (ONJ) [70].

Osteonecrosis of the Jaw

ONJ is a serious but rare complication of nitrogen-containing bisphosphonate treatment, with 0.1% incidence in osteoporotic patients and 3–10% in patients with bone metastases, who are treated with higher doses of the more potent intravenous bisphosphonates [71]. Interestingly, it has also been observed recently in cancer patients treated with denosumab [70]. ONJ represents the one of the adverse reactions where genetic influence has been studied and is a good example of the use of GWAS in the field of anti-osteoporotic drug pharmacogenomics. A total of six discovery candidate gene studies were published between 2010 and 2018 [72–77]. These studies investigated the effects of variants in several genes, which had been selected based on a potential role in BPs metabolism and/or ONJ pathogenesis (e.g. bone turnover). Most of these studies genotyped only a small number of variants and had small cohorts and are therefore susceptible to limitations such as inadequate power. None of the single nucleotide polymorphisms (SNPs) tested in these studies reached a significance level after accounting for multiple comparisons.

In the first report on the subject, published in 2008 on multiple myeloma patients treated with pamidronate or zoledronate, CYP2C8 (rs1934951, rs19934980, rs1341162 and rs17110453) polymorphisms reached genome-wide significance. This was rather surprising since bisphosphonates are not subjected to liver metabolism [78]. The association was, however,

not replicated in following studies on prostate cancer and multiple myeloma patients [64, 71]. In the second GWAS, which included more SNPs, copy number variations and also candidate SNPs in the insulin-like growth factor gene family, as well as in genes important in pharmacokinetics, patients with ONJ due to breast cancer (30 breast cancer patients who developed ONJ after treatment with zoledronate as cases, and 17 breast cancer patients who did not develop ONJ after treatment with BPs, as the control group. In addition, this study included 1726 healthy population controls to increase the power) were evaluated. RBMS3, a transcription factor involved in the regulation of collagen type I, was the only gene that reached genome-wide significance [79]. This study further showed that there was an interaction between RBMS3 and ZNF516 which affects bone mineral density. RBMS3 encodes an RNA-binding protein, which is associated with the up-regulation of collagen type I, which is an important component of the bone matrix [80].

Other genes that have been implicated in single studies include PPARG, encoding a transcription factor that favours differentiation of mesenchymal stem cells into adipocytes and thus decreases osteoblastogenesis; VEGF, encoding a modulator of angiogenesis and vasculogenesis; FDPS; and combined genotype score of polymophisms in RANK, OPG, COL1A1, MMP2 and OPN, which encode either regulatory or structural bone proteins [64, 71].

Using replication studies, five candidate gene studies have attempted to replicate the results of GWAS of Sarasquete ME, et al. [81–86]. These studies investigated the effect of CYP2C8 SNP, rs1934951, on the development of ONJ in other independent cohorts. All five studies failed to demonstrate significant association between SNP rs1934951 and ONJ development (p-value>0.05).

The lack of replication was the biggest limitation of both these studies. Moreover, both of these studies had limited sample sizes and the p-value for GWAS did not reach a genome-wide significance level of $5*10^{-8}$ [87]. However, these data, mainly from studies on cancer patients, show the potential for the use of genetic markers in the prediction of adverse reaction in the future, but the confirmation in larger patients' series is required.

Whole-exome sequencing (WES) determines the sequence of all protein-coding genes in human genome. This method covers<2% of human genome but contains >85% of known disease-related variants [88]. Based on abovementioned, WES is a cost-effective alternative to whole-genome sequencing. So far, two WES studies have been published [89, 90]. Kim et al. [90] identified four genes (ARSD, SLC25A5, CCNYL2, and PGYM) associated with ONJ with the lowest p-value (p-value<0.05) using WES and Gene set enrichment analysis (GSEA) methods. GSEA is a computational method that investigates genetic variants in a group of genes to elucidate the gene differences between cases and controls. This was the first study that combined WES and GSEA methods to investigate the function of SNPs between ONJ patients and non-ONJ participants.

The second WES study [89] performed both discovery and replication followed by meta-analysis. Moreover, the study included not only multiple myeloma patients but also other metastatic solid cancers as cases and controls. The meta-analysis identified SIRT1 SNP rs7896005 and HERC4 SNP rs3758392 to be associated with ONJ with the lowest p-value ($3.9*10^{-7}$) approaching genome-wide significance. The HERC4 SNP rs3758392 had the same p-value as rs7896005 because of high LD (r2 = 0.88). These two SNPs were both expression quantitative loci (eQTLs) for SIRT1. SIRT1 was a very compelling candidate gene of bone remodelling. Studies had shown that SIRT1 played a vital role in bone remodelling by affecting the Wnt signalling pathway [91–94] and RANK/RANKL/OPG pathway [95, 96].

Atypical Femoral Fracture

For over a decade, atypical fracture of the femoral bone has been a well-documented adverse drug reaction associated with long-term bisphosphonate use as well as denosumab [97]. The pathogenesis of atypical femoral fractures is

unclear, but a genetic predisposition has been suggested. The identification of these atypical femoral fractures in bisphosphonate-naïve individuals (about 7% of cases) and in monogenetic bone disorders [98, 99] has led to the hypothesis that genetic factors predispose to this type of fractures [100].

A systematic review found six published studies that investigated the role of genetics on atypical femoral fracture in a total of 44 patients [101]. The review also identified 23 cases of atypical femoral fracture associated with seven different monogenetic bone disorders, of which seven cases had been exposed to a bisphosphonate. A pilot study in 13 atypical femoral fracture patients and 268 controls identified a greater number of rare variants in atypical femoral fracture cases using exon array analysis. A whole-exome sequencing study in 3 sisters with atypical femoral fractures showed, among 37 shared genetic variants, a p.Asp188Tyr mutation in the GGPS1 gene in the mevalonate pathway, critical to osteoclast function, which is also inhibited by bisphosphonates. Other two studies completed targeted ALPL gene sequencing; an ALPL heterozygous mutation was found in 1 case of a cohort of 11 AFFs, whereas the second study comprising 10 AFF cases did not find mutations in ALPL. Targeted sequencing of ALPL, COL1A1, COL1A2 and SOX9 genes in 5 cases of AFF identified a variant in COL1A2 in 1 case. These findings suggest a genetic susceptibility for atypical femoral fracture.

Another study [102] was carried out aiming at the identification of common genetic variants that could be used for pre-emptive genetic testing. The study was based on genome-wide association assessment. The results of this study indicated that there is no common genetic variant that can be used for this purpose. The only significant finding on a genome-wide level was with four SNPs when cases were compared with population controls, but these were uncommon SNPs, all of which were single hits, meaning that these associations are likely false positives [103, 104], although two may theoretically be related to the treatment indication (NR3C1 and NTN1). None of these specific SNPs have, however, previously been implicated in atypical femoral fractures or osteoporosis [104–107]. After reducing the risk of confounding by indication with the use of a comparison to bisphosphonate-treated controls, no statistically significant association remained.

In summary, further studies of larger sample size are still warranted to identify possible rare genetic variation conferring a risk of atypical femoral fractures.

Towards Personalized Medicine

The most important application of pharmacogenetics is optimization of treatment outcomes and minimization of adverse effects from therapies. However, in clinical osteoporosis, there is a paradox. The gold standard for evaluating treatment efficacy in a population is based on randomized controlled trials. When applied at the individual level, such gold standard appears to be suboptimal for evaluating the treatment efficacy. Whilst randomized controlled trials come on the top of the hierarchy of evidence, individual patients often differ in their response to medical therapies. Consequently, there is a degree of reasonable uncertainty as to whether the medication which works in general for a group of people is also optimal for an individual person. Furthermore, in addition to the variability in treatment efficacy which has been well reported and documented, there is also a wide range of variability as far as adverse reactions associated with a specific medical therapy. Therefore, the goal of pharmacogenomics is to optimize the selection of medical therapy and tailor it for the specific individual.

On another front, pharmacogenetics and pharmacogenomic studies have suggested a number of genes that could be implicated in diverse pathophysiological pathways, e.g. changes in BMD and calcium metabolism (Fig. 22.3). However, the main challenge to these genetic suggestions is the poor replication and consistent data remain elusive. Therefore, further genetic studies are required, together with meticulous functional genomics assessment, to identify any

Fig. 22.3 Personalized medicine: The interaction between Genetic markers, enviormental risk factors, biochemical markers as well as the gold standard Bone mineral density (BMD)

specific molecular event that may have clinical effects to be able to contribute to the future medical therapy strategies development. In osteoporosis pharmacogenetics have focussed on one major phenotype, that is, changes in the BMD. Lastly, identifying the genes which are associated with response to medical therapy remains to be a challenging task. It is not clear how many genes are involved in the regulation of, or relevant to, the underlying medication response (e.g. safety and efficacy).

In conclusion, though there is potential for pharmacogenomics to improve osteoporosis management, this role has yet to be unravelled. For this target to be achieved, the scope should consider looking beyond the current knowledge of bone biology, drug disposition and mechanisms of actions. GWAS should be performed using powerful technologies like DNA microarrays, whole-exome sequencing or massively parallel sequencing. New relevant genes might be detected by using these approaches. In addition to common SNPs that have been studied so far, rare SNPs, short tandem repeats and copy number variations might also turn out to be important determinants of drug response. Another aspect that should be explored is the gene–gene interaction. Different drug responses can be viewed as a consequence of different gene expression. Besides DNA sequence variations, epigenetic processes like DNA methylation, miRNAs and histone modifications can influence profoundly gene expression. However, such studies are difficult to preform, owing to tissue specificity of these processes and difficulties in obtaining bone specimens. Furthermore, even when possible epigenetic marks are discovered, to be useful in standard clinical practice, it is vital that a representative pattern should be identified in the peripheral blood cells or plasma.

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Romosozumab: Optimizing the Anabolic Window

23

Yasser El Miedany

Introduction

Sclerostin is a secreted glycoprotein that is mainly expressed in bone as well as cartilage matrix and has been reported to suppress the mineralization of osteoblasts in cell culture environment [1, 2]. The function of sclerostin as an inhibitor of bone formation has been further demonstrated in transgenic mice. Sclerostin knock out (SOST-KO) mice displays a high bone mass with increased bone formation and bone strength [3, 4], whereas overexpression of sclerostin in mice results in low bone mass with decreased bone formation and bone strength [2, 5]. Sclerostin inhibits bone formation through inhibiting the Wnt/b-catenin signaling [6], and its expression is regulated by mechanical unloading and estrogen deficiency in osteocytes [4, 7–10]. Wnt/b-catenin signaling is important for osteoblast differentiation and proliferation [11]. Sclerostin has been found to be responsible for both the inhibition of the osteoblastogenesis and preosteocyte differentiation of osteoblasts [12, 13].

On another front, sclerostin also stimulates RANKL secretion from osteocytes to induce osteoclastogensis [14, 15], leading to an increase in bone resorption. In addition, osteoclasts induce osteoblasts for bone formation through the Wnt signaling pathway [16, 17]. Inhibitors of the Wnt signaling pathway (such as Dickkopf-related protein 1, DKK1) suppress the osteoclasts-mediated osteoblast bone formation [16]. It is also demonstrated that sclerostin is expressed in osteoclasts from aged mice, indicating that sclerostin contributes to the age-related decoupling of bone turnover [18]. Taken together, these data show that sclerostin plays an important role in modulating bone formation and bone turnover, through antagonizing the Wnt/b-catenin signaling pathway in osteoblasts and modulating RANKL level that act on osteoclasts (Fig. 23.1).

This chapter will discuss sclerostin as an emerging therapeutic and explain the dual action of romosozumab and its bone morphologic induced changes. In addition, the chapter will expand to present the time-dependent effect of romosozumab, its pharmacokinetics and clinical trials, anti-fracture efficacy, and sustainability. The chapter will then discuss the potential of romosozumab use in clinical practice, its place in recent guidelines, possibility of use for men living with osteoporosis, and healing enhancement of osteoporotic fractures. The chapter will then conclude by discussing romosozumab and its interaction with both cardiovascular and chronic kidney disease–mineral bone disorder.

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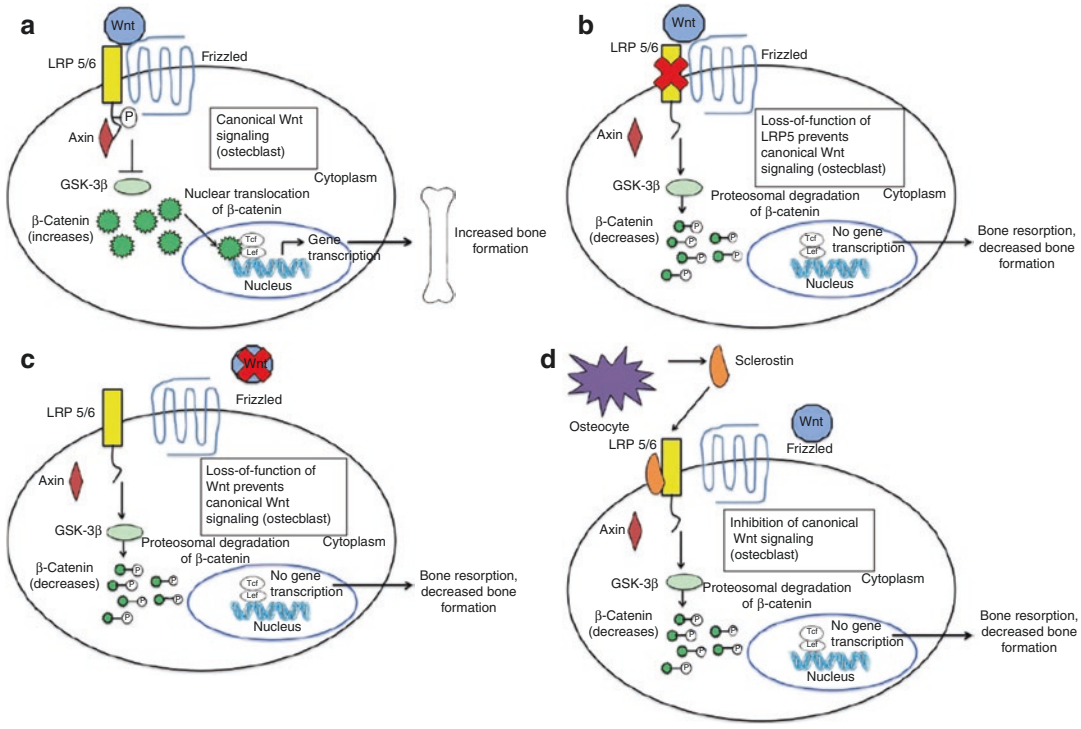

Fig. 23.1 The canonical Wnt-β-catenin signaling pathway and the effects of inhibition through loss of function mutations and sclerostin inhibition. (Notes: (**a**) When Wnt binds to the LRP-5 and -6 coreceptors and the specific Frizzled family receptor, THE inhibition of the β-catenin destruction complex occurs. Accumulated β-catenin in the cytoplasm enters the nucleus, leading to transcription of Wnt-responsive genes and bone formation. Panels (**b**), (**c**), and (**d**) show how various mechanisms inhibit the canonical Wnt-β-catenin signaling pathway. Due to the inability of Wnt to exert its effect due to (**b**) the loss of mutation of LRP-5 and LRP-6 coreceptors, (**c**) the loss of mutation of Wnt, and (**d**) the prevention of Wnt from binding to LRP-5 or LRP-6 coreceptors by sclerostin, the β-catenin destruction complex is assembled. β-Catenin is phosphorylated and degraded. Wnt-responsive genes are not activated, leading to an increased bone resorption and a decreased bone formation. Quoted with permission from [60] under open access scheme. Dove Medical Press. Shah AD, Shoback D, Lewiecki EM. Sclerostin inhibition: a novel therapeutic approach in the treatment of osteoporosis. Int J Womens Health. 2015;7:565–80.7)

Bone-Forming and Antiresorptive Effects of Romosozumab

Inhibiting antagonists of the Wnt signaling pathway provides an attractive strategy for the treatment of osteoporosis. Sclerostin monoclonal antibody (Scl-Ab) inhibits the function of sclerostin, thus re-activating the Wnt signaling pathway in osteoblasts which has provided an excellent therapeutic approach to enhance bone formation (Fig. 23.2). As sclerostin is mainly expressed in osteocytes [2], it is expected that Scl-Ab treatment is bone specific with minor side effects.

In normal rodents and nonhuman primates, Scl-Ab treatment has been reported to increase bone formation, bone mass, and bone strength in a dose-dependent manner [19, 20]. In a study of the animal model of osteoporosis, OVX rats, Scl-Ab treatment also significantly increased bone formation, bone mass, and bone strength of the animals [21]. The increase in bone formation is illustrated by the increase in osteoblasts number and serum bone formation markers, and a decrease in bone resorption as illustrated by decrease in osteoclast number [19–21].

Results of the animal studies were supported by bone biopsies from human. In iliac crest

biopsy samples obtained from postmenopausal women in the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) [22], large increases in bone formation were seen in cancellous and endocortical bone after 2 months of treatment with romosozumab, although the effect was no longer evident after 12 months of treatment. The eroded surface was significantly reduced at both timepoints; and trabecular bone volume, microarchitecture, and cortical thickness were significantly improved at 12 months [23].

It was expected that Wnt pathway activation would be purely anabolic and avoid the adverse events of osteonecrosis of the jaw and atypical femoral fracture associated with bisphosphonates and denosumab. Unexpectedly, small numbers of both adverse events have been reported in romosozumab clinical trials [24, 25]. Pure activation of bone formation should not induce oversuppression of bone remodeling – a proposed mechanism for atypical femoral fracture. However, the decrease in bone resorption, reflected in the suppression of bone resorption markers by romosozumab, is best explained by the fact that stimulating Wnt signaling also increases osteoprotegerin (OPG) formation. OPG is a natural inhibitor of RANKL. Thus, antagonizing sclerostin (and promoting Wnt pathway activation) has also an antiresorptive effects [26].

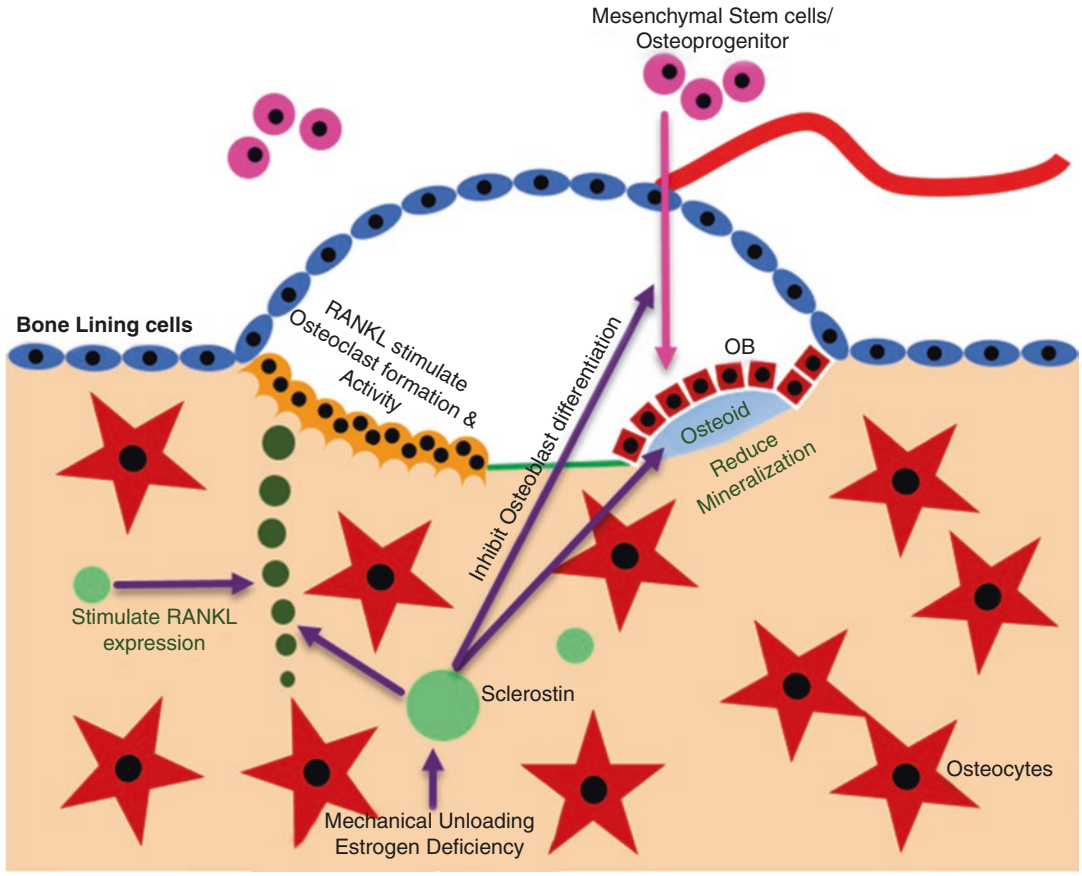

Fig. 23.2 Mechanism of action of romosozumab. Notes: Romosozumab is a human monoclonal antibody that binds sclerostin (an inhibitor of Wnt pathway signaling). When this monoclonal antibody binds to sclerostin, sclerostin cannot bind to the LRP-5 and LRP-6 receptors and is unable to exert its inhibitory effect. Wnt binds to LRP-5 or LRP-6 coreceptors and specific Frizzled family receptor, leading to activation of the Wnt signaling pathway and bone formation. Romosozumab has dual action effect on the bone. (Abbreviation: *LRP*, LDL-receptor-related protein)

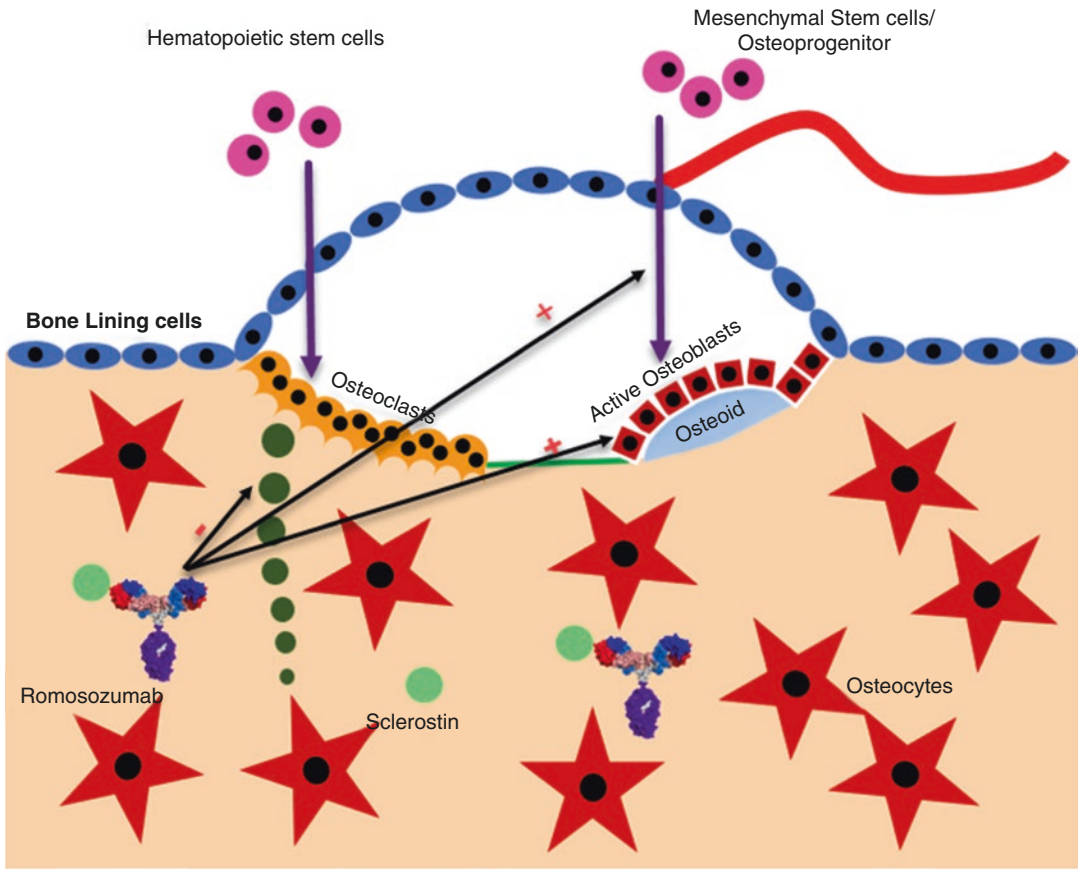

Fig. 23.2 (continued)

Overall the data indicate that the anabolic effect of sclerostin inhibition is achieved mainly by modeling-based bone formation; however, a smaller remodeling-based anabolic effect also occurs, with more new bone deposited on pre-resorbed crenated surfaces than is resorbed, and includes "spillover" of bone laid down upon quiescent surfaces adjacent to remodeling sites [27].

Bone Morphological Changes

Thickening of the cortex occur as a result of the modeling-based periosteal and endocortical bone formation, with a consequent increase of its total cross-sectional surface area. Similarly, modeling-based bone formation thickens the trabeculae and might improve connections between trabeculae. However, it is not fully clear whether modeling occurs upon the intracortical surfaces. In general, romosozumab anabolic effect leads to modification of the bone structure producing an absolute increase in the total mineralized matrix volume, with consequent increase in the BMD [28, 29].

The increase in BMD induced by antiresorptive agents is mostly the result of remodeling suppression, which enables more complete secondary mineralization of the slowly diminishing bone volume (in the case of bisphosphonates, which do not abolish remodeling completely) or stable bone volume (in the case of denosumab, which abolishes remodeling effectively) [30]. These differing morphological changes in structure and material composition probably have different effects on bone strength, raising the question of whether it is valid to compare the increase in BMD induced by anabolic agents versus antiresorptive agents [31].

Time-Dependent Effects of Romosozumab

Following treatment with romosozumab, there is an initial rapid increase in bone formation. In animal models, this increase has been associated with the activation of lining cells and the stimulation of modeling-based bone formation [32–34]. In both animals and humans, the stimulation of bone formation is transient. Detailed studies in rats and cynomolgus monkeys have demonstrated that maximal bone formation at the tissue level occurs within the first 3 months of sclerostin antibody treatment in cancellous bone with subsequent progressive attenuation to levels observed in control animals by 6 to 12 months, followed by a continued increase in spine bone mineral density (BMD) [35–37]. Similarly, results from clinical trials showed a continued progressive increase in spine BMD after bone formation markers decreased to baseline levels [38, 39]. Multiple tissue-based mechanisms could contribute to the continued increase in spine BMD with romosozumab treatment, following the self-regulation of bone formation. In addition to secondary mineralization of newly formed bone, this supports the notion that there may be effects at the remodeling unit at the resorptive and/or formative site that would result in a net positive bone balance and continued accrual of bone volume. As romosozumab reduces bone resorption markers as well as the surface extent of resorption in animal models [37], it has been suggested that inhibitory effects on resorption may extend to the individual remodeling unit and result in a reduction in final resorption depth. In addition, the effects on osteoblast function may extend to the remodeling unit, where romosozumab may affect the formative site, enhancing osteoblastic activity resulting in increased wall thickness.

To explore potential tissue-level mechanisms that could contribute to a progressive increase in spine BMD, a study [40] was carried out using kinetic reconstruction techniques to examine the effects of romosozumab, administered for 10 and 28 weeks, on modeling and remodeling units in vertebral cancellous bone from adult cynomolgus monkeys. Results revealed that romosozumab induced significant transient increases in mineral apposition rate in remodeling sites at week 3 that was not sustained with continued treatment. However, romosozumab treatment caused sustained improvement in fractional labeling of osteoid, an index of osteoblast efficiency, at remodeling formative sites at both weeks 10 and 28 that was the major contributor to significant increases in final wall thickness of remodeling packets. Remodeling wall thickness matched the final wall thickness of modeling packets at week 10. At both weeks 10 and 28, romosozumab significantly decreased eroded surface. At week 28, romosozumab also significantly reduced resorption period and final resorption depth. The reduced final resorption depth combined with the increased wall thickness resulted in a significant increase in bone balance at the level of the remodeling unit. The assessment of bone formation on the vertebral periosteal and endocortical surfaces following 28 weeks of treatment revealed that romosozumab significantly increased bone formation on these surfaces, which had attenuated by week 28, resulting in significant increases in new periosteal and endocortical bone by week 28.These data suggest that multiple factors potentially contribute to the increase in spine BMD with romosozumab treatment. In the early period of treatment, increased modeling-based bone formation, increased wall thickness at remodeling sites, a decrease in remodeling space secondary to decreased eroded surface in vertebral cancellous bone, and increased periosteal and endocortical bone formation in the vertebral cortex contribute to the early increase in spine BMD. Following the self-regulation of bone formation when modeling-based bone formation has attenuated, a decrease in remodeling space secondary to reduced eroded surface and a positive BB secondary to decreased final resorption depth and increased wall thickness contribute to the progressive increase in spine BMD with long-term treatment.

Pharmacokinetics

Romosozumab is an IgG2 monoclonal antibody generated by humanizing a mouse sclerostin monoclonal antibody. Generally, romosozumab is administrated subcutaneously (SC) with an absorption of 50–70% and a half-life of 6–7 days, as shown in the Phase I study mentioned above [41, 42]. In the clinical trial, a single SC dose of Romosozumab administered to healthy postmenopausal female and male volunteers was associated with a dose proportional increase in serum concentrations, with clearance decreasing with increasing dose [43].

Romosuzumab has been shown to have a nonlinear pharmacokinetic profile, which was most prevalent in the dosage cohorts between 1 and 3 mg/kg SC. Peak ROMO serum concentrations were observed within the first week after SC administration, and declines were observed in a biphasic manner in the highest SC doses that were given, with a half-life of 6–7 days.

Exposure (area under the curve, 0–inf) in subjects administered SC Romosozumab (1 and 5 mg/kg) was about 50 and 70%, compared to subjects administered IV Romosozumab [41]. Bioavailability was determined to be 81% after SC Romosozumab (210 mg) was administered once/month in healthy volunteers, patients with low bone mass, and those with postmenopausal osteoporosis.18 Clearance of ROMO from the body is decreased in patients with impaired renal function. The product monograph warns that caution is required in patients with severe renal impairment (glomerular filtration rate [eGFR] <30 mL/min/1.73 m2) or undergoing dialysis [44, 45].

Clinical Trials

Clinical research is medical research involving people. There are two types: observational studies and clinical trials. Clinical trials are research studies performed in people that are aimed at evaluating a medical, surgical, or behavioral intervention. They are the primary way that researchers find out if a new treatment, like a new drug or diet or medical device (for example, a pacemaker), is safe and effective in people. Often a clinical trial is used to learn if a new treatment is more effective and/or has less harmful side effects than the standard treatment.

Clinical trials of drugs are usually described based on their phase. The FDA typically requires Phase I, II, and III trials to be conducted to determine if the drug can be approved for use.

A Phase I trial tests an experimental treatment on a small group of often healthy people (20 to 80) to judge its safety and side effects and to find the correct drug dosage.

A Phase II trial uses more people (100 to 300). While the emphasis in Phase I is on safety, the emphasis in Phase II is on effectiveness. This phase aims to obtain preliminary data on whether the drug works in people who have a certain disease or condition. These trials also continue to study safety, including short-term side effects. This phase can last several years.

A Phase III trial gathers more information about safety and effectiveness, studying different populations and different dosages, using the drug in combination with other drugs. The number of subjects usually ranges from several hundred to about 3000 people. If the FDA agrees that the trial results are positive, it will approve the experimental drug or device.

A Phase IV trial for drugs or devices takes place after the medication is approved. The medication (or device) effectiveness and safety are monitored in large, diverse populations. Sometimes, the side effects of a drug may not become clear until more people have taken it over a longer period of time.

Profile of Romosozumab and its Potential in the Management of Osteoporosis

Through Phase I, II, and III trials of romosozumab, it was revealed that romosozumab treatment leads to a significant gain in bone density. A total of 12 months of romosozumab treatment leads to a bone density gain at the lumbar spine of 11.3%–13.3%, the total hip of 4.1%–6.9%, and

the femoral neck of 3.7%–5.9% [46]. Subcutaneous romosozumab 210 mg monthly led to the greatest BMD gain among the studied doses without an increased incidence of adverse effects. The gains in BMD with subcutaneous romosozumab 210 mg monthly were significantly greater as compared to patients treated with teriparatide or alendronate. Studies using bone turnover markers point to a distinct mechanism of action of romosozumab where unique coupling of the bone remodeling process occurs: an increase in bone formation and a decrease in bone resorption [46–49]. In a Phase III study, romosozumab as compared to placebo has been shown to reduce vertebral fractures by 73% after 1 year of treatment. Sequential therapy with romosozumab for 1 year followed by denosumab in the second year reduced vertebral fractures by 75% as compared to the group that received placebo for 1 year followed by denosumab in the second year [49]. The outcomes of clinical trials have been reviewed in several articles; below are the outcomes of each phase separately.

Phase I trials: pharmacokinetics, pharmacodynamics, and safety of romosozumab.

Being an IgG2 monoclonal antibody, romosozumab neutralizes the activity of human, monkey, and rat sclerostin and has a high binding affinity for human sclerostin with a pKd of 11.2–12.2 [50].

There are no specific studies published about the absorption, distribution, and excretion of romosozumab; however, it is likely similar to other monoclonal antibodies [51]. When subcutaneously administered, systemic absorption of monoclonal antibodies occurs via the lymphatic vessels. Because of their large molecular size, monoclonal antibodies distribute from the blood compartment to the peripheral tissue by convection or through endocytosis/pinocytosis via endothelial cells [52]. For monoclonal antibodies, the role of hepatic and renal excretion in elimination is minor. The elimination of monoclonal antibodies happens via protein catabolism, occurring through several mechanisms including less specific processes of proteolysis by the liver and reticuloendothelial system and nonspecific endocytosis. More specific elimination occurs at the target cell, a process involving endocytosis and intracellular degradation within the target cell. Target-mediated elimination has small capacity and hence is susceptible to saturation. Because of this, many but not all monoclonal antibodies exhibit nonlinear elimination pharmacokinetics. At low serum concentrations, rapid saturable target-mediated elimination regulates the elimination rate of the antibody. However, at higher serum concentrations, when target-mediated elimination is saturated, the elimination of antibody protein occurs more slowly via nonspecific endocytosis and other processes [52, 53].

Two pivotal Phase I trials of romosozumab assessed the safety, pharmacokinetics, and pharmacodynamics of this agent. The first study was a placebo-controlled, randomized study of 72 healthy subjects where patients received a single dose of romosozumab subcutaneously (0.1, 0.3, 1, 3, 5, or 10 mg/kg), intravenously (1 or 5 mg/kg), or placebo [48]. Patient follow-up ranged from 29 to 85 days depending on the dose of romosozumab administration.

There was a subsequent randomized, double-blind, placebo-controlled study of multiple doses of romosozumab in 48 healthy postmenopausal women and men. The postmenopausal women received six doses of 1 or 2 mg/kg every 2 weeks or three doses of 2 or 3 mg/kg once every 4 weeks or placebo. The healthy men received six doses of 1 mg/kg every 2 weeks or 3 mg/kg once every 4 weeks or placebo [47]. The study involved 3 months of treatment followed by 3 months of follow-up after treatment.

Romosozumab was found to demonstrate nonlinear pharmacokinetics similar to other monoclonal antibody treatments: clearance of romosozumab decreased as the dose of romosozumab increased.29 With single doses of romosozumab, serum concentrations declined in a biphasic manner after maximum concentration with half-lives of 11–18 days and then 6–7 days subsequently.29 After the administration of a single dose of romosozumab, serum levels of romosozumab peaked within the first week [47].

Patient development of antibodies directed against therapeutic monoclonal antibodies may affect the medication pharmacokinetics and

result in reduced efficacy [52]. Among the 54 patients who received single-dose romosozumab, six (11%) patients in the higher-dose groups developed antibodies against romosozumab. Only two of the patients had neutralizing antibodies, and there was no discernible effect of these antibodies on the pharmacokinetics and pharmacodynamics of romosozumab [48]. In 36 patients who received multiple doses of romosozumab, two patients developed neutralizing antibodies, while ten patients developed non-neutralizing antibodies. There were no apparent effects of any of these antibodies on pharmacokinetics and pharmacodynamics. There was one patient involved in a prior romosozumab study who was found to have pre-existing neutralizing antibodies against romosozumab. In this particular patient, serum concentrations of romosozumab declined rapidly after the first dose of romosozumab and were unmeasurable, despite receiving subsequent doses of romosozumab [47].

As with the treatment with antisclerostin antibodies in animal studies, Phase I clinical studies in which humans were administered romosozumab showed that romosozumab treatment led to a rapid increase in the bone formation markers of serum type I amino-terminal propeptide (P1NP), osteocalcin, and bone-specific alkaline phosphatase (BSAP). There was a decrease in the bone resorption marker, serum carboxy-terminal collagen crosslinks (CTX), confirming the notion of both increased bone formation and decreased bone resorption with the use of antisclerostin antibodies resulting in a large anabolic window, a period where romosozumab's effects are mainly osteoanabolic. Treatment with a single dose of romosozumab led to increases in BMD, 5.3% in the lumbar spine and 2.8% in the hip at 85 days, as compared to placebo.29 In patients treated for 3 months with multiple doses of romosozumab, there was an increase in lumbar spine BMD at 6 months.28 Aside from injection site reactions, the study subjects tolerated romosozumab at all doses. These encouraging results in Phase I studies led to Phase II studies evaluating the efficacy of romosozumab for the treatment of osteoporosis [47, 48].

Phase II Trials: Efficacy and Safety of Romosozumab

A Phase II randomized, placebo-controlled, parallel group, eight-group study evaluated the effectiveness and safety of romosozumab in postmenopausal women with low bone density [49]. The study included 419 postmenopausal women aged 55–85 years, with BMD T-scores < -2.0 and > -3.5. A total of 383 (91%) patients completed the study. The mean patient T-scores were as follows: lumbar spine −2.29, total hip −1.53, and femoral neck −1.93. Patients were randomized to receive romosozumab monthly (doses 70, 140, and 210 mg) or every 3 months (doses 140 and 210 mg), placebo, or open-label comparator group (oral alendronate 70 mg weekly or subcutaneous teriparatide 20 μg daily). The primary endpoint of the study was percentage change from baseline of lumbar spine BMD at 12 months in patients who received romosozumab as compared to the pooled placebo group.

At 12 months, pooled romosozumab group participants achieved a statistically significant increase in BMD at the lumbar spine, total hip, and femoral neck as compared to the pooled placebo group participants, regardless of romosozumab dose and frequency. Romosozumab 210 mg administered subcutaneously monthly was associated with the highest gain in BMD at 12 months (11.3% in the lumbar spine, 4.1% in the total hip, and 3.7% in the femoral neck) among the doses evaluated. The BMD gain on romosozumab 210 mg subcutaneously monthly was larger when compared to active comparators, such as subcutaneous teriparatide 20 μg daily and oral alendronate 70 mg weekly.30 A total of 12 months of treatment with romosozumab led to gains in trabecular and cortical compartments in the spine and hip as assessed by quantitative computed tomography (QCT) [54].

Bone formation markers, such as serum P1NP, showed a marked transitory increase that peaked at 1 month after initiating treatment. After peaking, serum P1NP returned to baseline or dropped below baseline at months 2–9 depending on the romosozumab dose. Serum CTX (a bone resorption marker) decreased the most in the first week

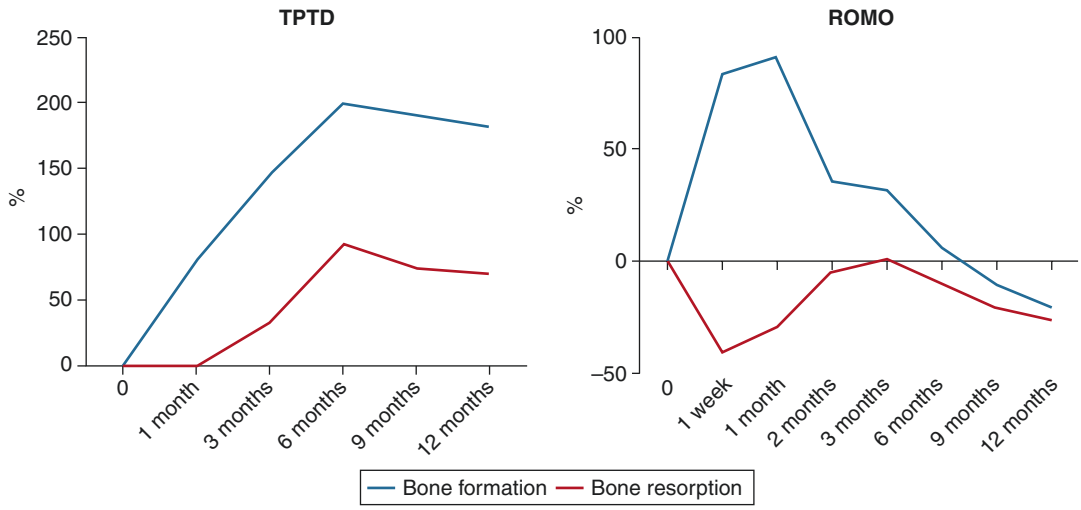

Fig. 23.3 Vascular effect of the Wnt (wingless/integrated) signaling pathway: the pathway is involved in both endothelial as well as media dysfunction. It has been linked to macrophage activation, proliferation of smooth muscle cell, migration of smooth muscle cell from the media into the intima, lipid accumulation by macrophage and smooth muscle cells, and finally calcification or atherosclerotic plaque progression

but remained below baseline up to month 12 of treatment (Fig. 23.3) [49, 55]. Romosozumab seems to cause a rapid initial gain in bone formation and also a more prolonged decrease in bone resorption, leading to a significant increase in BMD [49].30.

There were no significant differences in the percentage of serious adverse events between all groups. However, there were more injection site reactions with romosozumab treatment. The injection site reactions include pain, hematoma, erythema, discomfort, hemorrhage, or rash at the injection site. Binding antibodies were detected in 20% of patients receiving romosozumab, but only 3% of them were romosozumab-neutralizing antibodies. There was no relationship between romosozumab-neutralizing antibodies and measures of efficacy.

In the above-mentioned trial, patients continued their assigned treatment for an additional year. Patients were then randomized to receive denosumab treatment or placebo for the third year. In the second year on romosozumab, there was a continued gain of BMD in the spine and hip, but the magnitude of increase in the second year was smaller than that which occurred in the first year. After the first 2 years of romosozumab therapy, patients who switched to denosumab had a continued increase in BMD. Notably, the magnitude of gain was almost the same with BMD increases in the second year of romosozumab treatment but not as large as in the first year of therapy. Patients who stopped romosozumab at year 2 and did not receive further denosumab treatment had their bone density and bone turnover markers return to close to baseline values. After 3 years of treatment, there were no differences noted in regard to adverse events between treatment and placebo groups [56].

Phase III Trials: Efficacy, Effectiveness, and Safety of Romosozumab

In the ARCH study [57], 4093 women with severe osteoporosis (T score $\leqslant -2.5$ and a prevalent vertebral fracture) were randomized to romosozumab 210 mg monthly or alendronate 70 mg/week for 12 months followed by alendronate 70 mg/week for all patients.23 At 24 months, the risk of new vertebral fractures, clinical fractures, nonvertebral fractures, and hip fractures was reduced by 48%, 27%, 19%, and 38%, respec-

tively, in the romosozumab–alendronate group compared with the alendronate–alendronate group. In addition, at 24 months, BMD increased by 15.2% at the lumbar spine and 7.1% at the total hip in women treated with romosozumab–alendronate compared with 7.1% and 3.4%, respectively, in women treated with alendronate–alendronate.

In real life, most patients do not have the option of bone-forming treatment as first-line treatment, and most patients starting bone-forming treatment will therefore previously have been treated with antiresorptives, most often, bisphosphonates.

The aim of the STRUCTURE study [58] was therefore to compare the effects of romosozumab with teriparatide in postmenopausal women previously treated with bisphosphonates. STRUCTURE (STudy evaluating the effect of RomosozUmab Compared with Teriparatide in postmenopaUsal women with osteoporosis at high risk for fracture pReviously treated with bisphosphonatE therapy) is a randomized, open-label, international multicenter.38 It aimed to assess the effect of a 12-month treatment with either romosozumab or teriparatide on BMD after bisphosphonate treatment. The study included 436 postmenopausal women aged 55–85 years with osteoporosis (T-score ≤ -2.5 at the lumbar spine, femoral neck, or total hip) who had taken an oral bisphosphonate for >3 years before screening and, specifically, had taken weekly alendronate 1 year before screening. Patients also had to have a history of a vertebral fracture or a nonvertebral fracture after the age of 50 years. In the study, the mean patient T-scores were as follows: lumbar spine −2.2, total hip −2.9, and femoral neck −2.5. Patients, all of whom had previously received bisphosphonate treatment, were randomized to receive subcutaneous romosozumab or teriparatide. The primary endpoint of the study was total hip BMD on Dual-energy X-ray absorptiometry at month 12.

Romosozumab significantly increased total hip BMD (2.9%) and was superior to teriparatide (−0.5%). Romosozumab also led to superior gains in lumbar spine BMD as compared to teriparatide (9.8% in patients on romosozumab and 3.5% in patients on teriparatide). It is interesting to note that on QCT assessments, romosozumab treatment led to gains in BMD in the cortical as well as the integral compartments of the hip and improved the estimated hip strength (as opposed to teriparatide where there was a decrease in the estimated hip strength). Adverse effects in both treatment arms were well balanced. Therefore, romosozumab seems to be a good treatment option for patients who are transitioning from bisphosphonate therapy because it is well tolerated and also leads to BMD gains in the hip and spine.

The FRAME study (FRActure study in postmenopausal woMen with osteoporosis), carried out by Cosman and colleagues [59], is another Phase III multicenter, international, randomized, double-blind, placebo-controlled, parallel group study that compares the 1-year treatment of romosozumab followed by denosumab with the second cohort of subjects who received 1-year treatment with placebo followed by denosumab.27 The study included 7180 postmenopausal women aged 55–90 years, with a total hip or femoral neck BMD T-score of −2.5 to −3.5. The first year of the trial was completed by 6390 patients (89.1%), while 6026 patients (83.9%) completed the second year. The mean patient T-scores were as follows: lumbar spine −2.72, total hip −2.47, and femoral neck −2.75. Patients were randomized to receive romosozumab 210 mg monthly or placebo for the first year, followed by subcutaneous denosumab every 6 months for the second year. The primary endpoints for this study were vertebral fracture reduction at 12 and 24 months.

At the end of 12 months of romosozumab treatment, vertebral fractures were reduced by 73% (the incidence of vertebral fracture in the romosozumab group was 0.5% as compared to 1.8% in the placebo group). The romosozumab treatment group also had a 63% reduction in clinical fractures (composite of nonvertebral fracture and symptomatic vertebral fracture) as compared to the placebo group. At 24 months, the incidence of vertebral fractures was reduced by 75% in patients who received romosozumab in the first year and denosumab in the second year (vertebral

fracture incidence 0.6%) as compared to the group who received placebo in the first year and denosumab in the second year (vertebral fracture incidence 2.5%). There was no significant difference in nonvertebral fracture incidence at 12 and 24 months between the two groups. One possible explanation for the lower than expected nonvertebral fracture incidence in the placebo group was attributed to low nonvertebral fracture incidence in patients enrolled from the Latin America region (Colombia, Brazil, Argentina, Dominican Republic, and Mexico). Patients from the Latin America region consisted of 42.7% of patients enrolled in the study.

Consistent with the findings in Phase I and Phase II studies, there were significant gains in BMD by 12 months in the lumbar spine (13.3%), total hip (6.9%), and femoral neck (5.9%). With romosozumab treatment, serum P1NP (bone formation marker) increased rapidly and returned to baseline by 9 months of treatment. Serum CTX (bone resorption marker) decreased early during treatment and remained low during the 12 months of treatment. The change in bone turnover markers is consistent with prior studies and suggests that both increased bone formation and decreased bone resorption comprise a unique mechanism of action of romosozumab, one of the most potent osteoanabolic agents developed to date. Severe adverse events of hypersensitivity reactions to romosozumab were rare. There were mild injection site reactions in 5.2% of patients treated with romosozumab. There were two cases of osteonecrosis of the jaw and one case of atypical femoral fracture reported in the romosozumab treatment group [60].

Antifracture Efficacy

Two studies support the antifracture efficacy of this anabolic agent [61, 62]. Cosman et al. enrolled 7180 postmenopausal women with osteoporosis to monthly romosozumab (210 mg) or placebo for 12 months followed by denosumab (60 mg 6 monthly) for 12 months. At 12 months, risk reductions were reported for vertebral fractures by 73% ($P < 0.001$), for clinical fractures by 36% ($P = 0.008$) and non-vertebral fractures by 24% ($P = 0.10$). At 24 months, vertebral fracture risk was reduced by 75% ($P < 0.001$) [61].

Saag et al. [62] assigned 4093 postmenopausal women with osteoporosis and a fragility fracture to romosozumab (210 mg) or weekly alendronate (70 mg) for 12 months and then open label alendronate in both groups. Over 24 months, romosozumab/alendronate reduced vertebral fracture risk by 48% ($P < 0.001$), clinical fractures by 27% ($P < 0.001$), nonvertebral fracture by 19% ($P = 0.04$), and hip fracture by 38% ($P = 0.02$). At 12 months, romosozumab reduced new vertebral (risk ratio 0.63, 95% CI 0.47–0.85) and clinical (HR 0.72, 95% CI 0.54–0.96) fractures compared to alendronate. Non-vertebral fracture risk was also reduced by 26% with romosozumab, but this difference was not statistically significant ($P = 0.06$) [63].

Adverse Events

Adverse events associated with romosozumab were reported in 16.4% of patients receiving the drug in Phase III clinical trials. The most common adverse events that were listed include nasopharyngitis (1.0%), injection site erythema (1.1%), injection site pain (1.3%), and joint pain (1.9%) [64]. The initial 12-month component of the double-blinded FRAME trial included adverse events such as arthralgia (occurring in 13% of ROMO recipients and 12% of placebo recipient), nasopharyngitis (occurring in 12.8% of ROMO recipients and 12.2% of placebo recipients), back pain (occurring in 10.5% of Romosozumab recipients and 10.6% of placebo recipients), hypersensitivity (occurring in 6.8% of ROMO recipients and 6.9% of placebo recipients), injection-site reaction (occurring in 5.2% of Romosozumab recipients and 2.9% of placebo recipients), osteoarthritis (occurring in 7.8% of romosozumab recipients and 8.8% of placebo recipients), and atypical femoral fracture (occurring in <0.1% of romosozumab recipients and 0% of placebo recipients). Serious adverse events occurred as well, with 1.2% of Romosozumab patients and 1.1% of placebo recipients, respectively, experiencing a seri-

ous cardiovascular event, of which 0.5% of romosozumab-treated and 0.4% placebo-treated patients died. About 18% of patients in the romosozumab group (646 patients) developed anti-romosozumab antibodies during the first 15 months of the FRAME trial, and neutralizing antibodies were detected in 0.7% of patients in the same group (25 patients) [59].

The initial 12-month component of the double-blinded ARCH trial included adverse events such as back pain (occurring in 9.1% of romosozumab recipients and 11.3% of alendronate recipients), nasopharyngitis (occurring in 10.4% of ROMO recipients and 10.8% of alendronate recipients), osteoarthritis (occurring in 6.8% of ROMO recipients and 7.2% of alendronate recipients), hypersensitivity (occurring in 6% of Romosozumab recipients and 5.9% of ALN recipients), injection-site reaction (occurring in 4.4% of ROMO recipients and 2.6% of alendronate recipients), and hypocalcaemia (occurring in <0.1% of ROMO recipients and <0.1% of alendronate recipients). Serious adverse events were observed as well, with 2.5% of romosozumab recipients and 1.9% of alendronate recipients experiencing a serious cardiovascular event, of which 0.8% in the romosozumab group and 0.6% in the ALN group died. About 15.3% of patients in the romosozumab treatment group (310 patients) developed anti-romosozumab antibodies during the first 18 months of the ARCH trial, and neutralizing antibodies were detected in 0.6% of patient in the same group (12 patients) [57].

In the STRUCTURE trial [58], adverse drug events were detected and included nasopharyngitis (occurring in 13% of romosozumab recipients and 10% of teriparatide recipients), arthralgia (occurring in 10% of romosozumab recipients and 6% of teriparatide recipients), injection-site reaction (occurring in 8% of romosozumab recipients and 3% of teriparatide recipients), hypercalcemia (occurring in <1% of romosozumab recipients and 10% of teriparatide recipients), and hypocalcemia (occurring in 1% of romosozumab recipients and 0% of teriparatide recipients). Serious adverse events were observed as well, with 8% of romosozumab recipients and 11% teriparatide recipients, respectively. About 17% (37 patients) in the romosozumab group developed anti-romosozumab antibodies; however, neutralizing antibodies were not detected in ROMO recipients during the study [44].

Neoplasms were carefully assessed in these trials because of the known role of the Wnt signaling pathway, targeted by this therapy, in regulating cell proliferation. Overall romosozumab treatment was not judged to contribute to new tumor development in these trials [65].

Sustainability

In ovarectomized rats, it was noted that after giving anti-sclerosin therapy for 8 weeks, the increase in the BMD achieved started to decline gradually after stopping the treatment, particularly in the lumber vertebrae [66, 67]. The drop in the BMD was associated with an increase in the concentrations of CTX and a decrease in the level of circulating P1NP. Similar outcomes were reported while treating cynomolgus monkeys with romosozumab [68]. These changes are similar to that noted with teriparatide therapy, which require antiresorptive therapy to follow the anabolic treatment course.

Such experiences with both teriparatide and romosozumab highlight that whatever the bone anabolic therapeutic medication used, the gains achieved, whether modeling- or remodeling-based bone formation, are most likely going to be lost and an antiresorptive therapy is required to prevent such loss. One of the main reasons is that preventing the loss of the deposited bone on the quiescent periosteal surface is highly important as this bone increases the bone resistance to bending and hence increases the bone stiffness, more than depositing the same amount of bone on the inner bone surface [69].

The drop in the bone formation noted on continuing the romosozumab therapy can be explained by the suggestion that the WNT signaling in bone comes with an inbuilt self-regulation system. The transient increase in the P1NP with

romosozumab has attracted the attention. A study that used 2 different anti-sclerostin antibodies in mice or rates reported a rapid increase in modeling-based bone formation and a transient increase in mineral apposition rate in remodeling sites that was not sustained with continued treatment [125]. In this study, the mRNA levels of WNT signaling antagonists Sost and DKK1 were increased in osteoblastic cells, vertebrae, and Tibiae [70].

The finding that there was a compensatory increase in the DKK1 production in the bones consequent to sclerostin inhibition paved the way to another experiment in ovariectomized rates as well as in cynomolgus monkeys using a specific antibody with dual inhibitory effect of both sclerostin and DKK1. Results revealed that blocking both sclerostin and DKK1 led to a more robust impact than that of the blockage of either of any of them alone. In agreement with these findings are the outcomes of pharmacologic and genetic studies carried out on mice. Treating mice with anti-sclerostin antibody induced an increase in the expression of transcripts for antagonists of WNT signaling in the bones. These include Sost, DKK1, DKK2, Wif1, Sfrp2, Sfrp4, and Frzb [71], which, in turn, would play a role in restricting the osteoblast proliferation in the bones. These findings concur with earlier findings suggesting that the transient positive effect of anti-sclerostin antibody therapy can be attributed to a self-regulation process within the WNT signaling pathway.

The Clinical Potential of Romosozumab

The current options for treating osteoporosis are based mainly on antiresorptives, bisphosphonates followed by denosumab. The antiresorptives have significant antifracture efficacy, particularly against vertebral fractures but less so against non-vertebral fractures. While antiresorptives are the best option available for patients with mild-to-moderate osteoporosis, patients with severe osteoporosis particularly those at high risk of fracture need therapeutic intervention able to improve bone mass and micro-architecture in order to prevent future fractures. Currently, teriparatide and abaloparatide are the two main options available. Both medications are strong stimulators of osteoblasts and consequently induce bone formation. However, this anabolic effect is limited. This limitation has been attributed to the concomitant increase in bone resorption and the fact that these treatments are only used once and for a limited period (up to 24 months) due to safety concerns. In this context, romosozumab, with its dual-action mode of action and the potential for retreatment, is a very interesting new treatment modality [72].

Romosozumab was reported to increase the BMD of the lumbar spine and hip areas, as well as reduce the risk of vertebral and clinical fractures in postmenopausal women with osteoporosis. Studying the bone turnover markers in patients who received romosozumab therapy revealed an increase in the bone formation marker, whereas there was a decrease in the bone resorption markers [73–75]. This raised the suggestion that romosozumab has a dual action of romosozumab. Earlier reports revealed that the activation of the Wnt pathway in osteoblasts not only stimulates bone formation but also inhibits bone resorption by increasing osteoprotegerin (OPG) production [76]. The reduced bone resorption might also be caused by the deceased production of RANKL by osteocytes due to the inhibition of sclerostin [77]. In the Phase II study, s-P1NP increased by 91% after 1 month in women treated with romosozumab 210 mg monthly; however, the increase was temporary and s-P1NP was back to baseline after 6 months and even it dropped to 20% below baseline level after 12 months.25 That transient increase in bone formation measured by bone turnover markers in patients treated with romosozumab might be explained by the depletion of osteoblast progenitors or a compensatory increase in other inhibitors of bone formation such as dickkopf [78]. In the same study, s-CTX also returned toward baseline at 12 months, after the initial decrease [75].

Guidelines

The American Endocrine Society published its Clinical Practice Guideline for the pharmacological management of osteoporosis in postmenopausal women using romosozumab. The update was published in response to the recent approval of romosozumab by the United States Food and Drug Administration (FDA), the European Medicines Agency, Health Canada, and other agencies; and it represents a formal amendment to the Endocrine Society's recently published clinical practice guideline regarding the pharmacological management of postmenopausal osteoporosis [79].

The guideline for the management of postmenopausal osteoporosis is designed to provide the clinician with an evidence-based approach to the management of this condition. Several therapeutic options are available for the treatment of osteoporosis, and the framework presented evidence from clinical trials for the efficacy and safety of these interventions. An algorithm is presented to guide clinicians in the most appropriate therapeutic choices when discussing clinical decision making with the patient [79]. In addition, discussion about the efficacy and safety of this drug is contained within the Guideline Update and is based on a systematic review of the clinical trials for romosozumab [80–82].

For romosozumab therapy in postmenopausal women, the Endocrine Society [65] recommended that:

A.1 In postmenopausal women with osteoporosis at very high risk of fracture, such as those with severe osteoporosis (this is supposed to be, "i.e.," low T-score < −2.5 and fractures) or multiple vertebral fractures, we recommend romosozumab treatment for up to 1 year for the reduction of vertebral, hip, and nonvertebral fractures.

A.2 In postmenopausal women with osteoporosis who have completed a course of romosozumab, we recommend treatment with antiresorptive osteoporosis therapies to maintain bone mineral density gains and reduce fracture risk.

Technical Remarks

- The recommended dosage is 210 mg monthly by subcutaneous injection for 12 months.
  - Women at high risk of cardiovascular disease or stroke should not be considered for romosozumab pending further studies on cardiovascular risk associated with this treatment. High risk includes prior myocardial infarction or stroke.

The updated algorithm for the management of postmenopausal osteoporosis was based on the patient's fracture risk. The determination of the fracture risk carried out using the FRAX tool would be assessed using the measurement of the patient's lumbar spine and hip BMD and inserting femoral neck BMD value into the fracture risk assessment (FRAX) tool. Using that FRAX algorithm, subjects are stratified according to their risk into different categories: (1) low risk includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above −1.0, a 10-year hip fracture risk <3%, and 10-year risk of major osteoporotic fractures <20%; (2) moderate risk includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above −2.5, and 10-year hip fracture risk <3% or risk of major osteoporotic fractures <20%; (3) high risk includes a prior spine or hip fracture, or a BMD T-score at the hip or spine of −2.5 or below, or 10-year hip fracture risk ≥3%, or risk of major osteoporotic fracture risk ≥20%; and (4) very high risk includes multiple spine fractures and a BMD T-score at the hip or spine of −2.5 or below.

The Potential of Romosozumab Retreatment

Since osteoporosis is a chronic condition, which may lead to debilitating fractures, patients may need to change their therapy to another antiresorptive/anabolic agent or take a combination of 2 medications to help to prevent fractures. The option of providing a second course of bone-building therapy may benefit some patients with severe osteoporosis. This has not been applicable

in patients taking teriparatide, which is usually given for 18–24 months, for safety concern. The potential of having another course of romosozumab therapy sounds of interest, particularly for those patients with severe forms of osteoporosis or at high risk of fractures.

The results of the fourth year of Phase II study [83] revealed the outcomes of a second course of romosozumab. In the study, postmenopausal women with low bone mass (lumbar spine, total hip or femoral neck T score between −2.0 and − 3.5) were initially randomized to various doses of EVENITY or placebo for 24 months and then re-randomized to receive denosumab or placebo for the next 12 months (24 to 36 months), as previously reported. For months 36 to 48, all of these patients were then treated with EVENITY (210 mg) for 12 months.

In patients who initially received 210 mg of romosozumab followed by placebo and then a second course of romosozumab (n = 140), the second course led to significant increases in bone mineral density (BMD) to an extent similar to the initial romosozumab treatment: lumbar spine (12.7%), total hip (5.8%), and femoral neck (6.3%) during months 36 to 48. In those patients who received a second course of remosozumab after denosumab, romosozumab further increased BMD by 2.8% at the lumbar spine, while maintaining BMD at the total hip and femoral neck.

The adverse event profile in the second course of romosozumab 210 mg QM (month 36 to 48) was similar to the first course of romosozumab 210 mg QM (month 0 to 12). The incidence of adverse events in participants who had received a first course of romosozumab followed by placebo and then received a second course of romosozumab was generally comparable to that of participants who had received a first course of romosozumab followed by denosumab and then received a second course of romosozumab: 83.3% (60/72 participants) and 85.3% (58/68 participants), respectively. The incidence of adverse events was 88.9% (24/27 participants) in participants who received a first course of romosozumab during month 36 to month 48.

Serious adverse events were reported in 7 (5.0%) participants receiving a second course of romosozumab (breast cancer in 2 participants, lung cancer in 2 participants, myocardial infarction in 1 participant, inguinal hernia in 1 participant, and osteoarthritis in 1 participant) and in 1 (3.7%) participant receiving her first course of romosozumab in the second-course period (thyroid cancer); none were considered to be treatment related. No fatal events were reported in either group. Serious cardiovascular adverse events in participants receiving a second course of romosozumab were low and similar in frequency to those in participants receiving romosozumab during the first course, and also similar in frequency to those in participants receiving placebo from month 0 to month 24.

The adverse events of interest reported during the romosozumab second-course period included hypersensitivity, injection-site reactions, malignancy, and osteoarthritis. The adverse events potentially associated with hypersensitivity were reported in 11 (7.9%) participants receiving a second course of romosozumab and in 2 (7.4%) participants receiving their first course of romosozumab during the second-course period. Injection-site reactions, mostly mild in severity, were reported over the 12-month period in 10 (7.1%) participants receiving a second course of romosozumab and in 2 (7.4%) participants receiving their first course of romosozumab in the second-course period. Malignancy was reported in 5 (3.6%) participants receiving a second course of romosozumab and in 1 (3.7%) participant receiving her first course of romosozumab, and osteoarthritis was reported in 3 (2.1%) participants and in 3 (11.1%) participants, respectively. There were no reports of hyperostosis, hypocalcemia, positively adjudicated osteonecrosis of the jaw, or positively adjudicated atypical femur fracture. Overall, subject incidence of adverse events in participants receiving a second course of romosozumab was similar to that in participants who received placebo between month 0 and month 12.

As far as the romosozumab antibody, during the second-course period, the frequency of overall adverse events by antibody status was comparable between antibody-positive and antibody-negative participants. Furthermore,

binding antibody status did not have any impact on the mean percentage changes from month 0 at the lumbar spine, total hip, and femoral neck BMD at both month 24 and month 48.

Treatment in Male Osteoporosis

The safety and efficacy of romosozumab in men with osteoporosis was assessed in a Phase III randomized placebo-controlled trial [84]. This was a bridging study to extrapolate the fracture benefit observed in women with osteoporosis in FRAME to men by demonstrating that the BMD profile in the male population is comparable to that in the female population. The dosing strategy was modeled after that used in FRAME [59]. Two phase I studies of men and women provided the evidence of comparability between males and females in the pharmacokinetics of romosozumab [85, 86].

Thirty-one centers in Europe, Latin America, Japan, and North America shared in the study [84]. The work included men aged 55 to 90 years with a T-score at the lumbar spine, total hip, or femoral neck of ≤2.5 or ≤ 1.5 with a history of a fragility nonvertebral or vertebral fracture. The key exclusion criteria were a T-score at the total hip or femoral neck of ≤ −3.5, a history of hip fracture, the presence of metabolic or bone diseases or substantial laboratory abnormalities, or the current use of a medication affecting the bone metabolism (including oral and intravenous bisphosphonates, teriparatide, or any parathyroid hormone analogues, and denosumab). The subjects were randomized 2:1 to receive romosozumab 210 mg subcutaneously monthly or placebo for 12 months.

The primary objective of the present study was to evaluate the effect of treatment with romosozumab for 12 months compared with placebo on the percentage change from baseline in the lumbar spine BMD as assessed by DXA in men with osteoporosis. The secondary objectives were to evaluate the effect of treatment with romosozumab compared with placebo on percentage change from baseline in (1) TH and FN BMD at 12 months and (2) LS, TH, and FN BMD at 6 months. The exploratory objectives were to evaluate the effect of treatment with romosozumab for 12 months compared with placebo on (1) the percentage change from baseline in the serum bone formation marker procollagen type 1 N-terminal propeptide (P1NP) and bone resorption marker C-telopeptide of type 1 collagen (CTX) and (2) the bone histologic findings and histomorphometry (15) in a bone biopsy substudy of a subset of subjects. The safety objective was to characterize the (1) safety and tolerability of treatment with romosozumab for 12 months compared with placebo, as determined by adverse events reported by the trial-site physicians, and (2) formation of antiromosozumab antibodies during the 15-month trial period (12 months of treatment plus 3 months of follow-up). Potential cardiovascular-related serious adverse events, including deaths, and potential cases of osteonecrosis of the jaw and atypical femoral fracture were identified using predefined search strategies and adjudicated by their respective independent adjudication committees.

Results revealed that a total of 245 subjects were enrolled in the present study; 163 were randomized to receive romosozumab 210 mg QM and 82 to placebo QM for 12 months. After 12 months, the subjects receiving romosozumab had had a significantly greater mean increase from baseline in the LS BMD compared with the subjects receiving placebo (12.1% vs 1.2%; $P < 0.001$). Those receiving romosozumab also had significantly greater mean BMD increases from baseline (vs placebo) at the total hip (2.5% vs 20.5%; $P < 0.001$) and FN (2.2% vs 20.2%; $P < 0.001$) at month 12. Statistically significant differences in lumbar spine, total hip, and femoral neck BMD were observed between the romosozumab and placebo groups as early as month 6 (LS, 9% vs 0.3%; and TH, 1.6% vs 0.2%; $P < 0.001$; FN, 1.2% vs 0.0%; $P = 0.0033$).

As part of an exploratory objective, the percentage change from baseline in serum BTMs during the 12-month period was assessed. The P1NP levels increased early in subjects receiving romosozumab, peaking at month 1, when the median percentage change from baseline was 85.8% compared with 1.2% in the placebo group ($P < 0.001$). By month 3, the median percentage

change from baseline was 25.4% in the romosozumab group and 22.4% in the placebo group ($P < 0.001$). The median percentage change from baseline through the end of the study was 20.9% and 22.5% at month 6 ($P = 0.58$) and 219.7% and 26.2% at month 12 ($P = 0.0032$) for romosozumab and placebo, respectively. The CTX levels also changed early in the study in the subjects receiving romosozumab, with the greatest decrease at month 1, when the median change from baseline was 230.8% compared with 21.7% in those receiving placebo ($P < 0.001$). The CTX levels in the romosozumab group remained less than those in the placebo group throughout the study: 216.8% vs 28.2% at month 3 ($P = 0.15$), 224.2% vs 25.8% at month 6 ($P < 0.001$), and 227.8% vs 0.7% at month 12 ($P < 0.001$).

In conclusion, the BRIDGE study [84] reported that treatment with romosozumab 210 mg subcutaneously QM increased the spine and hip BMD compared with placebo at months 6 and 12 and was well tolerated in men with osteoporosis. Romosozumab, which has a dual effect of increasing bone formation and decreasing bone resorption, appears to be a new and promising bone-forming treatment for men with osteoporosis. This dual effect is a unique aspect of romosozumab that has not been observed with any other agent approved for the treatment of osteoporosis.

Sclerostin Antibody for Potential Healing Enhancement of Osteoporotic Fracture

The effects of Scl-Ab treatment on fracture healing have been investigated in various animal models. Scl-Ab treatment increases bone mass and strength at the fracture site in rats using either a closed femoral fracture model [87] or a femoral osteotomy fracture model [88, 89]. More bony tissue and less cartilage tissue have been observed at the fracture site in the rat femoral osteotomy fracture model [88] and cynomolgus monkey bilateral fibular osteotomy model [87], indicating that Scl-Ab treatment is able to enhance endochondral ossification during fracture healing. Similarly, the bone mass and strength are increased during fracture healing in SOST-KO mice, in both a femoral closed fracture model [90–92] and a tibial closed fracture model with external fixation [93]. In both models, the endochondral ossification is hastened as evidenced by increased cartilage removal [92, 93]. These studies indicate that downregulation of sclerostin expression enhanced fracture healing through faster endochondral ossification.

Scl-Ab treatment also enhances bone repair in osteoporotic condition. In a tibial drill-hole defect model in OVX rat, Scl-Ab treatment accelerates the intramembranous bone repair in both the trabecular bone and cortical bone of the defect region [94]. This indicates that Scl-Ab treatment also enhances bone formation and bone healing in OVX conditions. In addition, based on an earlier study in rat femoral osteotomy healing, Scl-Ab treatment has proven to enhance fracture healing through the hastened endochondral ossification and improved angiogenesis [88, 95]. Angiogenesis is essential for bone healing, in both normal and osteoporotic fracture healing [96, 97]. Given that Scl-Ab improves fracture healing in a rat longbone closed fracture model [87], rat femoral osteotomy [88], or cynomolgus monkey bilateral fibular osteotomy model [87]. Scl-Ab is also expected to be able to improve osteoporotic fracture healing. Clinical trials are essential to support the potential routine applications of Scl-Ab for fracture healing enhancement in osteoporotic patients, apart from the known effects of Scl-Ab in the prevention of secondary osteoporosis in this high-risk group.

Romosozumab and Cardiovascular Events

Vascular calcification is believed to be an important factor in connecting bone loss and cardiovascular events, both of which are mediated by oxidative stress and inflammation. Dyslipidemia and inflammation are major contributing factors to intimal calcification and considered risk factors for bone loss. In addition, medial calcification is associated with advanced age, diabetes mellitus,

and chronic kidney disease. Furthermore, the presence of osteogenesis footprints (such as alkaline phosphatase, osteocalcin, and collagen), osteoblast/chondrocytes transcription factors (e.g., RUNX2 [runt-related transcription factor 2] and SOX9 [Sry-related HMG box 9]), various signaling pathways (including RANK-RANKL signaling pathway and Wnt (wingless/integrated) signaling pathway), bone morphogenic proteins, hormones (for instance, parathyroid hormone, estrogen, leptin, and adiponectin), oxidized lipids, and vitamins (D and K) in both conditions, all signify shared pathophysiologic mechanisms between bone and vascular calcification. The process of coronary calcification is very similar to bone development [98].

Although the development of coronary artery calcification was considered a passive and degenerative process, it had been recently appreciated that newly developed calcification is an active process, which is mainly induced by inflammation followed by osteogenic differentiation and mineralization of the vessel wall [99, 100]. Understanding the pathophysiological mechanisms of developing cardiovascular complications after romosozumab treatment may point to a method of reducing cardiovascular events in romosozumab receivers.

The Wnt pathway, BMPs (bone morphogenic proteins), parathyroid hormone, and IGF-1 (insulin-like growth factor I) are regulators of osteoblasts growth, differentiation, and mineralization.10 The Wnt pathway is categorized into 3 parts: the canonical Wnt-β-catenin, the noncanonical Wnt–planar cell polarity, and the calcium-dependent pathways. The role of Wnt–β-catenin signaling pathway in skeletal development [101], adipocyte differentiation [102], cardiovascular homeostasis [103], atherosclerosis, vascular calcification [104], lipid metabolism, and glucose metabolism has been previously reported. Wnt proteins can influence many cell types involved in the cardiovascular system, in health and disease, and many studies aimed at understanding their specific contributions in various cell populations. In endothelial cells, Wnt3a was shown to promote the production of reactive oxygen species leading to endothelial dysfunction [105]. Other studies demonstrate that Wnt5a is expressed in endothelial cells in human atheroma and promotes endothelial inflammation, though these effects were β-catenin independent [106].

In addition to their migratory capacity, Wnts have been shown to modulate monocyte/macrophage inflammatory state. Wnt5a was found to be expressed by human macrophages in atherosclerotic lesions, and macrophage Wnt5a expression was enhanced on oxidized LDL (low-density lipoprotein) treatment in vitro [107]. Other studies demonstrated that β-catenin regulates cell migration and transcription after lipopolysaccharide treatment [108] and that β-catenin inhibition ameliorates sepsis-related inflammation [109]. In contrast, several studies revealed that canonical Wnt signaling may dampen inflammation in macrophages.

Furthermore, in addition to endothelial cells and macrophages, it has been demonstrated that Wnts play an important role in vascular smooth muscle cell biology. For instance, reduced Wnt signaling via LRP6 mutation was shown to promote aortic medial hyperplasia through the inhibition of vascular smooth muscle cell differentiation and enhanced proliferation (Fig. 23.4) [110, 111].

Bisphosphonate and Cardiovascular Consequences

The effects of bisphosphonates on cardiovascular outcomes are controversial. They seem to have no harmful effects on atherosclerotic cardiovascular events. However, it was reported that they were associated with higher incidence of acute myocardial infarction in elderly men [112]. Bisphosphonates could potentially decrease arterial wall calcification and cardiovascular mortality but have no effect on arterial stiffness or cardiovascular events [113, 114]. They seem to have some roles in the appearance of atherosclerosis manifestation, possibly by releasing bone-related biomarker (such as osteocalcin, FGF-23 [fibroblast growth factor-23], sclerostin, and so on) into the blood and affecting calcium homeostasis at the level of the vascular wall. However, further studies are needed to elucidate the mechanism of bisphosphonates in the cardiovascular system [115].

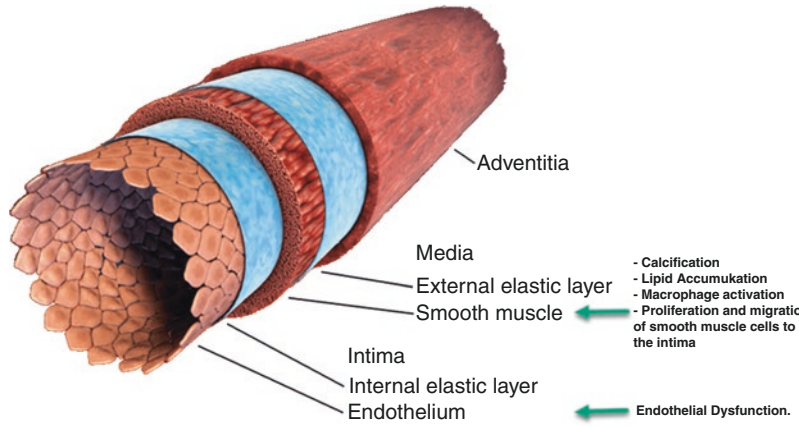

Fig. 23.4 Changes in the levels of bone formation markers and bone resorption markers with subcutaneous injections of TPTD (20 μg daily) or ROMO (210 mg once monthly) for 1 year. (Notes: Quoted with permission from [60] under open access scheme. Reproduced from Appelman-Dijkstra NM, Papapoulos SE. Modulating bone resorption and bone formation in opposite directions in the treatment of postmenopausal osteoporosis. Drugs. 2015;75(10):1049–105,836 which was originally sourced from Leder BZ, Tsai JN, Uihlein AV, et al., Two years of Denosumab and teriparatide administration in postmenopausal women with osteoporosis (The DATA Extension Study): a randomized controlled trial, J Clin Endocrinol Metab, 2014;99(5):1694–1700, by permission of Oxford University Press.49. Abbreviations: *ROMO*, romosozumab; *TPTD*, teriparatide)

Romosozumab/Alendronate and Atherosclerosis

Blocking sclerostin can transiently dysregulate cellular cholesterol homeostasis. Furthermore, the activation of LRPs (low-density lipoprotein receptor-related protein) via blocking of their inhibitors may increase LDL uptake and cellular lipid accumulation. Additionally, the activation of the Wnt pathway can potentially promote inflammation83 and lipid uptake [116]. However, alendronate can block FPPS (farnesyl pyrophosphate synthase – an enzyme distal to HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase; (the site of statin action) and lower cholesterol level, which results in less lipid uptake, inflammation, and calcification. In other words, Wnt has bidirectional correlation with atherosclerosis (or cardiovascular events), and LRPs have dual function for cholesterol and Wnt activation. Blocking sclerostin can increase lipid uptake through LRPs. However, applying a method to block fat accumulation can ameliorate the harmful consequences of sclerostin blockers without losing the beneficial effects of Wnt signaling on atherosclerosis regression. Thus, alendronate can ameliorate the harmful effects of romosozumab through its effects on lipid metabolism. However, it is important to mention that adding statins (by blocking HMG-CoA reductase), PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitors (by reducing LDL), and scavenger receptors blocker (such as antibody against endothelial CD36 [cluster of differentiation 36] which participates in cell fatty acid uptake) may reduce lipid uptake and improve the clinical outcome of treatment with romosozumab [98, 117].

ROMO and Renal/Vascular Disease

The chronic kidney disease–mineral bone disorder (CKD-MBD) is a new acronym coined in 2006 in recognition that the skeletal (renal osteodystrophy) and mineral disorders caused by CKD are critical contributors to the high cardiovascular morbidity and mortality and fracture rates. Similar to what is observed in the general population, low bone tissue mineralization inversely associates with pathological cardiovascular calcification in CKD. Despite its vast clinical significance, the precise nature of this reciprocal relationship remains obscure [118].

CKD-MBD develops early in the course of kidney disease and is already clinically detectable in stage 2 CKD. Increasing evidence indicates that circulating Wnt (Wingless) signaling inhibitors may play a crucial role in the pathogenesis of CKDMBD. In fact, mounting evidence points to a central role of a disturbed Wnt–β--catenin signaling in the pathogenesis of CKD-MBD. This opens perspectives for targeted therapy, including pharmacological neutralization of sclerostin or DKK1 (Dickkopf-related protein (1) by monoclonal antibodies. Moe et al. [119] observed improved bone properties in an animal model of progressive CKD treated with anti-sclerostin antibodies; however, only when the parathyroid hormone levels were low. In another animal model of early CKD, Fang et al. [120] demonstrated that the combination of DKK1 neutralization and phosphate binder therapy was sufficient to decrease vascular calcification and to correct renal osteodystrophy. The extrapolation of these exciting experimental data to the clinical setting warrants caution, mainly in view of the clinical and experimental data suggesting that both Wnt inhibitors may attenuate the progression of vascular calcification and that the beneficial effects of Wnt inhibitor may differ depending on the precise type of CKD-MBD. In one prospective randomized study [121] which included 261 postmenopausal women receiving romosozumab over 12 months, there were no reports of remarkable cardiovascular side effects. Of note, patients with an estimated creatinine clearance below 30 ml/min were excluded from this trial.

In conclusion, there is great clinical potential for romosozumab for the treatment of osteoporosis. Romosozumab is the first osteoporosis treatment that exerts dual action, as it stimulates bone formation, based on both modeling as well as remodeling and in the meantime inhibits bone resorption. This led to significant increases in bone mass and bone strength and most importantly significant reductions in the risk of fractures. It has also been demonstrated that the fracture risk reductions are more prominent than the reported reductions with any strong antiresorptive treatment.

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24 New Frontiers in Osteoporosis Management: Optimizing Sequential and Combination Therapy

Yasser El Miedany

Introduction

The bone microstructure, composition, and volume are maintained by bone remodeling, a cellular activity carried out by bone multicellular units (BMUs). BMUs are focally transient teams of osteoclasts and osteoblasts that respectively resorb a volume of old bone and then deposit an equal volume of new bone at the same location. During young adulthood, bone remodeling is balanced; i.e., an equal volume of bone is resorbed and subsequently replaced so no net loss or gain occurs [1]. Around midlife, bone formation by the osteoblasts of the basic multicellular units (BMUs) decreases, producing remodeling imbalance. At menopause time, the imbalance worsens with bone remodeling becoming rapid, with increase in the BMUs number, yet less bone is deposited than they resorb, resulting in bone loss, a reduction in bone volume, and consequent microstructural deterioration. This process occurs by each of the many BMUs initiated at the three (intracortical, endocortical, trabecular) components of the endosteal (inner) bone surface [2]. As a result, cortical bones become porous and thin, whereas trabeculae become thin, perforated, and disconnected, causing bone fragility. With advancing age, bone loss from the trabecular compartment lessens because trabeculae with their surfaces disappear (remodeling requires a surface to be initiated upon). Bone loss becomes predominantly cortical as intracortical surface area increases facilitating initiation of unbalanced intracortical remodeling [3, 4]. The microstructural deterioration produces bone fragility out of proportion to the bone loss producing it [5]. Anti-resorptive agents act by reducing the rate of bone remodeling so that fewer BMUs are available to remodel bone; hence, it reduces the fracture risk. However, bone fragility is not abolished by these drugs as the existing microstructural deterioration is not reversed. On the other hand, anabolic agents reduce fracture risk by stimulating new bone formation, which partly restores bone volume and microstructure [6]. This raises a question: Is anti-resorptive therapy the best treatment option for patients at highest risk for future fractures?

The burden of fragility fractures is increasing in absolute terms. One important factor that favors this notion is that patients' management is based mainly on DXA scan results. Patients identified as eligible for treatment are only those whose T-score lies in the osteoporosis range, whereas those whose T-score is not in the osteoporosis range do not receive any treatment. Women with osteopenia have been identified as the source of over 60% of all fragility fractures [7]. This may represent a real challenge. A fracture that occurs in people with low bone mass in

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the setting of minimal trauma – such as a fall from standing height – meets the criteria for the *clinical diagnosis of osteoporosis* and qualifies this particular individual for being at high risk of further fractures. This can be explained by the fact that bone weakness or fragility is related not only to quantitative aspects but also to structural and qualitative aspects that cannot be easily assessed in standard practice. Similarly, another cohort of patients who are at the highest risk of fracture are those with a silent vertebral fracture. Unfortunately, vertebral fractures are always missed as they are often asymptomatic and are reported as coincident findings in the X-ray report. Therefore, targeted screening and notification using spine imaging is, probably, as important as BMD testing.

As a chronic degenerative disease, osteoporosis requires long-term management. However, none of the currently available anti-osteoporotic agents has proven efficacy and safety beyond 10 years of treatment. Furthermore, long-term treatment with the most potent anti-resorptives, namely, bisphosphonates and denosumab, has been associated with rare, but severe adverse events, such as osteonecrosis of the jaw (ONJ) [8, 9] and atypical femoral fractures (AFF) [10, 11]. These adverse events appear to be time-related, leading expert panels of scientific societies and the US Food and Drug Administration (FDA) to recommend reevaluation of continuing therapy beyond 3 and 5 years on an individual basis [12, 13]. On the other hand, osteoanabolic agents can be administered only for a relatively short period, ranging from 1 year for romosozumab to 2 years for parathryroid hormone therapy. Therefore, transitioning from one therapy to another is quite common in clinical routine. Keeping in view the above facts, the real challenge to treat osteoporosis on a long-term basis is to set the optimal treatment strategy for each individual patient, e.g., how to use the available osteoanabolic and anti-resorptive agents, sequentially or in combination, in the most effective and safe way [14].

This chapter will review the unmet needs for prevention and management of bone fragility. It will then discuss the existing evidence regarding sequential and combination treatment for osteoporosis, classifying data under four studied scenarios: anti-resorptives after osteoanabolics, osteoanabolics after anti-resorptives, anti-resorptives after anti-resorptives, and finally combination of both anti-resorptive and anabolic therapy agents.

Unmet Needs in the Management of Bone Fragility

The word "osteoporosis" is often used synonymously with bone fragility, but women with osteopenia are not free of the risk of fracture [7, 15]. Indeed, most women and men sustaining fragility fractures have osteopenia and even some have "normal" BMD [16]. Women with osteopenia at risk for fracture can be identified by measuring microstructural deterioration [17, 18] but high-resolution imaging methods are not yet widely available. The use of clinical risk factor assessment tools such as FRAX has met with variable success [19, 20]. Challenges also arise in the uptake and adherence to therapy, in part, because of concerns regarding the serious but uncommon long-term adverse effects of therapy [21, 22].

Anti-resorptive agents are the first-line and most commonly used treatments for prevention and treatment of bone fragility [23]. Apart from denosumab, which virtually abolishes remodeling, most anti-resorptives slow unbalanced remodeling, so microstructural deterioration continues to occur albeit more slowly [24]. This lower rate of remodeling reduces fracture risk compared to untreated women in whom rapid remodeling continues to deteriorate the skeleton. This is a relative risk reduction. In absolute terms, fracture risk does not decrease during anti-resorptive therapy because microstructural deterioration present is not reversed and the slow continued unsuppressed and unbalanced remodeling continues to deteriorate bone. This, in part, may explain why fracture risk reduction with anti-resorptives is modest. Teriparatide increases bone matrix volume predominantly through remodeling-based bone formation [25]. It is likely that the anabolic effect of abaloparatide,

which acts via the same receptor as teriparatide, is also remodeling based like teriparatide, although rigorous assessment of its mechanism of action has not been undertaken [26]. Both reduce the risk of vertebral and non-vertebral fractures [27, 28] but no adequately designed trials have been done to determine whether hip fracture risk is reduced (Fig. 24.1).

Romosozumab has been recently licensed for the management of osteoporosis and fragility fracture prevention. Romosozumab is a dual acting agent that increases bone formation and also reduces bone resorption. It is administered once monthly for 1 year and produces marked increases in spine and hip BMD, almost certainly as a result of an early increase in bone modeling. The latest guidelines from the Endocrine Society, USA (2020), has suggested Romosozumab be considered as a first-line therapy in patients with multiple vertebral fractures or hip fracture and BMD in the osteoporotic range [29], in addition to being considered for individuals who have failed anti-resorptive treatments.

Two large phase 3 trials of romosozumab were conducted to test its efficacy in vertebral and non-vertebral fracture risk reduction [30–32]. Neither was powered to show an effect on hip fracture risk. In the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) trial, 7180 postmenopausal women were treated with monthly injections of romosozumab or placebo. An analysis that compared romosozumab with placebo using a direct approach [3, 30] rather than a network approach [31] showed a 73% reduction in the risk of vertebral fractures (risk ratio [RR], 0.27; 95% confidence interval [CI], 0.16–0.47) but no significant effect on the risk of hip or nonvertebral fractures. Romosozumab and

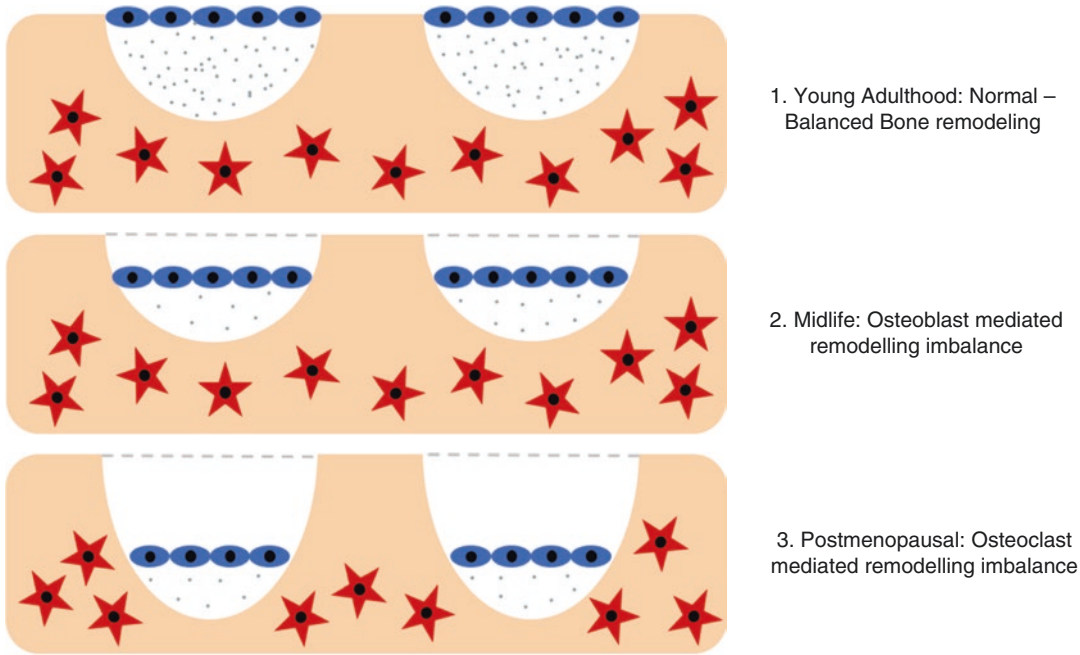

Fig. 24.1 Structural changes in bone with osteoporosis medications. The anti-resorptive medications (bisphosphonates and denosumab) and anabolic medications (teriparatide and likely abaloparatide) produce very different structural changes in bone. Although both classes increase trabecular bone, their effects on cortical bone are different. Bisphosphonates and denosumab do not expand periosteal bone but do decrease the endosteal diameter by an increase in endosteal bone volume. Anti-resorptives also reduce cortical porosity. Anabolic agents lead to an increase in periosteal bone with a simultaneous increase in endosteal bone resorption resulting in a bone without a large change in cortical thickness. At the same time, anabolic agents increase cortical porosity. Despite the increase in cortical porosity, the larger bone has increased strength. NC no change. (Quoted under open access scheme from Choksi et al. [212])

placebo treatments were followed by 12 months with the anti-resorptive agent denosumab to maintain/increase the gains in BMD. At 24 months, those treated with romosozumab followed by denosumab demonstrated a 75% lower risk for new vertebral fractures (RR, 0.25; 95% CI, 0.16–0.40). In the follow-up extension to the FRAME study, which investigated an additional year of denosumab treatment, similar significant reductions in relative risk and increases in spine and hip BMD with the initial therapy with romosozumab were sustained at 36 months [33].

In the trial, Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) [32] (number of patients: 4093), 1 year of treatment with romosozumab followed by 1 year of alendronate was compared with 2 years of treatment with alendronate in postmenopausal women at high risk of fracture [5, 32]. The ARCH trial showed that romosozumab/alendronate as compared with alendronate/alendronate resulted in a 48% reduction in the risk of vertebral fractures at 24 months (RR, 0.52; 95% CI, 0.40–0.66), a 38% reduction in the risk of hip fractures at 24 months (hazard ratio [HR], 0.62; 95% CI, 0.42–0.92), and a 19% reduction in the risk of nonvertebral fractures at 24 months (HR, 0.81; 95% CI, 0.66–0.99) [32].

Clinical Vs Radiologic Osteoporosis

Osteoporotic fractures occur spontaneously or as a result of minimal trauma from day-to-day activities [34]. In 90% of all hip fractures, the leading mechanism of trauma is a simple fall [35–38], indicating bone fragility in these patients. Early detection of an impaired quality of bone is crucial in the prevention of osteoporotic fractures. Previous studies suggest broad under-diagnosis of osteoporosis [6, 39], and the opportunity to start bone modulating therapies before the occurrence of an osteoporotic fracture is missed in up to 84% of osteoporotic fracture cases [40].

The assessment of bone mineral density (BMD) as a surrogate marker of bone strength using non-invasive methods like dual-energy X-ray absorptiometry (DXA) is widely regarded as the gold-standard for diagnostic screening and as a guide prior to therapeutic decisions [41]. However, BMD accounts for only 60% of the variation in bone fragility [42], because it is unable to depict differences in bone material composition and structural design. Both characteristics influence bone strength to a large extent [43]. On the other hand, the occurrence of low trauma fracture would reflect the bone strength status and has been considered as a marker of clinical osteoporosis.

In vivo, bone experiences different loads from different directions and in different intensity and frequency over time. Bone has two main structural responses to changing loading patterns: altering structural density and increasing the degree of structural orientation along the acting force vectors, i.e., anisotropy [43–45].

These adaptive responses would not be possible without the existence of continuous bone remodeling. In bone remodeling, bone tissue is removed by osteoclastic resorption and new bone is formed by osteoblasts. In the early life span after skeletal maturity the amounts of bone removed and replaced with each cycle of bone remodeling are usually equal to each other, leaving the total volume of bone unchanged. With aging and in the setting of osteoporosis, the balance of bone resorption and formation becomes negative. The bone loss in aged and osteoporotic bone is a consequence of imbalanced and excessive bone remodeling [46]. The microstructural changes caused by this remodeling imbalance compromises bone strength disproportionately to the net bone loss leading to this deterioration [5, 47].

As bone remodeling occurs on osseous surfaces, osteoporotic bone loss is a function of surface available for bone remodeling. In individuals less than 65 years of age, the largest surface available for bone remodeling is the trabecular bone. In this population, trabecular bone – due to its lesser density when compared to cortical bone – provides only about 20% of the skeletal bone mass but it is responsible for most of the turnover [43, 48, 49]. Thus, the bone loss in early osteoporosis is mainly a trabecular bone loss.

With increasing age, the cortical bone becomes more and more porous and, therefore, its endocortical surface increases. As a consequence, the largest loss of absolute bone mass due to osteoporosis occurs in cortical bone by intracortical rather than endocortical or trabecular remodeling [46, 50, 51].

Such changes have important clinical implications. Women who attain high peak bone mass, as they pass to the postmenopausal period and start to lose bone, though they sustain microstructural deterioration, their BMD measurement decreases only to the osteopenia range or even remains in the low normal range. This may give a false impression that their fracture risk is low; hence, no treatment is suggested [52]. This may sound reasonable, supported by the finding that the fracture risk in osteopenic women is lower than that in those with osteoporosis; however, women with osteopenia are not immune from fractures. In fact, 60–70% of those women who sustain low trauma fractures have osteopenia (or even normal bone mineral density) [53]. This led to the conclusion that an important reason of bone fragility in women with osteopenia or even normal bone mineral density is microstructural deterioration [54, 55]. Another clinical implication is the finding that the transition from early trabecular to later cortical bone loss is consistent with the epidemiological data on osteoporotic fractures. Vertebral compression fractures, being "trabecular fractures," are more common in individuals aged less than 65 years. With increasing cortical bone loss after the age of 65 years, hip fractures, being rather "cortical fractures," become more frequent [56].

Pathophysiology: What Is and Is Not Achievable Using Different Osteoporosis Therapies?

All factors influencing bone's structural strength express their effects through a final common cellular machinery of bone remodeling. Bone remodeling, a sequential process of bone resorption and formation, occurs throughout life renewing the composition of the mineralized matrix volume [57]. During young adulthood, bone remodeling is balanced – an equal volume of bone is resorbed and subsequently replaced so no net loss or gain occurs [1]. Around midlife, bone formation by the osteoblasts of the basic multicellular units (BMUs) decreases, producing remodeling imbalance [58]. In addition, as a consequence of the estrogen deficiency accompanying menopause, remodeling imbalance worsens and the rate of remodeling increases—less bone is deposited than was resorbed by each of the many BMUs initiated upon the three (intracortical, endocortical, trabecular) components of the endosteal (inner) bone surface [59] (Fig. 24.2).

It is useful to consider the mechanisms of bone loss in terms of the sequential changes at the single cross-sectional location as it travels perpendicular to the plane section. The resorption of bone volume and its replacement by osteoid tissue, followed by primary then secondary mineralization of the osteoid tissue, are not instantaneous events [60–62]. East step had a specific time course, such that the resorptive phase induced by the osteoclasts takes about 3 weeks; this is followed by a reversal phase, 1–3 weeks, which represents the time taken by the osteoblasts to differentiate and proliferate. The next step is the bone formation phase which takes up to 3 months [63]. During this phase, the osteoid tissue is deposited first and then endures fast primary mineralization within days of deposition to become bone. The last step of secondary mineralization takes 12–24 months to complete which represent the slower phase of bone mineralization. This phase is characterized by the enlargement of the calcium hydroxyapatite crystals which were deposited during the primary mineralization phase, with water displacement. This process gives the bone its resistance to bending, which is a vital character of bones that enables them to act as a lever [64].

The sequence of these four phases creates a state of normal delay, producing a transient state of focal deficit in the bone matrix and its mineral content [60]. This temporary state is reversible fully without any consequent permanent microstructural decline. In young adults, at any specific

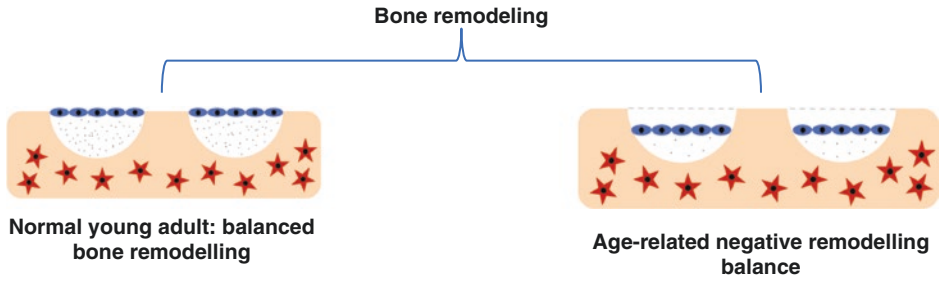

Fig. 24.2 Reversible and irreversible deficits in bone volume is based on the cellular mechanisms of remodeling: (1) Normal-depth resorption cavity, completely refilled with new mineralized bone (mineralization occurs in 2 phases: primary (dotted) and secondary (yellow). In your adulthood, the deficit is reversible as the cavities are completely refilled with matrix, which undergoes slow secondary mineralization. (2) Resorption cavity of normal depth that is incompletely refilled by a subnormal amount of new bone. The lost bone is represented by the clear area between the original bone surface (dotted line) and the new surface location. Remodeling imbalance occurs when the excavated cavities are not being filled and the osteoid tissue gets mineralized, thereby causing bone loss and microstructural deterioration of the reduced bone volume. (3) Exacerbation of the irreversible deficit by menopause related estrogen deficiency, which increases the life span of the osteoclasts (causing resorption cavity of excessive depth) and reduces the lifespan of the osteoblasts (leading to deposition of less bone in the larger cavity), which further aggravates remodeling imbalance and focal microstructural deterioration

time, there are several cavities excavated by BMU at different stages of their remodeling cycle. Considering that in average there are 10% of bone volume undergoing remodeling per year, there is a state of reversible deficit mainly in the mineral content (bearing in mind that secondary mineralization takes 1–2 years to complete). Consequently, the new osteons of cortical bones and hemiosteons of trabecular bones are completely reconstructed months before they become fully mineralized [60].

At midlife (45–50 years old) in both sexes, the process of aging is associated with an increase in the rate of bone remodeling in both cancellous and cortical bone. The remodeling that occur around mid-life is characterized by reduction in the volume of the resorbed bone by each BMU, associated with an even bigger reduction in the volume of the bone deposited by the BMU at the same location, resulting in a negative remodeling balance. Morphologically, this remodeling imbalance leads to irreversible bone loss, deterioration of the bone microstructure, and consequently increased bone fragility. This process is replicated each time bone is remodeled trying to repair matrix damage. As the deposited bone is less than reabsorbed one, this leads to the development of permanent microstructural changes [65–67], namely, increased cortical porosity, cortical thinning, complete loss of trabeculae connections, and disconnection of the trabeculae with each other and the cortex [64].

By menopause, with associated estrogen deficiency (which lead to increase in the osteoclast life span and concurrent reduction in the osteoblast life span), there is an exacerbation of this irreversible bone loss state as a result of deposition of less bone in the larger cavity. This aggravates the remodeling imbalance, leading to excavation of larger cavities and focal microstructural decline [68].

Therapeutic Implications

Anti-resorptive Therapy

Bisphosphonates Bisphosphonates (alendronate, risedronate and zoledronic acid) are currently first-line treatment and the most common anti-resorptive therapy used. The anti-resorptive efficacy of bisphosphonates depend on inhibition of farnesyl pyrophosphate (FPP) synthase, required for osteoclast resorptive function, as well as their affinity for mineral which influences uptake, distribution, and retention in the

bone [69–71]. Bisphosphonates slow but do not abolish remodeling. Consequently, these drugs reduce the number of BMUs turning over in the skeleton [23, 72, 73]. The bisphosphonates, similar to all other anti-resorptive agents, do not reduce the irreversible component of the deficit in the matrix and its mineral content (which developed as a results of the remodeling imbalance). However, the acute reduction in the number of resorption cavities excavated slows the decline in bone volume [23, 72]. Also, the fewer resorption cavities result in fewer stress concentrators [74]. Thirdly, most of the resorption cavities are partly refilled, reducing focal stress by distributing the load more widely. Lastly, the newly deposited matrix undergoes rapid primary mineralization, while matrix deposited several months earlier (before starting the bisphosphonate therapy) undergoes slower state of secondary mineralization [75].

However, high affinity binding agents, like alendronate, have a reduced ability to penetrate and distribute widely in deeper cortical matrix (bisphosphonates bind mainly to the superficial matrix beneath the endosteal surface and do not distribute into deeper volumes of cortical bone as widely as they distribute in the thin trabecular plates), so that when osteoclasts remodel deeper layers of the cortical bone they encounter matrix free of bisphosphonates and continue to resorb bone. Therefore, unbalanced remodeling continues in deeper cortical bone despite bisphosphonate therapy.

The net result of bisphosphonate therapy is an increase in the mineral content of diminishing total bone volume, features that might increase bone fragility and the risk of fracture [76].

Denosumab Remodeling suppression with denosumab is greater than that achieved with any other anti-resorptive agent [77]. Denosumab is widely distributed throughout both the cortical and trabecular bone, thus more completely suppression of the new BMUs in both cortical and trabecular bone (in comparison to bisphosphonates) [23, 72, 73]. Similar to bisphosphonates, the mineral content of the total bone matrix volume increases, but the total bone matrix volume might not be less, or might decrease less, than that achieved during bisphosphonate therapy as little remodeling takes place [73].

Changes in BMD During the first 6–12 months of anti-resorptive therapy, there is an early rapid increase in the BMD. This increase is not attributed to increase or restoration in the bone mass or bone volume (i.e., the increase does not represent an anabolic effect). In contrast to anabolic therapy which adds bone upon the periosteal and endosteal surfaces, anti-resorptive medications slow the removal of bone. This is achieved though the reduction of the number of excavation cavities, and primary mineralization of the already excavated cavities shortly developed before the initiation of bisphosphonate therapy. As far as the cavities developed several months before treatment, secondary mineralization of the matrix occurs.

Beyond the first year of anti-resorptive therapy, the slow continued increase in BMD is mostly a result of secondary mineralization, the slowest component of the formation phase of bone remodeling cycle and thereby, the last to reach completion [60–62]. However, in patients receiving bisphosphonate medication, the increase in the matrix mineral density and BMD cease to occur, as secondary mineralization is complete after 3–5 years of bisphosphonate therapy [23, 72]. On the other hand, denosumab treatment is associated with a continued increase in BMD during 8–10 years of therapy [78].

Selective Estrogen Receptor Modulators (SERM) The stability of BMD or slow continued increase in BMD during 3–10 years reported with powerful remodeling suppressors (e.g., bisphosphonates and denosumab) is not observed with weak remodeling suppressants such as calcium or SERM, which slow the remodeling rate by only 20–30% of the pre-treatment rate [79, 80]. Therefore, the bone continues to be remodeled to a greater extent than with bisphosphonates or denosumab.

Similar to bisphosphonates as well as denosumab, at the onset of therapy, SERM inhibit remodeling with a result of incomplete refill of the excavated cavities which occur in the first 6–12 months of treatment, but in contrast, during the same period (6–12 months of therapy), most (70–80%) of the pre-treatment BMU continue to remodel bone and thus only a modest early net increase in BMD of a fewer percentage points occurs [6].

Beyond a 12 month of therapy with these weaker anti-resorptive medications, the remodeling rate stabilizes at 70–80% of the pre-treatment rate. The 20–30% fewer cavities excavated during the first 6–12 months incompletely refill, but similar number of BMUs, or even more, excavate new cavities, producing a net decrease in BMD. The decrease in BMD is detectable because there is little, if any, concurrent increase in matrix mineral density obscuring the decrease in bone volume (as occurs with powerful remodeling agents). Most of the matrix is still rapidly renewed and replaced with young bone. Continued unbalanced remodeling decreases total bone matrix volume and produces microstructure deterioration, features that probably account for the lack of evidence of non-vertebral or hip fracture risk reduction reported with these weaker drugs [81, 82].

Anabolic Therapy

Reconstruction of the bones ("cure" of the bone thinning and fragility) requires anabolic therapy. Anabolic skeletal effects can be achieved through changes in bone remodeling, bone modeling, or a combination of both. Two anabolic medications are available for clinical use in patients with severe bone loss and microstructural declining who are expected to benefit from restoration of the lost bone: Teriparatide (PTH 1–34) and abaloparatide. Teriparatide is formed of the first 34-amino acids of the parathyroid hormone (PTH) [83], the hormone product of the parathyroid hormone. Abaloparatide is formed of 34-amino acids peptide; the first 21-amino acids are identical to those of the parathyroid hormone–related protein (PTHrP), with substitutions up to amino acid 36. PTHrP acts as an autocrine and paracrine regulator in many tissues [84–87]. In bone PTHrP is produced by the cells of the osteoblast lineage.

Circulating PTH and PTHrP use a common G protein-coupled receptor (GPCR), PTH1 receptor (PTH1R), to activate target cells. The biological activity achieved by both PTH and PTHrP is included within the amino-terminal 36-residues [84]. Both teriparatide and abaloparatide are administered by daily subcut injections as the pharmacokinetics require a brief peak circulating level of PTH activity returning to baseline within 3 h to achieve the anabolic effect [85].

In iliac crest bone, intermittent administration of teriparatide stimulates modeling-based bone formation on cancellous, endosteal, and periosteal surfaces, an effect that is most evident in the early stages of treatment [88]. However, the majority of the anabolic effect in cancellous bone is achieved through remodeling with overfilling of remodeling units (Fig. 24.2). In cortical bone, the effects vary according to site; increased total bone area, increased cortical porosity, and the formation of hypomineralized new bone can occur in the early stages of treatment, which results in little change or a decrease in BMD at sites such as the hip and radius [89].

However, increased bone strength has been reported with longer-term treatment in the hip, and cortical thickness mapping has shown localized increases at sites that are subjected to mechanical loading [90–93]. The effects of abaloparatide have not been reported in full detail; however, in postmenopausal women treated for 12–18 months with abaloparatide, bone remodeling indices in cancellous iliac crest bone were generally similar to those in a placebo group, and to those treated with teriparatide [26, 94]. Table 24.1 shows the main characteristics of both teriparatide and abalopratide.

Romosozumab

Sclerostin is an osteocyte-derived inhibitor of bone formation [114]. The anabolic effects of sclerostin inhibition are mediated through an early and transient increase in bone formation

Table 24.1 The main characteristics of both teriparatide and abaloparatide agents

	Teriparatide	Abaloparatide
Structure	The first 34-amino acids of the parathyroid hormone.	34-amino acid peptide, of which the first 21-amino acids are identical with those of the parathyroid hormone–related protein.
Function	Hormone released by parathyroid gland.	Autocrine and paracrine regulator in many tissues. In the bone it is produced by cells of the osteoblast lineage.
Receptor to activate target cells	G protein-coupled receptor (GPCR), PTH1 receptor (PTH1R).	G protein-coupled receptor (GPCR), PTH1 receptor (PTH1R).
Anabolic effect	70% remodeling-dependent (mediated through PTH1R) 30% modeling-dependent (increased modelling-based bone formation upon the periosteal surface; increased remodeling as well as modeling-based bone formation upon the endocortical and trabecular surfaces).	Mainly remodeling-based rather than modeling-based (not yet fully studied, remains an open question). There are claims of an anabolic effect with relatively less bone resorptive effect of abaloparatide, based on the measurements of biomarkers [102–104].
Effects on bone cells	1. Early phase: osteocyts and osteoblast precursors: promote RANKL production which enhances osteoclast formation and bone resorption. 2. Second phase: production of local factors from osteoclasts and resorbed matrix which initiate bone formation by BMUs [95–98].	Physiological regulator of bone formation by promoting the differentiation of committed osteoblast precursors and by inhibiting apoptosis of mature osteoblasts and osteocytes [99–101].
Impact on BMU	Act on existing BMUs in different stages: Reversal phase: promote osteoblast lineage differentiation into mature osteoid producing cells. Formation phase: inhibit osteoblast apoptosis which lead to increased matrix production [84, 96].	Exact effect on BMU and bone remodeling has been fully reported. In postmenopausal women treated for 12–18 months with abaloparatide, bone remodeling indices in cancellous iliac crease bone were generally similar to those treated with teriparatide [26, 94].
Bone morphology	Early phase: the initial increased new BMU formation leads to increases in the excavated cavities numbers (mainly upon intracortical canal, endocortical, and trabecular surfaces [95, 98]. This leads to increased porosity mainly in the cortex adjacent to the medullary canal (unlikely to increase bone fragility at this location [98]). Formation phase: deposition of incompletely mineralized bone leads to increase in bone matrix per unit volume. Crosslinks: the remodeling-based bone formation replaces matrix collagen crosslink by advanced glycation end products with new and less glycosylated bone [26, 105]	There are claims of an anabolic effect with relatively less bone resorptive effect of abaloparatide, based on measurements of biomarkers [102–104].
Time of onset	The anabolic effect of teriparatide is rapid and demonstrable within 3 months.	Not reported. There were reports showing that abaloparatide have sequences susceptible to proteolysis [108]. Inactivation after subcut injection might reduce the amount of agonist presented to target cells, making abaloparatide weaker in vivo agonists of PTH1R than teriparatide [109–113]
Stopping therapy	Stopping teriparatide therapy is consistently followed by bone loss, therefore, it is recommended to administer anti-resorptive therapy at the time of stopping teriparatide therapy [106, 107].	

combined with a sustained decrease in bone resorption. In iliac crest biopsy samples obtained from postmenopausal women in the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) [115], large increases in bone formation were seen in cancellous and endocortical bone after 2 months of treatment with romosozumab (a monoclonal antibody that binds and inhibits sclerostin), although the effect was no longer evident after 12 months of treatment. The eroded surface was significantly reduced at both timepoints, and trabecular bone volume, microarchitecture, and cortical thickness were significantly improved at 12 months.

Modeling-based periosteal and endocortical bone formation thickens the cortex and increases its total cross-sectional area. Modeling-based bone formation lead to thickening of the trabeculae and might improve connections between trabeculae. Whether modeling occurs upon intracortical surfaces is not clear [6]. Thus, the anabolic effect of romosozumab shows that it produces an absolute increase in the total mineralized matrix volume which increases BMD by modifying bone structure [95–98].

As with teriparatide, anti-sclerostin therapy needs to be followed by anti-resorptive agents [6].

Does the Sequence Matter?

The availability of different osteoporosis therapy options, with two main different mechanisms of action, whether anabolic or potent raised the question which treatment modality is the best for the patient and which medication to start treatment with. Both anabolic and anti-resorptive agents (bisphosphonates, denosumab) have been shown to improve bone mineral density (BMD) and reduce the risk of fracture in patients who have not been on prior osteoporosis treatments [116–122]. One clue came from studies which revealed that effects of most osteoporosis medications differ in patients who have already been pre-treated with other potent osteoporosis medications [123–128]. Studies on patients treated with de novo parathyroid hormone therapy (PTH), namely, teriparatide, revealed that BMD responses to initial PTH followed by potent anti-resorptive therapy are substantial in both spine and hip sites as a result of the effects of both components of the treatment sequence. In contrast, several studies have indicated that hip BMD responses to PTH treatment are lower in patients who have already been pre-treated with potent anti-resorptive therapies and consistently decline transiently for the first year or even longer [129–133]. Although there are no fracture endpoint trials in these anti-resorptive pre-treated patients, the substantial differences in BMD outcome, particularly for the hip region, suggest that PTH effects against fracture could also differ in these pre-treated patients. More than 50% of PTH prescriptions are written for this group of patients, so these observations have important clinical significance [134–136].

Further insight was gained from the studies carried out using the newly approved anabolic medication romosozumab. In the trial, Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) (n = 4093), 1 year of treatment with romosozumab followed by 1 year of alendronate was compared with 2 years of treatment with alendronate in postmenopausal women at high risk of fracture [32]. The ARCH trial showed that romosozumab/alendronate as compared with alendronate/alendronate resulted in a 48% reduction in the risk of vertebral fractures at 24 months (RR, 0.52; 95% CI, 0.40–0.66), a 38% reduction in the risk of hip fractures at 24 months (hazard ratio [HR], 0.62; 95% CI, 0.42–0.92), and a 19% reduction in the risk of nonvertebral fractures at 24 months (HR, 0.81; 95% CI, 0.66–0.99).

A second clue came from the variation of response to therapy according to the site. Studies revealed that the effects of treatment sequence at the hip are more dramatic than those found for the spine. In the spine, the effects of PTH therapy after bisphosphonates and denosumab remain positive, although slightly blunted [129–133]. Furthermore, even after transition from denosumab to PTH, the resultant spine BMD level was the same 2 years after the transition as it was when the sequence began with PTH followed by denosumab [133]. The findings are very different

for the hip region. In treatment-naïve postmenopausal women, for over 19–24 months with teriparatide therapy, resulted in an average gain of about 3% in the total hip and neck of the femur [133, 134]. After teriparatide, transition to a bisphosphonate led to further increase of about 2% in both sites (total hip and femoral neck) after 1 year [137, 138]. After transition from teriparatide to sequential denosumab, BMD increments in the total hip and femoral neck FN are even higher (about 6% in both sites after 1 year of denosumab) [133].

When individuals established on potent antiresorptive therapies are switched to parathyroid hormone therapy, changes in the hip BMD are below baseline for the first 12 months, remaining unchanged from baseline at 18 months and slightly above baseline at 24 months [23, 25–27, 29, 129–131]. The findings differ somewhat after switching from bisphosphonates compared to switching from denosumab. At 18 months, hip BMD is slightly above baseline after switching from bisphosphonates but still below baseline after switching from denosumab. Furthermore, after 24 months of parathyroid hormone therapy, hip BMD is increased by 2–3% after a switch from bisphosphonates but still below baseline after a switch from denosumab [133, 139].

The impact on BMD of a 48-month treatment sequence was studied formally by Leder and colleagues [133]. This study allows direct comparison of a 4-year sequence of teriparatide for 2 years, followed by denosumab for 2 years, compared with the opposite sequence, denosumab for 2 years followed by PTH for 2 years. Over 4 years, in the group that transitioned from teriparatide therapy to denosumab, mean total hip and femoral neck BMD increased 6.6% and 8.3%, respectively. In contrast, in those who switched from denosumab to teriparatide, BMD at both the total hip and femoral neck declined precipitously for the entire first year and levels were still below the end of denosumab treatment baseline for the total hip and just above that baseline for the neck of the femur. The entire 48-month sequence when denosumab is administered first, followed by PTH, resulted in mean total hip and neck of the femur increments of 2.8% and 4.9% (approximately 50% lower hip BMD gains compared with the sequence of teriparatide followed by denosumab, all significantly different versus the former sequence). Furthermore, after transition from 24 months of denosumab to 24 months of teriparatide, progressive bone loss at the radius was also found, in contrast to a slight increase in radius BMD when teriparatide was given followed by denosumab.

Optimizing Osteoporosis Therapy: Combination and Sequential Therapies

As osteoporosis therapy options have expanded, and clinical guidelines have begun to embrace the concept of limited treatment courses and "drug holidays," the choices that physicians must make when initiating, electing to continue, or switching therapies have become more complex. Combining or sequencing treatments with anabolic and resorptive agents have been studied for some time, in an effort to achieve synergism by capitalizing on distinct modes of action of different agents. Different scenarios have been suggested for such form of management. These include the following.

Sequential Therapy

Anti-resorptives After Anabolic Agents for the Treatment of Osteoporosis

When teriparatide therapy is commenced and maintained, biomarkers (both urine as well as serum) of bone remodeling return to their pretreatment baseline measures before the end of the 24-month course while BMD continues to increase over the entire period of management. This apparent discrepancy may be clarified by histomorphometric analysis which revealed the ability of teriparatide to continue stimulating modeling-based bone formation even while remodeling rates revert to baseline [140]. However, when teriparatide therapy is stopped, BMD decreases quickly (though faster in postmenopausal women compared to eugonadal

men) [141]. However, while early study suggested that some antifracture efficacy may be maintained for up to 18 months after the drug has been stopped [142], it is likely that most of the teriparatide beneficial effects do eventually disappear.

Numerous studies have investigated strategies to maintain teriparatide-induced gains in bone mass after the drug is discontinued. Some studies even showed that the teriparatide-induced BMD gains are maintained or even further increased with sequential anti-resorptive treatment [137, 143]. In a 30-month observational follow-up study which included 1262 patients after stopping their teriparatide therapy, total hip and femoral neck BMD returned to baseline among patients receiving no further treatment, while in the 60% of women who started another anti-resorptive therapy, mainly bisphosphonates, BMD remained stable or was further increased [138].

The EUROFORS study documented the stabilizing and/or beneficial effect of a sequential anti-resorptive agent. In this study, postmenopausal women with severe osteoporosis, treated with teriparatide for 1 year, were randomized to raloxifene, no treatment, or continue taking teriparatide; raloxifene prevented bone loss, as measured by BMD, at the lumbar spine in contrast to those patients who did not receive active treatment, while inducing further increases in the total hip BMD [144]. Furthermore, the risk of new vertebral fractures was reduced by 41% among patients who started anti-resoprtives within 6 months after stopping teriparatide treatment [142].

In the DATA-Switch study, 2 years of teriparatide therapy followed by 2 years of denosumab resulted in further increases in the BMD (100). Results of the study showed that when denosumab is given for 2 years after 2 years of teriparatide, there was an additional increase in the spine BMD by 9.4% (18.3% total 4-year increase) and increased total hip BMD an additional 4.8% (6.6% total 4-year increase), gains that appear to be significantly greater than what can be achieved with bisphosphonates therapy after teriparatide [133, 145]. Moreover, denosumab was also able to further increase BMD in patients who previously received 2 years of combined teriparatide/denosumab therapy [133].

In other publications of the abaloparatide trial by Bone et al. [146], alendronate was administered after abaloparatide (given for 18 months), which maintained the fracture risk reduction relative to placebo. Unfortunately, the design of this study does not address the question of whether stopping abaloparatide produces loss of benefits as found with teriparatide, which requires an arm with abaloparatide given placebo. However, the likelihood is that stopping abaloparatide will result in loss of benefits.

The extension of FRAME study investigated the efficacy of 1-year treatment with romosozumab followed by 2 years of denosumab [33]. In specific, BMD increased further after switching romosozumab to denosumab; at the end of the 36-month period, the subjects who received romosozumab followed by denosumab achieved significantly higher BMD increases from baseline compared to the placebo-to- denosumab group (LS: 10.6; TH: 5.2%; FN: 4.8%) [33].

Additionally, although all subjects received active treatment during the last 2 years of the study, patients who received romosozumab during the first year exhibited significantly higher fracture risk reductions compared with those who received placebo (66%, 27%, and 21% for vertebral, clinical, and nonvertebral fractures, respectively). In contrast, in the extension of the ARCH study, postmenopausal women transitioning to ALN after 1 year of romosozumab maintained the BMD gains at lumbar spine, total hip, and femoral neck BMD, which were initially achieved with romosozumab without further increases [32]. However, over a total period of 24 months of treatment with romosozumab followed by alendronate resulted in a higher fracture risk reduction of 48% for vertebral fractures, 27% for clinical fractures, 19% for non-vertebral fractures, and 38% for TH fractures compared with alendronate alone [32].

Anabolics After Anti-resorptive Agents for the Treatment of Osteoporosis

Several studies reported on using anabolic agents after anti-resorptive therapy. The commonest

focused on the bisphosphonates to teriparatide sequence. On the other hand, limited data are available for the sequence of raloxifene or denosumab to teriparatide or other sequences. So far, there are not studies available, to the best of our knowledge, regarding the sequence of anti-resorptive abaloparatide therapy. The assessment of biomarkers in the bisphosphonates to teriparatide sequence revealed that both bone formation and resorption markers increase consistently after switching from anti-resorptives to teriparatide.

As far changes in the BMD, after switching from bisphosphonates to teriparatide, an increase in the lumbar spine BMD has been observed in all studies. Overall, the mean increase in BMD was in the range of 4.1–10.2% after 12–24 months on teriparatide. Interestingly, on switching from denosumab to teriparatide, there was an initial transient decrease in the lumbar spine BMD, with quick recovery and final increase observed [133]. The increase in the lumbar spine BMD has been reported to be higher after switching to teriparatide than continuing the same anti-resorptive treatment [147]. However, the increases in BMD at both the lumbar spine and total hip were observed to be lower than those achieved when teriparatide is administered in osteoporosis therapy naïve patients [148] (although similar increases have been reported in another everyday practice study including a small number of patients) [149]. Notably, when teriparatide was administered in patients with poor response to previous anti-resorptive treatment, a similar increase in BMD was observed compared to those patients who showed sufficient response to previous treatment [27]. Furthermore, higher increase in BMD was observed when teriparatide was administered following raloxifene in comparison to alendronate [150, 151]. Limited data from head-to-head comparative studies with bisphosphonates showed a superior lumbar spine BMD response to teriparatide when previously treated with etidronate over risedronate and alendronate [129], or risedronate over alendronate [135].

On the contrary, there has been initial decline in both the total hip and femoral neck BMD below baseline after switching from risedronate, alendronate, or denosumab to teriparatide which lasts for 6–12 months [129, 133, 135, 148, 150–153]. Although there is no head-to-head comparative study, this total hip BMD loss may be more prominent and prolonged with denosumab than bisphosphonates [16, 133]. Upon continuing teriparatide therapy, this decrease in the total hip and femoral neck BMD is reversed, reaching to a final increase of small magnitude at the end of most, but not all, studies [14]. In contrast, this decline in the BMD at both total hip and femoral neck was not observed after switching raloxifene to teriparatide [29, 30]: BMD at the total hip as well as femoral neck remained essentially unaffected for 6 months and then increased up to the end of the relevant studies [150, 151]. This data suggests that the more potent the anti-resorptive previously used, the lower and slower the response in the BMD at both the total hip and femoral neck to teriparatide.

On another front, considering another anabolic agent, romosozumab, the decrease in the total hip and femoral neck BMD has not been observed when alendronate was switched to romosozumab, which led to a progressive increase in BMD at both sites (total hip and femoral neck) similar to lumbar spine [153]. On the contrary, following denosumab, a second romosozumab course in a small number of patients (n = 16) led to an increase in the lumbar spine BMD (2.3%), whereas the total hip BMD was maintained. However, these patients had received an initial 2-year treatment with romosozumab before denosumab, which may have distorted the net effect of romosozumab after denosumab [14].

Considering the distal forearm, limited data revealed a decrease in radius BMD after switching from denosumab or other anti-resorptives to teriparatide [133, 147]. Contrary to the total hip and femoral neck BMD, radius BMD does not seem to recover after 24 months of teriparatide therapy following denosumab [133].

Regarding the effect of teriparatide on bone quality after switching from anti-resorptives to anabolic therapy, earlier studies revealed that teriparatide therapy increased both cortical turnover and cortical bone formation similarly in patients previously treated with alendronate and treatment naïve individuals, although the former

initially have lower bone turnover than the latter cohort [154, 155]. Teriparatide was reported to reduce the accumulation of microdamage in the iliac crest of patients previously treated with alendronate [156]. Previous bisphosphonate administration may have null or minimal impact on the favorable effects of teriparatide on bone mineral and organic matrix properties, including initial mineralization, mineral maturity/crystallinity, and collagen maturity [157, 158]. Limited data showed a potential superiority of teriparatide on the bone biomechanical properties when switching from risedronate over alendronate [159], or raloxifene over alendronate [130]; however, there are insufficient comparative data for valid conclusions. Importantly, in the unique to-date, head-to-head comparative study, the estimated hip strength was increased when alendronate was switched to romosozumab, whereas decreased at six months when switched to teriparatide, findings which are largely in line with BMD results [153].

Regarding fracture efficacy, there is no anti-resorptive to osteoanabolic study with fractures as primary endpoint. Unfortunately, small sample sizes and numbers of fractures in the abovementioned studies do not allow the drawing of secure conclusions. Although it can be assumed that the increase in the lumbar spine BMD may imply higher anti-fracture efficacy, it remains unknown whether the initial decline in the total hip/femoral neck BMD may increase fracture risk when bisphosphonates or denosumab treatment switches to teriparatide [160]. Although switching to teriparatide is a common practice in patients who did not respond to anti-resorptives or those having completed the maximum duration of anti-resorptive therapy, this is probably not the optimal sequence, at least in high-risk patients, as it could lead to transient loss of the total hip/femoral neck BMD and strength. In this regard, starting treatment with bisphosphonate or denosumab rather than anabolic agent should be carefully considered, especially in high-risk patients. A more secure sequence would more likely be teriparatide following raloxifene, as it does not seem to negatively impact on the total hip/femoral neck BMD in contrast to bisphosphonates or denosumab. Alternatively, romosozumab, where available, instead of teriparatide may be used after anti-resorptives; however, more comparative data are still needed [14, 160].

Anti-resorptives Sequential to Anti-resorptives for the Treatment of Osteoporosis (Anastasia)

Transitioning from one anti-resorptive to another is probably the most common treatment sequence in standard clinical practice. However, a logic query can be raised: Is it meaningful to switch to another, alleged to be more potent, anti-resorptive? It is possible that ensuring better compliance such as that expected with parenteral osteoporosis therapy, e.g., with zoledronate infusion or denosumab injection, along with possibly higher efficacy could improve bone status in patients having a high fracture risk, despite treatment with oral anti-resorptives.

In patients who received alendronate therapy for a mean of 4 years, a single zoledronate infusion maintained their lumbar BMD for the next 12 months. Assessing the bone turnover biomarkers, they decreased during the first 3-months, while returned to baseline levels at 6 months and increased thereafter [161]. One study revealed that zoledronate infusion therapy was preferred by the majority of patients over alendronate [161]. Similarly, in the DAPS study, patients expressed preference for denosumab over weekly alendronate and showed better compliance/persistence to treatment with denosumab compared to alendronate [126]. Furthermore, in postmenopausal women previously treated with oral bisphosphonates, denosumab significantly increased BMD at all skeletal sites [162] and was more efficacious in terms of BMD accrual and bone turnover markers suppression compared to all available bisphosphonates [125, 127, 128, 163]. However, it is worth noting that, in patients previously treated with bisphosphonates, the BMD increases attained with denosumab were more modest compared to treatment-naïve patients treated with denosumab; however, they were still significant [127, 128, 164]. On the other hand, denosumab administration resulted in similarly suppressed bone turnover markers,

despite the lower baseline levels in patients pretreated with bisphosphonates compared to treatment-naïve patients [164, 165]. Up to date, there are no anti-fracture efficacy data in patients transitioning from bisphosphonates to denosumab or generally from one anti-resorptive to another.

Finally, transition to an anti-resorptive, particularly a potent oral or intravenous BP, is mandatory to maintain BMD gains and avoid the rebound increase in fracture risk in patients discontinuing denosumab [166, 167]. Alendronate administered for 1 year following 1 year of denosumab treatment-maintained BMD at the lumbar spine as well as both the total hip and femoral neck [126, 168]. On the contrary, several case series of limited power suggested that both zoledronate and risedronate resulted in retaining of only part of the BMD gains achieved with denosumab [169–171]. In the DATA follow-up study, BMD increases achieved after 2–4 years of denosumab therapy were maintained only in patients that continued denosumab or were promptly switched to bisphosphonates [172]. In the only randomized controlled trial (RCT) published on the topic up to date, a single zoledronate infusion given 6 months after the last denosumab injection prevented bone loss for the following 2 years [173].

Combination Therapy

Combination therapies have been investigated for efficacy and safety in severe osteoporosis conditions. Combination therapy refers to coadministration of an osteoanabolic agent (most studies referring to teriparatide) with a variety of anti-resorptive agents, or HRT with other anti-resorptives [174]. Most studies evaluated differences between combination and monotherapy in terms of areal BMD. Few studies evaluated the volumetric BMD using quantitative computed tomography (QCT). However, none of the studies has evaluated or been designed or adequately powered to assess differences in fracture incidence between the combination therapy and monotherapy [175]. Therefore, combining anti-resorptive and anabolic therapy can be considered as a missed opportunity for two reasons [176]. First, no studies have been done demonstrating greater antifracture efficacy than achieved by either treatment alone. This is a valid reason for a cautionary approach to the uptake of this regimen. The second reason is the widely held belief that anti-resorptive therapy, "blunts," (suppresses) remodeling-based bone formation by teriparatide therapy. The notion of blunting was based on the assumption that a higher BMD or higher P1NP mean more bone formation and a lack of response means less bone formation [177–179].

Combination Therapies with Anabolics and Anti-resorptive Agents

Several combinations of anabolics and anti-resorptive agents have been evaluated over the past years. The combination of teriparatide and raloxifene has been assessed in both previously treated osteoporotic and drug-naïve postmenopausal women. In patients previously treated with raloxifene for at least 1 year, the addition of teriparatide has induced greater increases in both the lumbar spine and total hip BMD compared to raloxifene monotherapy [180]. In this study, however, superiority of the combination therapy versus teriparatide monotherapy could not be demonstrated since a treatment arm with teriparatide alone was not included. In subsequent studies, the combination of teriparatide/raloxifene was directly compared to teriparatide monotherapy in both drug-naïve and previously treated patients. In osteoporotic women previously treated with raloxifene, 18 months of teriparatide/raloxifene combination did not achieve greater BMD increases compared to teriparatide monotherapy at any skeletal site measured [131, 181]. In contrast, the addition of raloxifene in postmenopausal women already on teriparatide for 9 months resulted in greater increases in lumbar spine BMD with no difference in total hip BMD compared to teriparatide monotherapy [61, 182]. The above findings imply that the net effect of teriparatide/raloxifene combination on BMD may be affected by the nature of the previous anti-resorptive or anabolic therapy. On the other hand, in a 6-month trial in drug-naïve patients,

teriparatide/raloxifene achieved greater increase in total hip BMD, but not lumbar spine BMD or femoral neck BMD compared to teriparatide monotherapy [183].

The combination of teriparatide with a bisphosphonate has demonstrated inconsistent results. The outcomes were attributed to the type of bisphosphonate used, the route of administration (oral alendronate/ibandronate or parenteral zoledronate), and the history of previous treatment. Three studies have evaluated the teriparatide/bisphosphonate combination in drug-naïve osteoporotic women, two with alendronate, and one with zoledronate. In previously treatment-naïve women, coadministration of teriparatide/alendronate following a 6-month alendronate monotherapy achieved smaller BMD gains at both the lumbar spine and total hip compared to teriparatide monotherapy [184]. In contrast, another study reported the superiority of the teriparatide/alendronate combination in total hip and femoral neck BMD compared to teriparatide monotherapy; however, in the latter study, the dose of teriparatide was 40 μg/day, which is double the approved dose.

The combination of teriparatide and zoledronate was compared with both teriparatide and zoledronate monotherapy for the treatment of naïve postmenopausal osteoporosis women [185]. At 12 months of treatment, the combination achieved greater increases in both the total hip and femoral neck BMD compared to teriparatide monotherapy, with no difference in lumbar spine BMD, implying an additive effect of the teriparatide/zoledronate combination in the hip region compared with teriparatide monotherapy at least in the early treatment period. It has been noted that the combination of teriparatide/zoledronate was not superior than zoledronate monotherapy in hip BMD. Clinical fractures were less in the combination group compared to both zoledronate and teriparatide monotherapy but reached statistical significance only compared with zoldredonate monotherapy [185].

In long-term alendronate-treated postmenopausal women, the addition of teriparatide therapy resulted in greater increases in lumbar spine and total hip BMD compared to alendronate monotherapy [65, 186] and teriparatide monotherapy [131]. In addition, hip BMD did not decline in the teriparatide/alendronate combination group, in contrast to what has been reported in studies with parathyroid hormone or teriparatide monotherapy after the withdrawal of antiresorptives [181].

Similar results were obtained when alendronate was added in postmenopausal women previously treated with teriparatide for 9 months. Both areal and volumetric lumbar spine and total hip BMD increases were greater with the teriparatide/alendronate combination compared to teriparatide monotherapy [182].

The combination of ibandronate with parathyroid hormone 1–84 was also studied in 44 postmenopausal women diagnosed to have osteoporosis. The patients were randomized to receive 3 months of parathyroid hormone 1–84 followed by 9 months of oral ibandronate 150 mg/month (repeated in two cycles) or 6 months of combined parathyroid hormone/ibandronate followed by 18 months of ibandronate alone [187]. Increases in both areal and volumetric BMD were similar between treatment groups at all skeletal sites measured. Risedronate has been evaluated as a combination treatment with TPTD in male osteoporosis [188]. This was a randomized, double-blinded study of risedronate (35 mg weekly plus placebo injection), teriparatide (20 μg subcutaneously daily plus placebo tablet), or both risedronate plus teriparatide (combination) for 18 months in 29 men with low BMD. The primary endpoint was percentage change in lumbar spine BMD at 18 months. Secondary outcomes included changes in bone markers and BMD at other sites and interim time-points. All therapies increased lumbar spine BMD as compared with baseline ($p < 0.05$), but there were no between-group differences at 18 months. Total hip BMD increased to a greater extent in the combination group (mean ± SEM, 3.86 ± 1.1%) versus teriparatide (0.29 ± 0.95%) or risedronate (0.82 ± 0.95%; $p < 0.05$ for both). Femoral neck BMD also increased more in the combination group (8.45 ± 1.8%) versus risedronate (0.50 ± 1.7%; $p = 0.002$) but was not different from teriparatide alone. In the combination

group, P1NP and CTX increased rapidly, mirroring the teriparatide-alone arm. There were no between-group differences in adverse events. The combination of teriparatide and risedronate increased BMD at the lumbar, total hips, and the femoral neck and provided greater BMD increases at the total hip than monotherapy. The results suggest the combination of risedronate and teriparatide therapy holds promise as a treatment for osteoporosis [188].

Among all combination treatments published so far, the studies of teriparatide and denosumab co-administration demonstrated the best and most promising results. In the DATA trial, which included a cohort of largely treatment-naïve postmenopausal women, the teriparatide/ denosumab combination treatment induced greater increases in all the three sites: lumbar spine, total hip, and femoral neck as well as radius BMD compared to either agent alone after 12 [189] and 24 months of therapy [190]. BMD changes with the teriparatide/denosumab combination in this study were similar to those seen with the teriparatide/zoledronate combination in the first 6 months [185], although the magnitude does not refer to direct comparison. However, in contrast to the terparatide/zoledronate combination, BMD levels continued to increase with the teriparatide/ denosumab combination after the first 6 months, when the waning effect of zoledronate on bone resorption is seen. In the DATA-HD trial, the combination of denosumab with higher teriparatide dose (40 μg) increased lumbar spine as well as total hip BMD more than the standard teriparatide 20 μg/denosumab combination therapy [191, 192], further supporting the rationale of using this combination in severe osteoporosis.

Regarding the other two currently commercially available osteoanabolic agents, abaloparatide and romosozumab, there are no studies published so far on the coadministration of either drug with an anti-resorptive agent.

Combination Treatment with Hormone Replacement Therapy

Hormone replacement therapy (HRT) has been tested as a combination treatment with oral bisphosphonates, such as alendronate, risedronate, and cyclic etidronate, as well as with calcitonin and parathyroid hormone analogues.

Earlier studies published assessing the combination of HRT with another anti-resorptive agent revealed significantly greater increases in both lumbar spine and total hip BMD compared to monotherapy with either HRT or the anti-resorptive medication [193–198]. This beneficial effect was sustained up to 4 years in the combination with bisphosphonates [194], but only up to the first year of therapy with calcitonin [197].

Various parathyroid hormone analogues have also demonstrated beneficial effects in BMD gains when added to HRT in postmenopausal women with osteoporosis [199–201]. Limitations of these studies include the lack of a teriparatide monotherapy arm and of fracture risk assessment. It should also be highlighted that all studies preceded the publication of the teriparatide Fracture Prevention Trial [120] and the approval of teriparatide 20 μg/day for the treatment of osteoporosis used teriparatide doses higher than the currently approved teriparatide doses. In these studies, the teriparatide/HRT combination increased BMD more than HRT alone, but these increases were comparable to teriparatide monotherapy.

Challenges with the Outcomes of Sequential and Combined Osteoporosis Therapy

Most of the comparator studies use changes in BMD and bone remodeling markers as the outcome variable. By themselves, they can be considered problematic endpoints. Remodeling-based anabolic therapy increases bone matrix volume by replacing more fully mineralized bone with young less fully mineralized bone. Modeling-based anabolic therapy adds young less fully mineralized bone to existing older bone. Imaging using radiation transmission often results in a net reduction in BMD because young less mineralized bone transmits rather than attenuates photons, leading to the inference that bone "loss" and fragility have occurred. Anti-resorptives slow remodeling. Matrix no longer

"turned over" undergoes more complete mineralization increasing BMD leading to the inference that bone "volume" or "mass" has increased, and that bone strength has increased even though the matrix becomes less ductile. These challenges were discussed in the article written by Ramchand and Seeman [202].

As an example, even if an increase or lack of an increase in BMD is accepted on face value, the results of Black et al. study [176] do not support the notion of blunting. Relative to parathyroid hormone therapy alone, combined therapy (1) did not produce a smaller increment in spine or femoral neck BMD, (2) did produce a greater increase in total hip BMD, (3) did reduce the decline in distal radius BMD, and (4) did prevent the reduction in total hip and femoral neck vBMD produced by parathyroid hormone alone. Curiously, the increase in total hip and femoral neck cortical volume by PTH, a modeling effect, was prevented by combined therapy. Moreover, combined therapy increased trabecular vBMD less than parathyroid hormone alone but this may be a benefit, not blunting. The anti-resorptive might prevent a PTH-mediated increase in intracortical remodeling, cortical porosity, and the increase in cortical fragments that look like "trabeculae" [203]. Blunting of the rise in P1NP and CTX is likely to be the result of suppressed remodeling, not a reduction in the net volumes of bone deposited or resorbed, respectively [204]. If blunting of the BMD response was due to fewer BMUs, then blunting should be more severe with the coadministration of PTH with zolendronate, denosumab, or osteoprotegerin (OPG, an endogenous inhibitor of RANKL) than with alendronate. The opposite is reported, and many studies report additive effects [205, 206].

The difficulties in using BMD are also present using high-resolution peripheral computed tomography. Tsai et al. [207] report that combined PTH 1–34 and denosumab increased cortical vBMD, yet PTH 1–34 reduced it and denosumab had no effect. Combined therapy increased cortical matrix mineral density, yet PTH 1–34 decreased it and denosumab had no effect. Combined therapy had no effect on porosity, yet PTH 1–34 increased it while denosumab had no effect. These findings do not add up, probably because there are methodological challenges in segmenting (separating) the cortical and trabecular compartments and quantifying porosity and trabecular density because low image resolution and changes in matrix mineral density influence the quantification of microstructure [208–210].

The Way Forward

In the long-term management of osteoporosis, transitioning from one treatment agent to another is quite common in standard practice and in several cases is probably a necessity. Setting the optimal long-term management plan tailored to the individual patient's needs, preferences as well as comorbidities are vital to ensure best compliance and adherence to therapy yet is a challenge to the treating physician.

A major challenge in standard practice is the protocol of patients' management adopted. The standard protocols recommend starting with the generic bisphosphonates and keep the anabolics until the last step of management; consequently, anabolic agents are restricted for patients with severe osteoporosis. On the other hand, the treat–to-target approach recommend setting up the treatment protocol subject to the patient's BMD measurement and risk of fracture. Another challenge is the duration of therapy. While osteoanabolics increases BMD and reduces fracture risk, they are administered for a maximum of 12 months (romosozumab) and up to 24 months (teriparatide, abaloparatide). Third challenge is the cost, as generic anti-resorptives are cost-effective, while osteoanabolics are of high cost. Fourthly, loss of BMD gains has been reported after some anti-resorptives (e.g., denosumab) as well as most of the anabolics known so far. Therefore, sequential treatment with an anti-resorptive agent is strongly recommended for these patients. Lastly, osteoporosis therapeutic

agents vary in their effect on the bones. Among anti-resorptives, denosumab has the best performance, at least in terms of BMD accrual. Similarly, all osteoanabolics induce a state of positive remodeling balance.

Transitioning from an anti-resorptive to an osteoanabolic agent is less effective than the opposite, as the BMD increase is more modest and delayed, probably because the chronically suppressed bone turnover needs more time to be enhanced than in treatment-naïve individuals receiving an osteoanabolic as the initial therapeutic approach. Changes in remodeling activity, leading to changes in cortical porosity, may also be responsible for part of the BMD changes observed in this setting. It seems that the more potent the anti-resorptive previously used, the lower and slower the responses of bone turnover markers and BMD to the osteoanabolic agent. The sequences that have been studied are mainly bisphosphonates and raloxifene followed by teriparatide and romosozumab. The anti-resorptive osteoanabolic treatment sequence could be considered in patients with severe disease who do not improve or exhibit treatment failure under an anti-resorptive agent, e.g., fractures while on treatment and/or significant bone loss despite several years of treatment administration.

Transitioning from an anti-resorptive to another anti-resorptive given at larger intervals is the more likely scenario in the standard practice. Anti-resorptives given intravenously or subcutaneously could also improve patients' compliance. Transitioning from a bisphosphonate to another bisphosphonate is expected to maintain BMD values whereas transitioning from a bisphosphonate to denosumab may probably induce a further increase of the BMD values. Zoledronate or alendronate are recommended to follow denosumab treatment to maintain most of the BMD gains achieved and prevent the increase of fracture risk, especially that of multiple vertebral fractures. The sequential use of an osteoanabolic after another osteoanabolic agent has not been investigated up to date. Concerns regarding safety issues exist. Furthermore, cumulative use is not recommended to exceed 2 years during a patient's lifetime, at least for teriparatide and abaloparatide [14, 211].

Combinations of parathyroid hormone analogues, mainly teriparatide, with various anti-resorptives have been tested in patients with severe osteoporosis. Among them, only the combination of teriparatide with denosumab has shown clear, long-term advantage over teriparatide monotherapy, especially in the hip, while the combination of teriparatide with zoledronate has a similar effect but of a potentially shorter term. The other two currently available osteoanabolic agents, namely, abaloparatide and romosozumab, have not been tested in combination with an anti-resorptive up to date. Notably, the majority of healthcare systems do not regularly fund or endorse osteoporosis combination therapy; this has been attributed to the considerable higher cost and the lack of fracture data supporting its superiority against monotherapy. However, in most healthcare systems and in cases of a well-documented severe disease, the off-label coadministration could be applied [14].

In conclusion, the increase in BMD produced by anti-resorptive agents is mostly the result of remodeling suppression, which enables more complete secondary mineralization of the slowly diminishing bone volume (in the case of bisphosphonate) or stable bone volume (in the case of denosumab, which effectively abolishes remodeling). The differences in morphological changes in structure, composition, and its impact on bone strength raised the question of the validity and significance of comparing the increase in BMD produced by anabolic versus anti-resorptive therapies, also calling into question the value of adopting new policies of management such as sequential or combined therapy. In the long-term osteoporosis management, transitioning from one treatment agent to another is quite common in standard practice and in many cases is a necessity. Given that in all the published studies investigating sequential or combination treatment fracture data are scarce, outcomes are based

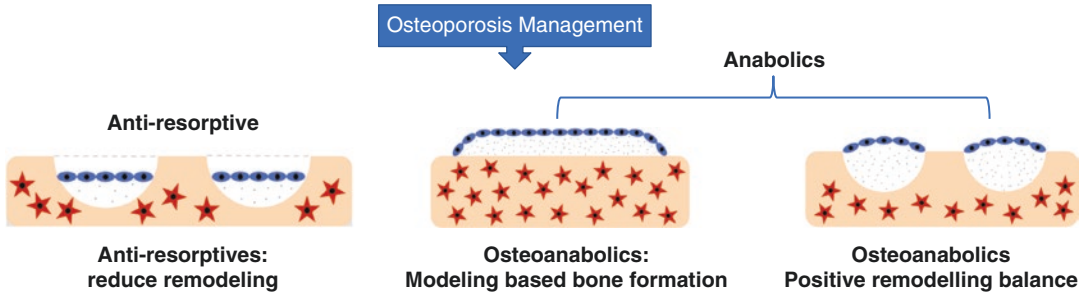

Fig. 24.3 Osteoporosis management: Effects of anti-resorptive and osteoanabolic medications on the bone remodeling and modeling process. During young adulthood, bone remodeling is balanced – an equal volume of bone is resorbed and subsequently replaced so no net loss or gain occurs. Age-related bone loss is associated with an increase in remodeling and a negative remodeling balance in individual bone remodeling units. Anti-resorptive agents act predominantly by reducing the remodeling rate. Anabolic agents produce their effects by increasing bone modeling as well as remodeling, leading to a positive remodeling balance

mostly on BMD, as a surrogate marker of bone strength, and as an endpoint to draw conclusions regarding the efficacy of each sequential or combination modality (Fig. 24.3).

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Part VI

Disparities in Bone Health

Osteoporosis in Men

25

Yasser El Miedany

Introduction

Osteoporosis is defined as an asymptomatic bone disease characterized by low bone mineral density (BMD) and deterioration of microarchitecture of the skeleton, leading to an increased fracture risk [1]. Osteoporosis-related fractures are classically recognized as a significant women's health issue but are now increasingly viewed as an important health care problem in men as well [2]. Although fewer men sustain osteoporotic fractures than women during aging, osteoporosis-related mortality and morbidity rates are higher in men [3].

Studies carried out over the past 2 decades on male osteoporosis have increased the awareness of the problem and have improved our understanding of the pathogenesis of osteoporosis and fragility fractures in men. However, in contrast to the wealth of data and published guidelines about the management and efficacy of different pharmacological agents in the management of postmenopausal osteoporosis, treatment recommendations and information regarding the efficacy of different osteoporotic therapies in men is relatively limited. Furthermore, most of the randomized controlled trials (RCTs) undertaken in men did not present enough statistical power to address drug effects on fracture risk (particularly non-vertebral fractures), mainly due to the small samples of the populations included. Actually, in most RCTs, the primary endpoints were the change in the BMD and markers of bone turnover. Nevertheless, the effects of bisphosphonates, denosumab, and teriparatide, on surrogate outcomes, such as BMD and markers of bone turnover, were similar to those reported in pivotal RCTs undertaken in postmenopausal women, for which vertebral and non-vertebral anti-fracture efficacy has been clearly demonstrated, suggesting that these agents should be effective in men as well as in women [4–8].

The key challenge facing healthcare professionals and policymakers is to ensure that men who are clearly at high risk of suffering fragility fractures get the care they need. First and foremost, this includes men who have already suffered a fragility fracture. A broken bone is a very clear signal of elevated future fracture risk; nevertheless osteoporosis assessment and treatment rates among these men are very low, being mostly under 20%. The second most important cohort are men with prostate cancer treated with androgen depletion therapy as well as those on steroid therapy. This chapter will discuss bone changes across the men's life span, epidemiology and pathophysiology of osteoporosis in men, male osteoporosis in the elderly, and differences between men and women. The chapter will then discuss the journey toward making of the diagno-

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sis of osteoporosis in men, case finding, and the best approach toward management of the disease.

Bone Changes Across the Men's Life Span

Bone is a living organ that keeps on changing; that is, old bone is removed and replaced by new healthy bone. During childhood, more bone is produced than removed; therefore, the skeleton grows in both size and strength. For most people, bone mass peaks during the third decade of life. By this age, standard men have typically accumulated more bone mass than women. After this point, the amount of bone in the skeleton plateau then begins to decline slowly as removal of old bone exceeds formation of new bone.

Unlike women, men do not have a menopause. As such, they do not present with a midlife loss of sex steroid production and, hence, do not experience accelerated bone loss and fracture risk increase, unless they develop hypogonadism or are prescribed androgen deprivation therapy for prostate cancer [2, 4]. Therefore, in their fifties, in comparison to women, men do not experience the rapid loss of bone mass that women sustain in the years following menopause. Yet, bone loss proceeds slowly, starting at the middle age (Fig. 25.1).

By the age of 65 or 70, both men and women lose bone mass at the same rate, and the absorption of calcium, an essential nutrient for bone health throughout life, decreases in both sexes. Consequently, excessive bone loss causes bone to become fragile and more likely to fracture. Fractures resulting from osteoporosis most commonly occur in the hip, spine, and wrist and can be permanently disabling. Hip fractures are especially of concern for its high rates of mortality and morbidity. Perhaps because such fractures tend to occur at older ages in men than in women, men who sustain hip fractures are more likely, than women, to die from complications.

According to World Population Prospects 2019 (United Nations, 2019), by 2050, 1 in 6 people in the world will be over the age of 65, up from 1 in 11 in 2019 [9]. Bearing in mind the current limited service provided for male osteoporosis, the demographic tsunami of aging of the world's male population represents a challenge on its own. Furthermore, as osteoporosis does not discriminate between the sexes, osteoporotic fractures affecting one in five men versus one in three women aged over 50 years; its impact will be felt in the coming decades in the majority of the world's regions. Therefore, the elimination of the osteoporosis evidence treatment gap for men is a vital component of the approach toward tackling this unprecedented threat to the sustainability of our healthcare systems.

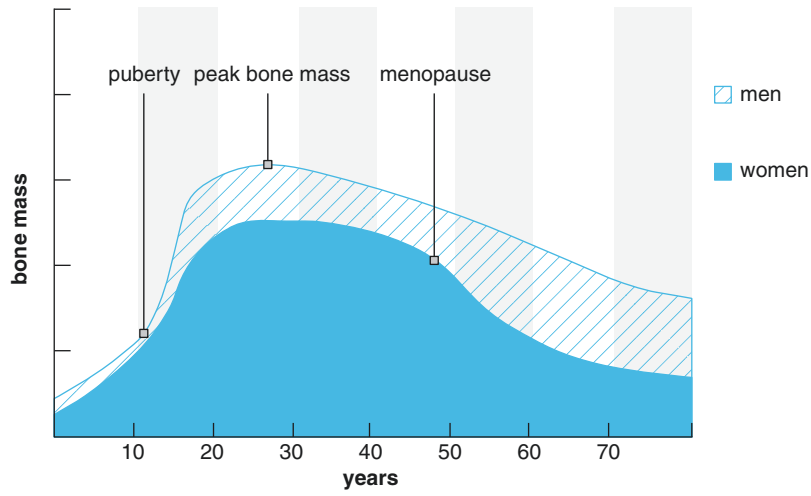

Fig. 25.1 Bone mass throughout the life cycle. (Quoted from: Osteoporosis in men: why change needs to happen. https://www.iofbonehealth.org/data-publications/reports/osteoporosis-men-why-change-needs-happen under open access scheme)

Epidemiology of Osteoporosis in Men

Early in adult life there are more fractures in men than women, but the great majority of these fractures are traumatic in origin and not related to osteoporosis, although there is some evidence [10] that even traumatic fracture history may be a risk for later osteoporotic (low trauma) fracture. With aging, the incidence of osteoporotic fracture increases in both men and women, with men having hip fractures about 10 years later in life than women [11]. Worldwide, it has been estimated that 39% of annual osteoporotic fractures occur in men [12–14]. Stratifying men according to their age, data revealed that at the age of 60-year-old, for an average man, there is a chance of approximately 25% possibility of having an osteoporotic fracture during his lifetime [15]; by the age of 85 years, over 30 percent of men will have a femoral neck T-score at or below −2.5 [16]; and by the age of 90 years, one of every six men will have a hip fracture. The prevalence of vertebral or hip fracture in older men is approximately one-third that in women (5–6% versus 16–18%), and Colles' fracture one-sixth as common (2.5 versus 16%) [17, 18].

As the population of men aged over 60 years who are potentially at risk of suffering fragility fractures will continue to grow in Europe, Northern America, and Oceania, while in Asia and Latin America the rate of growth of the male population aged 60 years or over will be exponential, it is expected that men will be living long enough to fracture (Fig. 25.2). Audits from several countries have shown that a significant proportion of men who suffer hip fractures have broken other bones before they broke their hip [20–23]. Furthermore, a study from Sweden, which followed a cohort of older men for 22 years, reported that 27% of men who had suffered a hip fracture sustained subsequent fractures in their remaining lifetime [24]. When men suffer fractures caused by osteoporosis – like women – too many become trapped in the fragility fracture cycle [25].

In terms of mortality related to fragility fractures, men fare particularly badly and are the "weaker sex." Epidemiological studies also revealed that the mortality rate associated with hip fractures [11–13, 18], as well as vertebral and other major fractures [19], is higher in men than in women. In addition, men are even less likely than women to be evaluated or receive antiresorptive therapy after a hip fracture (4.5 versus 49.5%, respectively) [12, 20]. A national registry study [26] from Denmark published in 2010 echoed the findings of previous studies [27–30]: Hip fractures in men are associated with greater mortality compared with women, with rates as high as 37% in the first year following fracture. In addition, mortality is increased after most fragility fractures in men, not only following hip fractures [31].

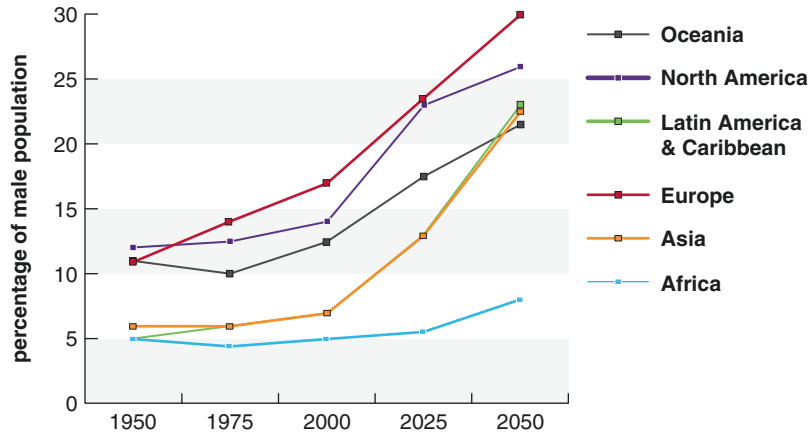

Fig. 25.2 Proportion of men aged ≥60 years by the world region 1950–2050. (Quoted from: Osteoporosis in men: why change needs to happen. https://www.iofbonehealth.org/data-publications/reports/osteoporosis-men-why-change-needs-happen under open access scheme)

Pathophysiology

Evidence Gathered from Attaining Peak Bone Mass There are three main scenarios that may contribute to developing osteoporosis. These include: (1) decreased bone mass which may occur on the background of an already low peak bone, (2) excessive bone resorption after achieving the peak bone mass, or (3) decreased bone formation during the remodeling process. However, in individual patients, all the three processes are likely to contribute, in varying degrees, to developing osteoporosis.

In men, the process of attaining peak bone mass starts during puberty when bone mineral density (BMD) increases markedly in response to increasing sex steroid production [32, 33]. Much of this apparent increase, particularly for cortical bone, is due to an increase in bone size. Peak spinal bone density is reached at approximately 20 years [34–36], while the peak density of the radius and femoral shaft is reached somewhat later [35–37] (Fig. 25.3).

The vital role played by the production of normal sex steroid hormones in the acquisition of peak bone mass is confirmed by the findings of low bone mass in young men with idiopathic hypogonadotropic hypogonadism (IHH) [38, 39]. Because idiopathic hypogonadotropic hypogonadism (IHH) is almost always a congenital abnormality due to gonadotropin-releasing hor-

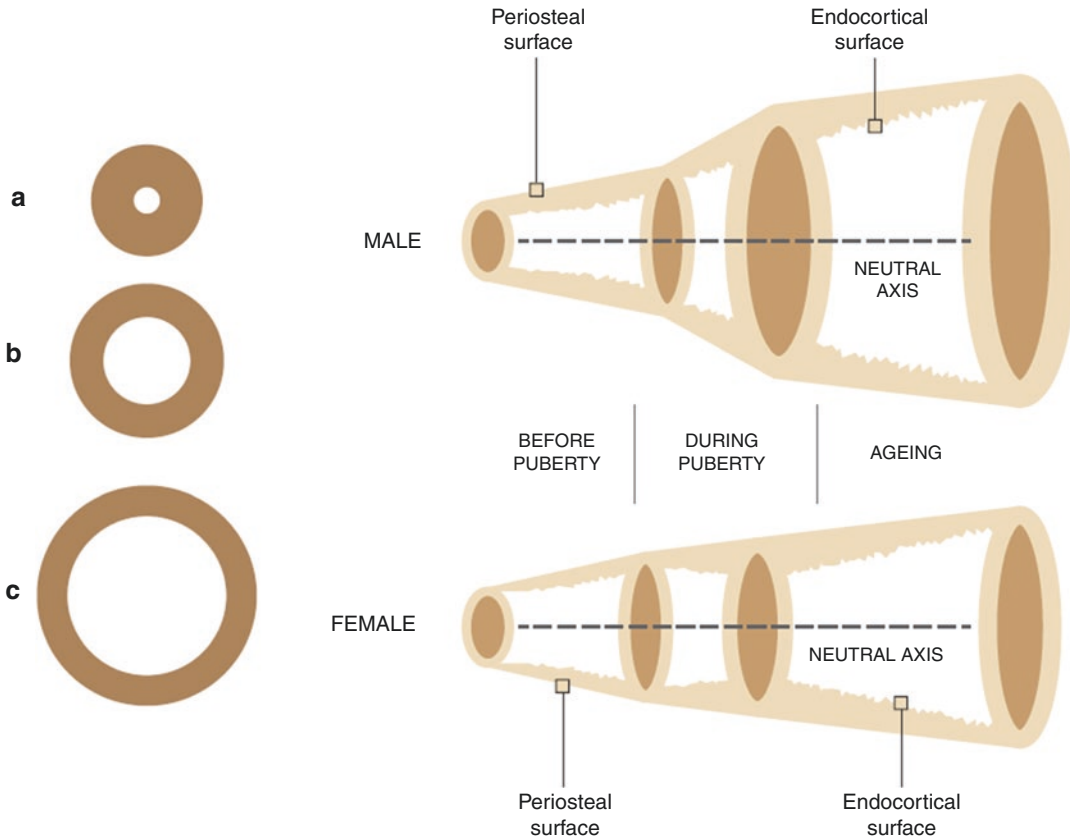

Fig. 25.3 The influence of bone geometry on bone strength. (Quoted from [IOF] under open access scheme: Osteoporosis in men: why change needs to happen. https://www.iofbonehealth.org/data-publications/reports/osteoporosis-men-why-change-needs-happen.) Left: For the same areal BMD, bone C has progressively greater bending strength and axial strength than bone B and bone A because the mass of bone C is distributed further away from the centre. Right: Sex and ageing differences in periosteal apposition and endocortical resorption in tubular bones

mone (GnRH) deficiency, this disorder provides a valuable model to assess the effects of hypogonadism on pubertal bone development (i.e., the attainment of peak bone mass). Both cortical and trabecular bone densities are markedly decreased in these men [39]. Low bone mass can be detected even before the attainment of skeletal maturity, suggesting that idiopathic hypogonadotropic hypogonadism (IHH) causes inadequate pubertal bone accretion rather than post-maturity bone loss.

Although the observation that peak BMD is reduced in men with congenital hypogonadism supports the important role of gonadal steroids in bone development, queries are still raised as these findings do not indicate whether androgens, estrogens, or both are primarily responsible for the increase in BMD and the attainment of peak bone mass during the puberty period. Reports that BMD is markedly reduced in men with null mutations in the estrogen receptor-alpha (which means that responsiveness to estrogen is essentially absent), or in men with null mutation in the aromatase gene (which indicates that the synthesis of estradiol is virtually absent), strongly suggest that estrogens play a vital role and provide the primary hormonal stimulus to the attainment of peak bone mass in men [39, 40].

Another important determinant of peak bone density is the timing of puberty. In adult men with the history of constitutionally delayed puberty, BMD of the radius, lumbar spine, and proximal femur is significantly lower than in age-matched normal men, and it does not appear to improve with time [40, 41]. Similar findings have been reported in adolescent boys with delayed puberty. These observations suggest that there is a critical time period during which the skeleton is responsive to sex steroids. Other factors that determine peak bone mass are genetic predisposition, chronic illnesses, and medications that negatively impact bone density accrual [42].

Age-Related Bone Loss After the peak bone mass is attained in men, there is a loss of approximately 30% of the trabecular bone and 20% of the cortical bone during their lifetimes. While trabecular bone loss appears to start in young adult life, cortical bone loss is either less pronounced or begins later in life [43]. In some studies, the decline in femoral neck density began shortly after the attainment of peak bone mass [44, 45], and the rate of femoral neck bone loss increases with aging [45, 46]. One study reported that bone mineral content of the proximal and distal radius declined at a rate of approximately 1% per year after the age of 30 years, whereas another study found that cortical BMD remained stable until later in life [43, 47].

As far as spinal BMD, patterns of change vary depending upon the measurement technique. When measured by quantitative computed tomography (QCT), which assesses only vertebral body trabecular BMD, spine BMD declines more rapidly than hip or radius BMD [47, 48]. The assessment of the BMD using DXA scan, mid-lateral lumbar spine view, there is an annual percentage change of −1.4% (i.e., loss) in the BMD [49]. When spine BMD is measured by dual-energy x-ray absorptiometry (DXA) in the posterior-anterior projection, it often appears to increase in older men [46, 49, 50], likely due to degenerative changes in the posterior spinous elements. Therefore, posterior-anterior DXA should be interpreted cautiously when assessing the bone density of the spine in older men [49].

The Role of Hormones In spite of the crucial role played by gonadal steroids in the attainment of peak bone mass, it is less clear whether they play a significant role in the age-related bone loss process. In contrast to women, where the age-related gonadal steroid decline rate is abrupt, it is less sharp and rather delicate in men. The impact of these more subtle declines on the male skeleton remains not fully unclear. However, gonadal levels at the extremes of deficiency have been associated with low BMD and bone loss in older men. Numerous epidemiologic studies have reported associations between gonadal steroids and BMD or fractures [51–55]. These associations are weak, however, as might be expected when studying different populations and relating a single hormone measurement to complex endpoints like bone density and fracture.

Testosterone Some studies have reported significant associations between testosterone, free testosterone, and/or bioavailable testosterone and BMD, and rates of bone loss, as well as prevalent fragility fractures [51–53]. In the Osteoporotic Fractures in Men Study (MrOS) research [51], a cross-sectional and longitudinal study of 2447 men over age 65 years, the prevalence of osteoporosis in the hip or rapid hip bone loss was threefold higher in men whose total testosterone levels were <200 ng/dL (6.9 nmol/L) compared with >200 ng/dL.

Estrogen Interestingly, in men, associations of bone density with estrogens have been slightly stronger than associations with androgens [54]. In the MrOS study, the prevalence of osteoporosis in the hip (T-score < −2.5) increased progressively as total or bioavailable estradiol levels fell [51]. In addition, low serum estradiol levels have been associated with an increased risk of future hip fracture in men [41, 55]. Fracture risk appears to be even greater in men with low serum estradiol and testosterone concentrations [54, 55].

Estrogen Versus Testosterone Several studies have evaluated the relative contributions of sex steroids in the regulation of bone resorption and formation (as measured by urinary and serum markers and BMD) in adult men [56–58]. The outcomes of these studies revealed that estrogen appears to have the dominant effect on bone resorption and formation. In one physiologic study of induced hypogonadism, 198 healthy men (ages 20–50 years old) were treated with a GnRH agonist (to temporarily suppress endogenous sex steroid production) and were then randomized to receive 0 (placebo), 1.25, 2.5, 5, or 10 g of a testosterone gel daily for 16 weeks [58]. A second group of 202 healthy men received the same agents plus anastrozole (to suppress aromatization of testosterone to estradiol). By comparing changes in bone turnover markers, BMD by DXA, and BMD by QCT between men who did and did not receive anastrozole, the study demonstrated that increases in bone resorption and decreases in BMD in hypogonadal men were largely due to estrogen deficiency. The risk of developing hypogonadal bone loss appeared to be small until serum estradiol levels fell below 10 pg/mL and/or serum testosterone levels fell below 200 ng/dL.

Complete Androgen Insensitivity Subjects with complete androgen insensitivity provide a valuable model to assess whether the sexual dimorphism in peak bone density is genetically or hormonally determined. In these subjects, who are genetic males but phenotypic females, radius density is lower than that of normal men but similar to that of normal women. In contrast, lumbar spine density is lower than expected for either men or women of the same age [59–61]. These findings suggest that androgen action contributes to the normal sexual dimorphism in cortical bone density and that the Y chromosome, per se, is not sufficient to guarantee the higher cortical density of normal men. The insufficient replacement of estradiol after gonadectomy, however, cannot be excluded as a reason for these results. In one study, noncompliance with estrogen replacement therapy after gonadectomy correlated with lower lumbar spine bone density [60].

Other Hormones Other hormonal changes that may be associated with age-related bone loss include higher serum parathyroid hormone (PTH) concentrations and lower serum 25-hydroxyvitamin D and insulin-like growth factor 1 (IGF-1) concentrations [62–64]. The suppression of gonadal steroids in older men with a GnRH agonist increases the skeletal responsiveness to pharmacologic doses of exogenous PTH, an observation that might help to explain bone loss in men with hypogonadism [65].

Secondary Osteoporosis

In contract with primary osteoporosis, secondary osteoporosis is common in both men and women. Therefore, subjects prone to develop osteoporosis attributed to secondary causes need a thorough evaluation consisting of medical history, physical examination, and laboratory testing. In some [66] but not all [67] studies, secondary causes of osteo-

porosis [68] are more common in men than women. Two causes of secondary osteoporosis that relate to medical therapy are of particular concern because of their heightened fracture risk and prevalence: glucocorticoid-induced osteoporosis and androgen depletion therapy (ADT).

Glucocorticoid-Induced Osteoporosis It is the most common iatrogenic cause of secondary osteoporosis and is especially important as increased fracture risk has been reported as early as 3 months after starting oral glucocorticoid therapy. Men are less likely than women to have attention paid to the increased fracture risk associated with glucocorticoid therapy [69, 70]. The most important aspect of glucocorticoid-induced osteoporosis is the realization that the patient is at risk soon after starting oral glucocorticoids.

Androgen Depletion Therapy (ADT) It was reported that men undergoing androgen deprivation therapy (ADT) for prostate cancer are prone to develop drug-associated osteoporosis. Such men may have a generally good prognosis [71] but fracture risk [72] is elevated (as high as 20% fracture risk in 5 years) because of their very low serum levels of both testosterone and estradiol [73]. The severity of the bone loss and dramatically increased fracture risk are underappreciated, and only a minority of these men are evaluated and/or treated for ADT induced osteoporosis.

There are many other secondary causes of osteoporosis in men, shown in Table 25.1. Other important causes include hypercalciuria, hyperparathyroidism, inflammatory arthritis and inflammatory bowel disease, bariatric surgery, and causes of hypogonadism in addition to ADT.

Differences Between Men and Women

Patients with osteoporosis whether men or women have changes in both trabecular and cortical bone, leading to fractures of the proximal femur, in addition to vertebrae and radii. It is important to note that there are differences in aging-associated changes in bone on comparing men to women. Using high-resolution quantitative computed tomography of the distal forearm, Khosla et al. [74] demonstrated that, as they age, women lose trabeculae and have greater spacing between trabeculae. Men, on the other hand, only have thinning of trabeculae as they age. Studies

Table 25.1 Osteoporosis in men: primary and secondary causes of osteoporosis in men

Primary osteoporosis			Secondary osteoporosis	
	Type I	Type II	Diseases	Medications
Age	Age: <70	Age: >70	Alcoholism Chronic obstructive pulmonary disease *Gastrointestinal disorders:* malabsorption syndromes, inflammatory bowel disease, celiac sprue, primary biliary cirrhosis, gastrectomy/bariatric surgery *Poor nutrition:* low serum levels of vitamin D, low calcium. *Renal:* Chronic kidney disease Hypercalciuria *Endocrine*: Hypogonadism Hyperparathyroidism Hyperthyroidism Cushing's syndrome *Inflammatory arthritis:* Rheumatoid arthritis	Glucocorticoids ADT PPI SERM Dopamine exposure Thiazolidinediones Enzyme inducing anti-platelets Chronic opiate analgesics Cancer chemotherapy
Causes	Specific genetic syndromes Cryptic secondary osteoporosis	Relation with muscle, sarcopenia		
Fracture site	Vertebrae	Hip and vertebra		

using quantitative computed tomography with finite element analysis [75] have shown that women lose more cortical bone in vertebrae than men. Men have larger bones at peak bone mass; and with aging, more periosteal bone is deposited in long bones, compared to women [76]. These differences may explain why men fracture later in life than women.

It has been generally accepted that sex hormones play an important role in primary osteoporosis. Indeed, the abrupt loss of estrogen at the menopause is considered the major reason for Type 1 primary osteoporosis in women. Men do not have a dramatic loss of androgens with aging, but most reports have shown that serum testosterone levels decline with aging [77]. Sex hormone binding globulin increases with aging, lowering bioavailable or free testosterone even further. However, in a report [78] from Australia, healthy aging men did not show a decline in serum testosterone levels until the eighth or ninth decade. The authors postulated that chronic conditions found commonly in older men lead to lower serum testosterone levels, not aging per se. It will be necessary to study this further in many larger populations. Nonetheless, it has been difficult to demonstrate that the decrease in testosterone found empirically with aging in many men is the proximate cause of aging-associated bone loss.

Studies [51, 79] have shown that serum estradiol levels are more robustly associated with BMD in aging men. In this context, testosterone acts as a pro-hormone because the major source of circulating estradiol in men is the aromatization of testosterone.

Androgens may play a role in the sarcopenia associated with aging. In a study carried out to assess for sarcopenia in older adults [80, 81], older men with sarcopenia (defined by relative appendicular skeletal muscle mass) were more likely to have osteoporosis by DXA than men with normal relative appendicular skeletal muscle mass. There are androgen receptors on bone cells [80] and androgen deficiency-induced loss of muscle mass likely leads to decreased lower body strength and increased propensity to falling and thus more fractures. As interactions between muscle and bone are investigated, a new understanding of osteoporosis pathophysiology and potentially new therapeutic approaches may be forthcoming.

Male Osteoporosis in the Elderly

As noted earlier, men do not experience rapid bone loss as women do after menopause; instead; they undergo a slow bone loss with age [82]; this bone loss begins by the sixth decade at an average rate of 0.5–1.0% per year and is accompanied by the growing incidence of fractures [83]. Apart from secondary causes, aging is a primary cause of bone loss in men, and several factors have been linked to the aging process. These include the following.

Hormonal Changes during Aging Hormonal changes during aging are responsible for bone loss; in particular, decreased levels of sexual steroid and relative increase in cortisol negatively influence bone remodeling. It is widely accepted that the decrease in sex steroid concentrations with age is associated with decreased bone density and increased fracture risk in men [54, 84, 85]; nevertheless, the decline of testosterone in men is gradual and not common to all the aged population. The decrease in bioavailable estradiol more than in testosterone appears to be the cause of bone loss in old men.

The excess of glucocorticoids both endogenous and exogenous is known to be detrimental for bone; glucocorticoids affect bone mainly by decreasing osteoblasts function [86]. Glucocorticoid action is dependent upon the expression of 11 beta-hydroxysteroid dehydrogenase isozymes, which interconvert active cortisol and inactive cortisone. Bone tissue is able to convert cortisone into active cortisol thanks to this enzyme, whose expression increases with aging [87]. Thus, old persons are more sensible to endogenous and exogenous glucocorticoid; this results in a relative hypercortisolism and possibly in bone damage.

Age-Related Osteoblast Dysfunction In older adults, osteoblasts function is reduced with a consequent decrease in bone formation; processes involved in this mechanism have been studied with controversial results; age-related changes in osteoblasts recruitment, differentiation, and function have been analyzed. Osteoblasts derive from the differentiation of skeletal mesenchymal stem cells (MSC). The ancestral MSC is able to differentiate in vitro into osteoblasts, adipocytes, or chondrocytes [88] and to self-renew [89].

The ability of MSC to differentiate into osteoblasts has also been studied and a work done in mice suggests that age impairs this ability [90, 91]. Thus, this could be one of the mechanisms explaining reduction in bone formation with age. Moreover, osteoblasts may modify their environment by acquiring a typical senescent secretory phenotype involving inflammatory cytokines, growth factors, and proteases [92, 93], thus contributing to increased osteoclasts activity and bone loss.

Vitamin D Deficiency It is well known that vitamin D plays an important role in regulating calcium metabolism and that its deficiency leads to bone demineralization and increased fracture risk [94]. 1,25(OH)D3 binds its nuclear receptor (VDR) and contributes to calcium and phosphorus homeostasis; in the small intestinal cells, the activation of VDR increases calcium absorption and maintains appropriate calcium levels, thus improving bone mineralization [95].

If the calcium intake is reduced, parathyroid hormone rises, stimulating osteoclasts activity, thus increasing bone resorption with calcium and phosphorus release in the blood stream [95, 96]. It has been reported that hypovitaminosis D is largely prevalent among adult population of both genders and that the incidence of hypovitaminosis D increases with age due to changes in lifestyle but also to decreased cutaneous synthesis [97]. For the abovementioned reasons, hypovitaminosis D has to be considered in the diagnostic processes of male osteoporosis in the elderly and a correct vitamin D supplementation has to be guaranteed in order to ensure maximum benefit of treatment [98].

Risk Factors: Identifying Men at High Risk of Fracture

Risk factors are characteristics that increase the chances of developing a certain condition or disease. The incidence of hip fracture in men increases substantially after the age of 70 years. In addition to age, risk factors for osteoporosis in men include low body weight (i.e., body mass index of less than 20–25 kg per m^2), weight loss of more than 10% of body weight, physical inactivity, long-term corticosteroid use, androgen deprivation therapy (e.g., for prostate cancer), previous fragility fracture, and spinal cord injury, excessive alcohol consumption, current smoking, and history of falls within the past year [99]. A systematic review of risk factors for osteoporosis in men also found that hypogonadism, history of cerebrovascular accident, and history of diabetes are associated with an increased risk of fractures, although their clinical use in identifying men who need further bone measurement testing is unclear [100]. Previous fragility fracture represents one of the important risk factors. After one osteoporotic fracture, men and women have about the same, highly increased risk of another fracture [101]. Thus, programs aiming at the identification of patients who have fractured are important means of finding men who need osteoporosis management [102–106].

For older men without specific causes of osteoporosis, many of the risk factors found in women also are important in older men. The risk factors used in the FRAX calculator [104] or the Garvan nomogram [107] are used in men and women: age, weight or body mass index, current smoking, excess alcohol intake (≥3 units daily), oral glucocorticoid use, rheumatoid arthritis, previous fracture, parental history of fracture and recent fall history. Many experts would add low serum levels of 25-hydroxyvitamin D, general frailty, diabetes

mellitus, mobility disorders (e.g., Parkinson's disease, multiple sclerosis, cerebrovascular accidents, spinal cord injury), and many medications [108]. In addition to glucocorticoids and androgen deprivation therapy, the following drugs may be associated with increased fracture risk: proton pump inhibitors, anti-depressants, dopamine antagonists, thiazolidinediones, immunosuppressives (e.g., cyclosporine), enzyme-inducing antiseizure medications (e.g., phenytoin), opiate analgesics, and some cancer chemotherapy (e.g., cyclophosphamide). Hence, the evaluation of men at risk for osteoporosis must include a careful history, including medication use [79].

The Journey Toward Making of the Diagnosis of Osteoporosis in Men

History and Clinical Examination Osteoporosis in men is an underdiagnosed condition; therefore, careful medical history is vital to identify those patients at risk. The first and most important risk to be checked is a full history of any previous fractures. The presence of a fracture, even a traumatic one, increases the odds of developing osteoporosis later on in life. Fractures causing significant pain, disability, and functional impairment may be the initial presentation in most men with osteoporosis. Another symptom of fracture, that the patient might present with is a loss of height. The most common fracture sites in men are the hip, vertebrae, forearm, and humerus [2]. A history of height loss (>6 cm) may indicate silent vertebral osteoporotic fracture. The physical exam should include an assessment of gait and balance. The prevalence of secondary osteoporosis in men is as high as 50% of the cases. A focused osteoporosis history and physical assessment for the presence of secondary causes of osteoporosis is detailed below.

1. Endocrine causes:
   (a) Cushing syndrome: Easy bruising, weight gain, irregular periods, hirsutism, decreased libido, hoarseness, new onset diabetes mellitus and hypertension, facial plethora, moon facies, abdominal obesity, broad red striae, gynecomastia, supraclavicular fat pad elevation, buffalo hump, and thin extremities
   (b) Hypogonadism: Decreased libido, gynecomastia, loss of muscle mass, a decrease in shaving frequency, fatigue, irregular periods, hot flashes
   (c) Hyperparathyroidism: Hypercalcemia, polyuria, polydipsia, nephrolithiasis
   (d) Hyperthyroidism: Increase in appetite, weight loss, tremors, palpitations, insomnia, amenorrhea, goiter, and heat intolerance
2. Systemic causes:
   (a) Malabsorption: Weight loss, diarrhea, abdominal pain, signs of vitamin deficiencies
   (b) Chronic liver disease: Loss of appetite, jaundice, pruritis, ascites, palmar erythema, spider nevi
   (c) Multiple myeloma: Loss of appetite, weight loss, lytic bone lesions, hypercalcemia
   (d) Anorexia nervosa: Weight loss, body image distortion, amenorrhea, and low BMI
3. Genetic causes:
   (a) Osteogenesis imperfecta: History of recurrent fractures, blue sclera, family history of osteogenesis imperfecta, yellow teeth, triangular face, and frontal bossing
   (b) Hypophosphatasia: History of frequent fractures, tooth loss, bowed legs
4. Chronic conditions:
   (a) inflammatory arthritis
   (b) Diabetes mellitus
   (c) Chronic obstructive pulmonary disease (COPD)
   (d) Cancer
   (e) Organ transplantation
5. Medications:
   (a) Glucocorticoids, cyclosporin-A, tacrolimus, heparin, aromatase inhibitors, anticonvulsants, and long-term heparin [109]

Laboratory Assessment These need to be specific to each patient based on history and physical exam.

Renal insufficiency: creatinine, eGFR, Hypercalcemia secondary to hyperparathyroidism
25 (OH) vitamin D – Vitamin D deficiency
24-h urinary calcium – Idiopathic hypercalciuria may be indicated in men with idiopathic osteoporosis that occurs before the age of 60 years, or if initial diagnostic methods fail to determine a cause of low bone mass. Up to 40% of cases of osteoporosis in men are primary or idiopathic [110].
1 mg dexamethasone suppression test – Cushing syndrome
Serum and urine electrophoresis – Multiple myeloma
Thyroid function tests – Hyperthyroidism
Testosterone levels – Hypogonadism
Serum prolactin – Prolactinoma
Celiac antibodies – Celiac disease [111]

Case Finding

Screening

Many organizations now provide guidance for osteoporosis screening in males. These guidelines are part of an integrated approach aimed at identifying males who should undergo diagnostic assessment using DXA in order to inform treatment decisions. Although screening guidelines vary by organization, most rely on age and the identification of other clinical risk factors to identify males at risk for fracture. In the United States, the National Osteoporosis Foundation (NOF) [112], the Endocrine Society [40], and the International Society for Clinical Densitometry [68] guidelines are consistent in recommending a DXA scan for men aged 70 years and older and in younger men with prior fractures or other risk factors. The NOF guidelines recommend screening in men under the age of 70 years if they had glucocorticoid exposure or a prior fracture [112]. The Endocrine Society recommends screening in males younger than 70 years if they have risk factors such as prior fracture as an adult, low body weight, and smoking [113]; and the International Society for Clinical Densitometry guidelines include prior fracture or disease or medication associated with bone loss or low BMD [114]. Osteoporosis Canada recommends BMD screening for males aged 65 years and older, and in younger men with risk factors, including prior fracture, use of glucocorticoids or other high-risk medications, high alcohol intake, current smoking, and diseases associated with rapid bone loss, fracture, or osteoporosis [115]. The National Osteoporosis Guideline Group (NOGG) 2013 guidelines recommend the assessment of the 10-year major osteoporotic fracture probability in men aged 50 years and older using the UK Fracture Risk Assessment Tool (FRAX), an absolute risk assessment tool, with BMD testing, evaluated based on age and fracture probability using predetermined assessment thresholds [115].

Making the Diagnosis

The clinical diagnosis of osteoporosis is made on the basis of the widely accepted bone BMD T-score criteria established by the World Health Organization (WHO) [117] (Table 25.2). WHO Collaborating Centre and the International Osteoporosis Foundation (IOF) recommend BMD measurement using DXA at the femoral neck as the reference standard for diagnosing osteoporosis in men [118, 119]. The National Osteoporosis Guideline Group (NOGG) [116] in the United Kingdom endorses the WHO and IOF recommendations. The US National Osteoporosis Foundation (NOF) [112] and the Endocrine Society [113] recommend the use of central DXA of the hip and spine for osteoporosis diagnosis, with the Endocrine Society recommending the

Table 25.2 T-scores and WHO diagnostic criteria for osteoporosis [117]

Interpretation	T-score
Normal	–1.0 and higher
Osteopenia	–1.0 to –2.5
Osteoporosis	–2.5 and lower
Severe osteoporosis	–2.5 and lower with one or more fragility fractures

WHO World Health Organization

use of the forearm (1/3 radius) when spine or hip scans cannot be interpreted and for men with hyperparathyroidism or receiving androgen deprivation therapy for prostate cancer. Osteoporosis Canada [115] bases diagnosis on the lowest T-score value for the BMD measured at the lumbar spine, total hip, or femoral neck and, like the Endocrine Society, also recommends the use of forearm measurements if the lumbar spine or hip scans cannot be used.

There has been a long-standing controversy as to the normative database to use for men. DXA machines in the United States and most other parts of the world use a male normative database for calculating the T-score for men. The T-score is the number of standard deviations from the normal young mean bone density [120, 121]. Men have larger bones than women, which makes the bone density look greater on DXA, and the standard deviation of DXA is different from that of women. Studies of osteoporosis treatment in men have all included men diagnosed with osteoporosis based on the male normative database [122, 123]. In some studies, men fractured at a higher absolute BMD than women [124], but other studies suggest that men and women fracture at the same absolute BMD [125]. The FRAX calculation, which predicts 10-year fracture risk, uses the absolute femoral neck bone density for men and women, which means that the same standard is used for both sexes. The International Society for Bone Densitometry [114] and the International Osteoporosis Foundation [118] support the use of the white female database for the diagnosis of osteoporosis in men and women of various ethnic groups.

The International Society for Bone Densitometry recommends that if the spine or hip BMD cannot be obtained or cannot be interpreted because of artifacts, forearm BMD should be measured by DXA (usually distal 1/3 radius). Similarly, men on ADT should have DXA scanning of the distal forearm. In studies from several institutions [126–128], about 15% of men on ADT have osteoporosis only in the forearm (usually the distal 1/3 radius) with osteopenia or normal bone density in spine and hip. However, a study [129] shows that densitometers may overread osteoporosis in the forearm based on a male normative database. The difference between the male and female databases is particularly dramatic here, leading to apparently very low T-scores in the radius or forearm, compared to spine or hip. Thus, it will be important to reanalyze forearm BMD in populations of men on ADT, using the much larger female normative database [79].

Absolute Risk Assessment

Low BMD alone is a poor predictor of fracture in men, with one study finding that only 21% of elderly men who went on to have a non-vertebral fracture and 39% of men who went on to have a hip fracture had a T-score below −2.5 [11] This indicates a need for tools that predict fracture risk independently of, or in addition to, BMD. The use of risk assessment tools that include clinically relevant risk factors to predict fracture risk is being increasingly incorporated into osteoporosis screening and treating guidelines.

The WHO FRAX (http://www.shef.ac.uk/FRAX/index.aspx) has been incorporated into many national and international screening and treatment guidelines worldwide. FRAX is a computerized algorithm that calculates the 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture using clinical risk factors, with the optional inclusion of BMD. Risk factors included in FRAX are age, sex, weight, height, previous fracture, parental history of hip fracture, current smoking, secondary osteoporosis, glucocorticoid exposure, rheumatoid arthritis, three or more units of alcohol per day, and BMD at the femoral neck using DXA, if available. FRAX models currently exist for 53 countries and are calibrated to reflect country-specific epidemiology of fractures and mortality [130].

Other absolute risk assessment algorithms include the Canadian Association of Radiologists and Osteoporosis Canada (CAROC) tool, Garvan nomogram, and Q-fracture [131–133]. These tools differ in the number of clinical risk factors included, but all incorporate age and sex. The

CAROC [131], recommended for risk assessment by the Osteoporosis Canada guidelines, uses age, sex, and femoral neck T-score to determine initial 10-year absolute major fracture risk (low, moderate, or high) and adjusts risk upward in the presence of prolonged glucocorticoid use or fragility fractures after the age of 40 years. A patient with both of these risk adjustments is classified as high risk irrespective of BMD. The Garvan nomogram [132] was developed in Australia to predict hip or major osteoporotic fracture using age, sex, history of prior fractures, and femoral neck BMD or weight (if BMD unavailable). Q-fracture [133] was developed for use in the United Kingdom and uses 31 risk factors to calculate the 10-year probability of osteoporotic fracture or hip fracture, but does not include BMD as an input.

The performance of these tools has not been extensively studied in a male population. A study that evaluated the predictive performance of the Garvan nomogram and FRAX in a sample of Australian men in a clinical setting found that FRAX discriminates fracture risk poorly, but the number of men studied was small [134]. A validation study of the Canadian FRAX concluded that the model was well-calibrated and adequately discriminates hip fracture in men [135]. In an observational study of FRAX calibration and discrimination in the MrOS cohort, the tool showed fairly accurate predicted risk for hip fractures without BMD but did not predict the risk of major osteoporotic fractures as well [136]. The discrimination of the tool was poor for major osteoporotic fractures with or without the inclusion of BMD but was fair for hip fracture with the inclusion of BMD. These limited results highlight the need for further research into the development and validation of fracture risk assessment tools in men. One example of a developed model in a male cohort was that by LaFleur et al. [137] to estimate absolute fracture risk in a regional cohort of male veterans using data collected passively in routine healthcare operations. The algorithm predicted the absolute risk of hip or any major fracture using age, BMI, smoking, alcohol use, fall risk, number of clinic visits, and several comorbid diseases and drug exposures, and showed good to acceptable discrimination for hip fracture and any major fracture, respectively [138].

BMD Vs FRAX in Men

Using the female database for DXA scan reporting and osteoporosis diagnosis in men means that fewer men will have osteoporosis, which is not congruent with the epidemiology of osteoporosis [139], but if DXA and the FRAX are both used, a large proportion of older men will be candidates for osteoporosis treatment [140]. The rationale for using the white female database for all has been reported [114]. While it is encouraging that the combined use of both DXA and FRAX will identify many men at risk for fracture, there are no studies demonstrating that a man without osteoporosis by DXA but with a high fracture risk by FRAX will respond to treatment. An early study of some older women with risk factors for osteoporosis but without DXA-diagnosed osteoporosis did not have fewer fractures when treated with risedronate, whereas those with DXA-diagnosed osteoporosis did respond [141]. It was concluded that even in women, the relationship between FRAX risk and response to therapy is quite limited [142].

Nonetheless, International Society for Bone Densitometry and International Osteoporosis Foundation now advocate one normative database, but clearly a country-specific database calibrated to local fracture data in a given country would likely be superior for identifying people at risk for fracture [143]. For men, using the white female normative database will result in fewer men having a T-score < -2.5. Thus, the FRAX score should also be calculated, and many older men will be eligible for treatment by the criteria used in the United States: a 10-year hip fracture risk of >3% or a 10-year any major osteoporotic fracture risk of >20% [104]. In the United Kingdom, a case finding approach is used, combining risk factors from the medical history and physical examination with the calculation of FRAX without BMD measurement [116]. Men at intermediate risk by this method then undergo

DXA and FRAX is re-calculated. Men at low risk are reassured, and men at high-risk commence treatment. In the last mentioned group, DXA may be used to follow treatment response. A similar case-finding method is used by the United States Department of Veterans Affairs, although DXA is used in the initial clinical evaluation [144].

Management

Gaps in Access to Osteoporosis Therapy

A consequence of the fact that the majority of the major phase III clinical trials conducted to fulfil drug registration requirements with the world's regulatory authorities have been conducted in postmenopausal women is that osteoporosis medicines have been licensed to treat men, often, many years after they were first available for women. In fact, the evidence-base for treatment of osteoporosis in men has grown substantially in the last decade and, as such, access to medicines to treat osteoporosis in men needs to keep pace with this progress. Furthermore, as in women, adherence to treatment is a challenge in men because osteoporosis is a silent disorder without symptoms until there is a fracture. Medications generally do not make patients feel different, which may be one reason for the poor adherence to therapy. Therefore, men with osteoporosis need longitudinal care for this chronic condition.

Who to Treat

Men with the highest risk of fracture are the ones most likely to benefit from osteoporosis drug therapy; therefore treatment guidelines for male osteoporosis rely on the results of BMD screening and the presence of clinical risk factors to select those at high risk for fracture to treat with pharmacologic therapies. Although several guidelines for management of osteoporosis in men have been published, osteoporosis treatment should remain individualized through shared decision-making between the patient and the clinician. Men diagnosed to have osteoporosis can be stratified according to their gonadal status into eugonadal and hypogonadal:

Eugonadal Men For men who have not been diagnosed to have hypogonadism (or in hypogonadal men for who it is contraindicated to prescribe testosterone therapy) nonhormonal pharmacotherapy is advised mainly for: (1) men with osteoporosis (history of fragility fracture, or a T-score below −2.5 in men ≥50 years); (2) men ≥50 years with T-scores between −1.0 and −2.5 who are at high risk for fracture (e.g., using Fracture Risk Assessment Tool [FRAX] score of hip fracture >3% and/or major osteoporotic fracture of >20%). For those at moderate risk (10–20% major osteoporosis fracture risk or 1–3% hip fracture risk), the decision to treat should be based upon the presence of additional risk factors not considered in the risk assessment system and upon individual preference. It has to be noted that in the United Kingdom, the National Osteoporosis Guideline Group recommends an age-dependent intervention threshold for men (and women), which ranges from 7.5% to 30% for ages 50 to 80 years [116]. For clinicians in the United Kingdom, intervention thresholds may be accessed directly from the FRAX website.

In a study that carried out the analysis of data from a population-based cohort of 5880 older men (mean age 73.6 years), there was significant variation of the proportion of men identified for osteoporosis treatment which ranged between 2.2% and 25.3%, depending upon the different criteria used to assess osteoporosis and risk for fracture [145]. The use of BMD criteria proposed by the World Health Organization (WHO; femoral neck T-score ≤ −2.5 derived from female reference database) identified the fewest men for osteoporosis treatment, whereas the use of FRAX intervention thresholds set by the NOF for men with BMD T-scores between −1 and −2.5 identified the most men for treatment (25.3%). During the 10-year follow-up period, 177 (3%) men had a hip fracture. The observed 10-year fracture probabilities were highest (20.6%) among the men identified as having osteoporosis by the

WHO BMD criteria in comparison to 9.5% evaluated using FRAX thresholds set by the NOF.

The FRAX intervention thresholds as proposed by the NOF [112] increase the proportion of older men who are candidates for therapy, whereas restricting treatment only to men who meet the WHO BMD criteria reduces the total number of men treated, but may exclude some men who might benefit from treatment. As noted earlier in this chapter, the use of a male reference database (rather than a female reference database as proposed by the WHO) to calculate T-scores leads to the identification of many more men for treatment. Even with the FRAX-NOF thresholds, some high-risk patients with secondary causes of osteoporosis, such as men receiving high-dose glucocorticoids, gonadotropin-releasing hormone (GnRH) agonists, or who have undergone organ transplantation, should often be treated even if they fail to meet the criteria listed above.

Hypogonadal Men Men presenting with hypogonadism should receive testosterone replacement therapy, on the basis of current hypogonadism treatment guidelines, associated with a classical osteoporosis medication [6, 146]. Although testosterone has been demonstrated to prevent bone loss and to improve bone mass in hypogonadal men [2, 4, 5], there is still little evidence about long-term treatment and no data about its anti-fracture efficacy. Therefore, for testosterone-treated hypogonadal men who have a high risk for fracture, the addition of nonhormonal pharmacologic therapy to testosterone therapy is advisable. In the absence of definitive data upon which to objectively classify fracture risk in hypogonadal men, certain risk factors should be considered; these include the following:

- History of a recent fragility fracture, particularly with a BMD T-score below −2.5 at any skeletal site
- BMD T-scores below −3.5 or even below −3.0 if they have other risk factors for fracture
- BMD T-score < −2.5 (or fragility fracture) even after receiving adequate testosterone replacement therapy for two years (this is based upon the outcome of a clinical trial data in men showing that testosterone continues to improve BMD for at least two years [147])
- High-dose glucocorticoids
- Frequent falls

For hypogonadal men who are not taking testosterone (because of contraindications), the approach is the same as for eugonadal men.

Treatment Plan

Once a complete diagnostic work-up has defined the nature (primary or secondary) of osteoporosis, identified underlying causes and potentially modifiable risk factors for fragility fractures, and assessed the absolute risk of fracture (using a validated tool such as FRAX), the management of men presenting with osteoporosis should consist of the implementation of general nonpharmacologic measures and the prescription of a specific pharmacological agent.

General Nonpharmacologic Treatment

General measures for fracture prevention and treatment of osteoporosis in men are similar to those advised for women. Nonpharmacologic approaches include diet physical exercise, and avoidance of detrimental lifestyle factors (e.g., smoking, excessive alcohol consumption), as well as changes to reduce modifiable fracture risks. These approaches have already been incorporated into several osteoporosis clinical guidelines. For example, the NOF [112], Endocrine Society [113], and Osteoporosis Canada [115] all recommend adequate calcium and vitamin D intake and encourage regular weight-bearing and muscle-strengthening physical activity. The NOF [112] and Endocrine Society [113] also advocate tobacco cessation and the avoidance of excessive alcohol. Fall prevention strategies are recommended by Osteoporosis Canada and the NOF. The NOF and Osteoporosis Canada guide-

lines [115] are universal recommendations applicable to all men aged 50 years and older while the Endocrine Society guidelines apply to men with or at risk for osteoporosis. The NOGG [116] does not make any population-based recommendations, but does advise that general osteoporosis management should include the correction of calcium and vitamin D deficiencies, assessment of fall risks, and mobility maintenance.

The evidence surrounding the anti-fracture efficacy of these interventions in males is varied. While current smoking and consumption of ten or more alcoholic drinks per week are associated with moderately increased risk of fracture, the effects of smoking cessation and alcohol reduction have been less frequently studied [100]. One observational study in men showed that former smokers had a lower fracture risk than current smokers (although still a higher risk than never smokers) and the effect was longlasting [148]. The Framingham study demonstrated no significant change in hip fracture risk after decreasing alcohol consumption from heavy to light levels [149]. The evidence supporting calcium and vitamin D supplementation and physical activity is also mixed. A systematic review found that the effect of calcium intake on fracture outcomes in men was inconsistent, but there was substantial heterogeneity in how calcium intake was defined and assessed [100]. Concerning vitamin D, supplementation should always be considered to maintain its adequate level in the blood due to its implication for bone health and falls prevention [150]. A systematic review and meta-analysis found that daily supplementation with 800 IU of oral vitamin D was associated with decreased hip and nonvertebral fractures [151]. This study did not find any difference in effect between males and females, but the data on males were limited. Another systematic review of exercise interventions on fall-related fractures in patients with osteopenia or osteoporosis concluded that these interventions may reduce falls and fall-related fractures; however, most of these studies did not directly assess fall or fracture outcomes and the majority were conducted in postmenopausal females [152]. However, in general, patients presenting with osteoporosis and a high fracture risk should be instructed to lift objects using proper techniques and to avoid lifting objects that are too heavy, due to the potential risk of vertebral fractures.

In patients presenting with a secondary condition potentially associated with increased bone fragility and fracture osteoporosis risk (e.g. primary hyperparathyroidism, hypogonadism), this should, if possible, be removed and/or treated.

Pharmacological Agents

The goal of pharmacological therapy is to reduce the risk of fractures. Bisphosphonates, teriparatide, and denosumab have been tested versus placebo or an active agent in a number of RCTs undertaken in men presenting with primary (idiopathic and age-related) or hypogonadism-associated osteoporosis. Recently, the effectiveness and safety of romosozumab for the treatment of osteoporosis in men have also been studied in a phase III clinical trial.

In general, studies carried out to assess the efficacy of pharmacological management of men with osteoporosis included relatively small numbers of patients. Only one of them (with zoledronic acid) was designed to assess anti-fracture efficacy [153], and none of them assessed the long-term effect of treatment (e.g., due to absence of extension studies). Two RCTs included men and women [154, 155], and another study was conducted in a mixed population that also included men presenting with secondary osteoporosis [156]. Two "head-to-head" RCTs compared two active medications (zoledronic acid versus alendronate, strontium ranelate versus alendronate) [157, 158]. It has to be noted that strontium is no more available for its side effects. Another trial tested two active medications (alendronate and teriparatide) and their combination [159]; and one study assessed two different doses of teriparatide [160].

Selection of Therapeutic Agent

The selection of therapeutic agent can be individualized based on factors including fracture history, severity of osteoporosis (T-scores), the

risk for hip fracture, patterns of BMD [i.e., whether BMD is worse at sites where cortical bone (e.g. 1/3 radius) or trabecular bone (e.g. spine) predominate], comorbid conditions (e.g., peptic ulcer disease, gastroesophageal reflux, malabsorption syndromes, malignancy, etc.), cost, and other factors. For men with a recent hip fracture, treatment with zoledronic acid is suggested, whereas when teriparatide is administered, it is not advisable to be given with concomitant antiresorptive therapy.

Bisphosphonates

The main three bisphosphonate therapies, namely, alendronate, risedronate, and zoledronate, have positive effects on BMD and vertebral fracture risk. Bisphosphonates are equally effective in improving bone density in men with normal or low testosterone levels, and the decision to use androgens should be made independently of the decision to use a bisphosphonate. For most men who require pharmacologic therapy, oral bisphosphonates have been suggested as initial therapy because of their efficacy, favorable cost, and the availability of long-term safety data. In a meta-analysis of trials in men with osteoporosis, bisphosphonates reduced the risk of vertebral (six trials, relative risk [RR] 0.37, 95% CI 0.25–0.54) and nonvertebral (four trials, RR 0.60, 95% CI 0.40–0.90) fracture [161].

Alendronate

Oral alendronate has been tested against placebo or alfacalcidol in two RCTs undertaken in men with primary or hypogonadism-associated osteoporosis [122, 162]. In both studies, alendronate produced significantly higher increases of the BMD at the lumbar spine, femoral neck, and total hip, compared to placebo or alfacalcidol, after 2 or 3 years of treatment. The BMD response to alendronate was independent of age, smoking status, baseline free testosterone, and estradiol concentrations [122].

Orwoll et al. [122] randomized 241 men to receive oral alendronate 10 mg or placebo daily for 2 years. Although the trial was not powered for a fracture outcome, alendronate treatment was associated with a significant reduction of the risk of new morphometric vertebral fracture (odds ratio [OR] = 0.10, 95% confidence interval [CI]: 0.00–0.88). Alendronate also decreased the risk of new non-vertebral fracture by 22.6%, but this decrease was not statistically significant.

Ringe et al. [162] evaluated the efficacy of oral alendronate 10 mg versus alfacalcidol 1 μg daily in a 3-year open-label RCT of 134 men. Alendronate-treated patients experienced a significantly lower incidence of new vertebral fracture compared to placebo-treated subjects (OR = 0.36, 95% CI: 0.14–0.94). A nonsignificant lower incidence of new non-vertebral fracture with alendronate was also reported.

In a systematic review of RCTs of alendronate in men, Sawka et al. [163] pooled the results of these trials, incorporating prior information of anti-fracture efficacy in women. They estimated the ORs for incident fractures in men treated with alendronate: OR (95% CI) for vertebral fractures was 0.44 (0.23–0.83) and OR (95% CI) for non-vertebral fractures was 0.60 (0.29–1.44).

Risedronate

In a 2-year, open-label RCT, Ringe et al. [156] randomized 316 men with primary (59%) or secondary osteoporosis to receive oral risedronate 5 mg daily (with calcium 1000 mg and cholecalciferol 800 IU daily) or calcium and either cholecalciferol or alfacalcidol alone daily (alfacalcidol 1 μg daily in patients with prevalent vertebral fractures). Risedronate treatment significantly reduced the risk of new vertebral (61%) and non-vertebral fractures (45%) over 2 years of treatment, and significantly increased the BMD at the lumbar spine, femoral neck, and total hip. The authors did not report a separate analysis of the incidence of fractures in men presenting with primary versus secondary osteoporosis.

The beneficial effect on the BMD of oral risedronate 35 mg once weekly versus placebo was

evaluated in a 2-year, double-blind, placebo-controlled study including 284 men with primary osteoporosis [164]. Risedronate was demonstrated to produce a significantly greater increase of the BMD at the lumbar spine and hip compared to placebo. Very few fractures occurred during the study, and there were no significant differences between the risedronate and placebo groups.

Zoledronic Acid

Three RCTs investigated the beneficial effects of intravenous zoledronic acid 5 mg once yearly versus placebo or alendronate [153, 154, 157, 165, 166]. In a large, randomized, placebo-controlled trial, Lyles et al. [154] examined the efficacy of zoledronic acid in men (n = 508) and women (n = 1619) presenting with hip fracture [154, 165]. Approximately 22% of the men had secondary osteoporosis. Zoledronic acid showed a 35% (hazard ratio [HR] = 0.65, 95% CI: 0.50–0.84) reduced risk of new clinical fractures in the overall population compared with placebo, being effective in decreasing the risk of new clinical vertebral (HR = 0.54, 95% CI: 0.32–0.92) and non-vertebral fractures (HR = 0.73, 95% CI: 0.55–0.98). Further analysis was carried out to evaluate the beneficial effect of zoledronic acid in the subgroup of 508 men demonstrated that the increases of the BMD in men were of a similar magnitude to those observed in women in the same study [165]. Very few clinical fractures were observed in men, with no statistically significant differences between zoledronic acid and placebo.

Another fracture-endpoint RCT [153] investigated the efficacy of zoledronic acid versus placebo in 1199 men presenting with primary or hypogonadism-associated osteoporosis. A significantly lower proportion of men in the zoledronic acid group experienced one or more new morphometric vertebral fractures over 24 months as compared with men in the placebo group, with a relative risk reduction of 67%. Similar results were observed for moderate-to-severe and worsening morphometric vertebral fractures, while no significant difference was observed between groups in the incidence of new clinical fractures. Zoledronic acid also significantly increased the BMD at the lumbar spine, total hip, and femoral neck over 24 months, as compared to placebo. Total testosterone level did not affect the anti-fracture efficacy of zoledronic acid or its beneficial effects on the BMD.

In line with these findings, a 2-year head-to-head RCT comparing once-yearly zoledronic acid with once-weekly alendronate in men with primary or hypogonadism-associated osteoporosis demonstrated the noninferiority of zoledronic acid compared to alendronate in improving the BMD at the lumbar spine, femoral neck, and total hip [157].

Other Bisphosphonates

In a 3-year RCT of men (n = 23) and women (n = 78) with primary osteoporosis treated with oral pamidronate 150 mg daily or placebo, pamidronate decreased the incidence of new vertebral fractures by 67%, with a similar response in men and women [155]. Lumbar spine BMD increased significantly in pamidronate-treated patients, with a significantly greater increase compared to placebo. BMD response to pamidronate was similar in men and women (absolute increase: 0.047 g/cm^2 in women, 0.040 g/cm2 in men), although the mean percent change in women (10.13% ± 1.67%) was greater compared to men (5.98% ± 1.49%) due to the lower baseline BMD of the women.

Orwoll et al. [167] investigated the safety and efficacy of 150 mg monthly oral ibandronate versus placebo in a small, 1-year RCT of men with primary or hypogonadism-associated osteoporosis. After 1 year, ibandronate-treated men demonstrated a significantly greater increase of the lumbar spine, total hip, and femoral neck BMD compared to placebo-treated patients. The lumbar spine BMD response to ibandronate was independent of age, baseline body mass index, baseline total hip BMD, and ethnicity.

Contraindications or Intolerance to Oral Bisphosphonates

Intravenous (IV) bisphosphonates, zoledronic acid (ZA) and ibandronate, offer an alternative for individuals who cannot tolerate oral bisphosphonates or who find the dosing regimen more convenient. Zoledronate is the only IV bisphosphonate that has demonstrated efficacy for fracture prevention in men [153, 168], and it is therefore is considered the intravenous agent of choice.

Men who have esophageal disorders (achalasia, scleroderma involving the esophagus, esophageal strictures, varices), gastrointestinal intolerance to oral bisphosphonates, or an inability to follow the dosing requirements of oral bisphosphonates (including an inability to sit upright for 30–60 min and/or to swallow a pill) should not be treated with oral bisphosphonates. Oral bisphosphonates should also be avoided after certain types of bariatric surgery in which surgical anastomoses are present in the gastrointestinal tract (e.g., Roux-en-Y gastric bypass) [169].

Prior to receiving IV bisphosphonates, patients should be assessed for hypocalcemia, vitamin D deficiency, and renal impairment by measuring serum calcium, creatinine/eGFR, and 25(OH)D. It is unclear what level of 25(OH)D is desirable prior to IV bisphosphonate infusion, although many experts recommend levels of at least 20–25 ng/mL (50–62 nmol/L) [170].

In case of intolerance to or having a contraindication to oral or IV bisphosphonates or who have difficulty with the dosing requirements, other options include teriparatide (PTH 1-34) or denosumab.

Teriparatide

Unlike the chronic parathyroid hormone excess of hyperparathyroidism, which leads to bone loss, teriparatide is given as a once daily subcutaneous bolus injection. This intermittent administration activates osteoblasts and leads to increased bone formation, and fewer fractures in women. The changes in fracture surrogates (DXA and bone turnover markers) are similar in men and women [160, 171]. Teriparatide treatment for the management of primary osteoporosis in men has been evaluated in two well-designed RCTs as monotherapy or combination therapy [172–174].

Orwoll et al. [160] randomized 437 men with primary osteoporosis to receive teriparatide 20 μg, teriparatide 40 μg, or placebo injection daily. The trial was originally designed to last 2 years, but it was stopped after a median duration of 11 months. A follow-up safety study provided the opportunity to follow the patients up to 30 months after teriparatide discontinuation and to obtain radiographs at 18 months [173]. During the "core" study, indices of bone formation increased early in the course of therapy with teriparatide, followed by increases of markers of osteoclastic activity. Markers of bone turnover were stable or declined slightly in the placebo group. Daily treatment with teriparatide at both doses increased, dose-dependently, lumbar spine and femoral neck BMD. BMD changes were significantly greater in the teriparatide groups compared to the placebo group, beginning at 3 months. The BMD response to treatment was independent of baseline free testosterone, age, body mass index, baseline lumbar spine BMD, smoking, and alcohol intake. The time course and the magnitude of the changes of BMD in men treated with teriparatide were comparable with those observed in women [175]. From the original treatment trial baseline [160] to the 18-month visit of the follow-up study [173], there was a lower incidence of new moderate or severe vertebral fractures in the combined teriparatide groups compared to the placebo group (relative risk reduction = 83%; new vertebral fracture: placebo 11.7% versus combined teriparatide 5.7%, $P = 0.07$; new moderate or severe vertebral fractures: placebo 6.8% versus combined teriparatide 1.1%, $P = 0.01$).

Finkelstein et al. [159] randomized 83 men to receive alendronate (10 mg oral daily), teriparatide (40 μg subcutaneous daily), or the combination therapy for 30 months (with teriparatide

therapy starting at month 6). After 30 months, the BMD at the lumbar spine and femoral neck increased significantly more in the teriparatide group compared to the other two groups (alendronate alone or combination). Considering also the changes of the markers of bone turnover, the authors concluded that alendronate treatment impaired the ability of teriparatide to increase the BMD, due to an attenuation of the teriparatide-induced stimulation of bone formation.

In a prospective cohort substudy incorporating these data about teriparatide monotherapy in men (Finkelstein et al. [159]) and similar data from an identical protocol performed in postmenopausal women, Leder et al. [174] compared BMD response to teriparatide administration (months 0–30) and discontinuation (months 30–42) between males and females. During the teriparatide treatment, the magnitude of the BMD increases (lumbar spine, total hip, femoral neck) did not differ between men and women. The mean female–male difference (95% CI) in the change in BMD was 0.3 (−6.0, 6.6) at the lumbar spine, 0.1 (−4.9, 5.0) at the femoral neck, and 0.4 (−4.5, 5.2) at the total hip. Interestingly, during the 12 months of follow-up after teriparatide discontinuation, BMD response to discontinuation was different between the sexes. Lumbar spine BMD decreased by 7.1% ± 3.8% in women and by 4.1% ± 3.5% in men (P = 0.036). Total hip and femoral neck BMD also decreased significantly in women (3.8% ± 3.9% and 3.1% ± 4.3%, respectively), but remained stable in men. Overall, these results confirmed the comparable efficacy of teriparatide treatment in men and women but suggested a different trend in BMD response to discontinuation.

Denosumab

Denosumab, a monoclonal antibody that binds and neutralizes the activity of RANKL (a key osteoclast cytokine), may have a role for the treatment of osteoporosis in men who are intolerant of or unresponsive to other therapies and in those with some degree of renal function impairment. Denosumab increases BMD in men with low bone mass [176]. The anti-fracture efficacy of the antiresorptive denosumab has been clearly established in RCTs performed in postmenopausal women, but it has not yet been shown to reduce fracture risk in men, except for men with prostate cancer receiving androgen deprivation therapy [177–180].

The efficacy and safety of denosumab in men with low BMD (primary or hypogonadism-associated) have been investigated in a 2-year RCT performed in 242 patients (ADAMO study) [181]. This was a phase 3 study with 2 treatment periods: a previously reported 12-month double-blind, placebo-controlled phase and a 12-month open-label phase. Men from the original denosumab (long-term) and placebo (crossover) groups received 60 mg of denosumab subcut every 6 months. During the open-label phase, continued BMD increases occurred with long-term denosumab treatment (2.2% lumbar spine, 0.9% total hip, 1.3% femoral neck, 1.3% trochanter, and 0.2% 1/3 radius), resulting in cumulative 24-month gains from the baseline of 8.0%, 3.4%, 3.4%, 4.6%, and 0.7%, respectively (all P < 0.01). The crossover group showed BMD gains after 12 months of denosumab treatment similar to those of the long-term denosumab group during the first treatment year. Significant reductions in serum collagen type I C-telopeptide were observed after denosumab administration.

The BMD response to denosumab was independent of baseline testosterone level, lumbar spine BMD, 10-year risk of major osteoporotic fractures, age, race, previous osteoporotic fractures, and baseline serum beta-C-terminal telopeptide of type I collagen (CTX). Treatment with denosumab produced a significant (versus baseline and placebo) decrease of serum C-terminal telopeptide of type I collagen (CTX). Overall, the incidence of adverse events was similar between treatment groups, and no relevant safety issue with denosumab was reported (e.g., hypocalcemia, osteonecrosis of the jaw, complications of fracture healing, atypical femoral fractures).

BMD gains in the ADAMO study [181] were comparable to those reported in the RCT undertaken in postmenopausal women, in which verte-

bral, hip, and non-vertebral anti-fracture efficacy was demonstrated. Furthermore, the significant reduction in serum CTX with denosumab observed early after initiating treatment and the sustained reduction of bone turnover up to 12 months were consistent with what has been observed in postmenopausal women with osteoporosis [176].

In conclusion, although the ADAMO study was not designed to assess the anti-fracture efficacy of denosumab, the similarity of effects on surrogate markers (BMD and markers of bone turnover) in males and females with osteoporosis suggests that denosumab may be effective in reducing fracture risk in men with primary or hypogonadism-associated osteoporosis as well as in men with prostate cancer receiving androgen-deprivation therapy and postmenopausal women [177–180].

Romosozumab

Rosomozumab has been shown to have both bone stimulatory and antiresorptive properties, and has been specifically tested in clinical trials in men with osteoporosis [182, 183]. The effectiveness and safety of romosozumab for the treatment of osteoporosis in men has been studied in a phase III clinical trial [205]. The study included 245 men aged 55–90 years with a baseline bone mineral density (BMD) T-score at the lumbar spine, total hip, or femoral neck of ≤ -2.5 or ≤ -1.5 with a history of a fragility nonvertebral or vertebral fracture. The subjects were randomized 2:1 to receive romosozumab 210 mg subcutaneously monthly or placebo for 12 months (163 romosozumab, 82 placebo). The primary efficacy endpoint was percentage change from baseline in lumbar spine BMD at month 12. Results revealed that at month 12, the mean percentage change from baseline in the lumbar spine and total hip BMD was significantly greater for the romosozumab group than for the placebo group (Lumbar spine, 12.1% vs 1.2%; Total hip, 2.5% vs −0.5%; $P < 0.001$). Adverse events and serious adverse events were balanced between the two groups, with a numerical imbalance in the positively adjudicated cardiovascular serious adverse events [romosozumab, 8 (4.9%) vs placebo, 2 (2.5%)]. The study showed that romosozumab given by injection monthly for a 12-month period significantly increased the formation of new bones, compared to placebo, and was well tolerated in men with osteoporosis.

Combination/Sequential Therapy

In both men and women, adding a bisphosphonate to teriparatide (either started concurrently or prior to teriparatide) offers no additional benefit and may even impair the ability of parathyroid hormone monotherapy to increase spine and hip BMD. Combination therapy with denosumab and teriparatide increased BMD in women more than monotherapy with either agent. However, combination therapy with denosumab and teriparatide has not been studied in men. On the other hand, the immediate use of bisphosphonates after teriparatide is withdrawn may maintain or even increase BMD in men further (for further information, see Chap. 24 on optimizing Sequential and Combination therapy).

Monitoring the Response to Therapy

While there are a number of approaches to monitoring therapy, there is no consensus on the optimal approach. For patients starting on therapy, it is advisable to obtain a follow-up dual-energy x-ray absorptiometry (DXA) of hip and spine after two years; and if bone mineral density (BMD) is stable or improved, the BMD is monitored less frequently thereafter. There may be limitations to the use of spine DXA in aging men due to interference from osteophytes and vascular calcifications on the spine measurement. The use of biochemical markers of bone turnover to monitor response to therapy is not well studied in men and therefore, is not routinely recommended (for further information, see Chap. 18 on Treat to Target osteoporosis management).

Duration of Therapy

In contrast to teriparatide and romosozumab where treatment periods are fixed, currently, there is no consensus on how long to continue bisphosphonate therapy in men. In postmenopausal women with osteoporosis, alendronate, risedronate, and zoledronic acid have been shown to reduce fracture risk for 10, 7, and 6 years, respectively. Due to concerns about possible long-term risks of bisphosphonates, a "drug holiday" has been advised in selected groups of women and in men. In general, it has been suggested to suspend bisphosphonate treatment for men who have taken alendronate for five years or who have received zoledronate once yearly for three years if their BMD is stable, they have not had previous fragility fractures, did not develop any low trauma fracture and they are at low risk for fracture in the near future. Bone mineral density (BMD) should be monitored every two years after suspending therapy, and therapy should generally be resumed if BMD declines significantly or if the patient develops a new fragility fracture (for further information, see Chap. 18 on Treat to Target osteoporosis management).

In conclusion, osteoporosis in men is an important problem that has been inadequately appreciated. This has been partly attributed to the earlier disproportionate emphasis on osteoporosis in women, particularly, after menopause. Primary care physicians, health care professionals, and members of the public need to be aware of the problem and the possible risk factors. This will facilitate identifying men at higher risk of fracture, and assess and treat them whenever applicable. Among important risk factors are a prior fragility fracture (including an asymptomatic vertebral fracture), glucocorticoid use as well as excess alcohol and smoking. Also, positive family history of osteoporosis, recent history of low trauma fracture, and frequent falls important risk factors that should be considered. The assessment of absolute fracture risk are useful in guiding the treatment of osteoporosis. Bisphosphonates are effective in improving bone density in men whether their serum testosterone level is normal or low. The adjustment of serum vitamin D level, appropriate exercise program and fall-reduction measures, can help to reduce injuries. The aim is to facilitate early identification and treatment of men at risk for fragility fractures and consequently to reduce the substantial morbidity, mortality, and costs that can be incurred from osteoporosis-related fractures.

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26 Pediatric Osteoporosis and Optimizing Bone Health in Children

Yasser El Miedany

Introduction

Osteoporosis is a disease characterized by reduced bone mass and deterioration of bone microarchitecture, resulting in increased risk of fragility fractures. Once considered a disease of the aging, osteoporosis is now increasingly recognized in children. The fact that pediatricians may not recognize the risk for bone loss in children means that the bone loss will not be diagnosed or treated. In severe cases, this may result in subsequent low-trauma fractures (or fragility fractures), which represent the cardinal features of impaired bone health in children [1]. Furthermore, with less severe but more chronic forms of bone loss, a child may not reach his or her genetically determined peak bone mass. Thus, the child may be at greater risk for adult-onset osteoporosis as he or she will enter adulthood with lower bone mass than would otherwise be expected.

Pediatric bone health is determined by genetics, diet, mobility, and exercise, but it can also be affected by medications and chronic disease. Although a diagnosis of osteoporosis may inspire some pediatricians with special interest in metabolic bone diseases, general pediatricians should particularly be aware of the major differences in the diagnosis and management of osteoporosis in children [2].

This chapter will start by discussing bone acquisition during childhood and adolescence, followed by definition and etiology of pediatric osteoporosis. It will expand then to discuss types of pediatric osteoporosis, clinical signs, and risk factors, as well as predictors of fractures and DXA technicalities, interpretation, and reporting in children and adolescents. The chapter will then answer the question of "when osteoporosis should be suspected" and the process of making the diagnosis. The chapter will conclude with the management of osteoporosis in children and present an algorithm for the monitoring of therapy.

Bone Acquisition During Childhood and Adolescence

Bone is a living structure comprising a matrix of collagen (mostly of type I collagen fibers), packed with hydroxyapatite crystals, and noncollagenous proteins. The matrix gets mineralized with deposits of calcium and phosphate, which ensures resistance to fracture through an optimal balance of flexibility and stiffness [3].

Bone mass acquisition during childhood culminates in the achievement of peak bone mass, the amount of bone mass acquired when accrual plateaus after completion of growth and development.

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Bone mineral deposition begins during pregnancy, with two-thirds of in utero accrual occurring during the third trimester [4]. Bone mineral content (BMC) increases 40-fold from birth until adulthood, and peak bone mass is achieved toward the end of the second decade of life, although there may still be some net bone deposition into the third decade [5–10]. Approximately 40–60% of adult bone mass is accrued during the adolescent years, with 25% of peak bone mass acquired during the 2-year period around peak height velocity. After infancy, peak bone mineral accretion rates occur, on average, at 12.5 years for girls and 14.0 years for boys [11]. At age 18 years, approximately 90% of peak bone mass has been accrued [12].

Childhood and adolescence, therefore, are critical periods for skeletal mineralization. The timing of peak bone mass differs depending on the skeletal site considered, sex, maturational timing, and lifestyle factors. In fact, age of peak bone mass accrual lags behind age of peak height velocity by approximately 6–12 months in both boys and girls [11]. This dissociation between linear growth and bone mineral accrual may confer increased vulnerability to bone fragility and may explain, to some degree, the increased rate of forearm fractures in boys 10–14 years of age and in girls 8–12 years of age [13, 14]. After peak bone mass is achieved, there is a slow but progressive decline in bone mass until a theoretical fracture threshold is reached. Any condition interfering with optimal peak bone mass accrual can, therefore, increase fracture risk later in life.

The skeleton is an active organ, constantly undergoing remodeling, even after linear growth has been completed. During remodeling, bone formation, mediated via osteoblasts, and bone resorption, mediated by osteoclasts, occur concurrently. Remodeling is orchestrated by osteocytes and regulated by local cytokines as well as by circulating hormones, including parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (1,25-OH2-D), insulin-like growth factor 1 (IGF-1), and calcitonin. In young children, the rate of cortical bone remodeling is as high as 50% per year. Net bone mass depends on the balance between bone resorption and bone formation. If formation exceeds resorption, as it should during childhood and adolescence, net bone mass increases. If resorption exceeds formation, as in postmenopausal women, net bone mass is reduced [15].

Definition of Pediatric Osteoporosis

Osteoporosis in children has a different definition from that in adults. In adults, the World Health Organization has defined osteoporosis based on density, assessed by DXA scan. A cutoff point of a T-score of ≤ -2.5 at the lumbar spine, femur neck, or total hip has been identified to be diagnostic of osteoporosis. If this definition was applied to children, every child ever born would have osteoporosis. Therefore, in 2007, the International Society for Clinical Densitometry (ISCD) held a Pediatric Consensus Development Conference in Montreal and arrived at a definition of pediatric osteoporosis [16]. This was updated in 2019 [17] and stated that the diagnosis of osteoporosis in children and adolescents should not be made on the basis of densitometric criteria alone. In the absence of vertebral compression (crush) fractures, the diagnosis of osteoporosis is indicated by the presence of both a clinically significant fracture history and bone mineral density (BMD) Z-score ≤ -2.0. A clinically significant fracture history is one or more of the following: (1) two or more long-bone fractures by age 10 years; (2) three or more long-bone fractures at any age up to age 19 years; or one or more vertebral fractures (VFs) in the absence of high-energy trauma or local disease, and independent of BMD [18]. A BMD Z-score > -2.0 does not preclude the possibility of skeletal fragility and increased fracture risk. Consequently, the term osteopenia is no longer used in pediatrics because it has neither been defined nor demonstrated to be a risk factor for fractures.

Etiology of Pediatric Osteoporosis

There are many possible causes for osteoporosis in children. However, in general, pediatric osteoporosis is usually divided into primary and secondary forms (Table 26.1). As a rule, in

Table 26.1 Primary and secondary causes of osteoporosis in children

Primary bone disorders	Catabolic state	Chronic inflammatory diseases	Neuromuscular/immobility or decreased activity	Medications	Systemic
Osteogenesis imperfecta	Vitamin D deficiency	Juvenile idiopathic arthritis	Post trauma	Anticonvulsant	*Endocrine disorders:* Hypogonadism – Gonadal dysgenesis Hyperthyroidism Cushing syndrome Growth hormone deficiency Delayed puberty Diabetes Hyperprolactinemia Hyperparathyroidism Turner syndrome Klinefelter syndrome
Osteoporosis-pseudoglioma syndrome	Malignancy – acute lymphoblastic leukemia, lymphoma	Systemic lupus erythematosus	Spinal muscular atrophy	Glucocorticoids	
Homocystinuria	Cystic fibrosis Endocrine	Dermatomyositis	Cerebral palsy	Heparin	
Ehlers–Danlos syndrome (type I)	Psychiatric eating disorders - Anorexia nervosa/bulimia	Inflammatory bowel disease	Duchenne muscular dystrophy	Methotrexate (in oncology doses)	
Marfan syndrome	Inborn errors of metabolism: Glycogen storage disease Galactosemia Gaucher disease		Myopathies	Cyclosporine	
GSD type 1	Acquired immunodeficiency syndrome		Rett Syndrome	Radiation therapy	*Renal:* Nephrotic syndrome Chronic renal failure
Juvenile/early-onset Paget's disease	Female athlete triad disorder			Heparin	*Lung disease:* cystic fibrosis
Idiopathic juvenile osteoporosis					*Gastrointestinal* Celiac disease Inflammatory bowel disease chronic liver disease Cow's milk protein allergy
					Skin conditions: Epidermolysis bullosa

approaching a child with recurrent fractures, primary osteoporosis should be suspected only once a secondary cause has been ruled out [2].

Primary Bone Loss in Children

Primary osteoporosis occurs due to an intrinsic skeletal defect of genetic or idiopathic origin. Among the most exciting recent developments in the pediatric bone health field has been the elucidation of genes implicated in heritable bone fragility disorders. While the phenotypic heterogeneity in congenital bone fragility has been known for years, the spectrum of the genetic basis has only recently come to the surface [19].

Osteogenesis imperfecta (OI) is the most prevalent form of primary osteoporosis in children, with an incidence of 1 in 25,000 births [20], equally affecting both sexes. The term osteogenesis imperfecta refers to a structural genetic defect in the quantity or quality of bone type 1 collagen production and includes a wide spectrum of conditions ranging from mild forms to perinatally lethal ones. Although for three decades it has been recognized that the majority of patients with osteogenesis imperfecta had mutations in COL1A1 and COL1A2 genes (classically referred to as osteogenesis imperfecta types I, II, III, and IV based on disease severity), defects in several other genes have been also demonstrated to determine osteogenesis imperfecta. Over a dozen additional genetic causes have been described with novel pathobiology and often discrete clinical features [21, 22].

Several new attempts for classification of osteogenesis imperfecta have been suggested [23–25]. The original classification by Sillence [26] is still used on a clinical basis as it categorizes the severity of the condition in the individual child quite well: types I (mild), IV (moderate), II (lethal), and III (severe). Whereas type I patients have an increased fracture rate but deformity or final height reduction is uncommon, more severe perinatal forms (type III) present with multiple intrauterine fractures that heal with residual bony deformity leading to significant disability. The most severe form (type II) is not compatible with life due to pulmonary hypoplasia. Children with osteogenesis imperfecta can have both skeletal as well as extra-skeletal manifestations such as blue sclera, hypermobility, abnormalities of the craniocervical junction including basilar invagination, flat feet, dentinogenesis imperfecta, and hearing loss [27].

In practical terms, the diagnosis of osteogenesis imperfecta remains a possibility in any child with recurrent fractures once a secondary cause has been ruled out. Osteogenesis imperfecta is primarily based on clinical and radiological findings. In many cases, heritable bone fragility is suggested by the family history or typical physical stigmata (blue sclerae, dentinogenesis imperfecta). However, these findings are not universal even in the presence of type I collagen mutations [28]. Typical X-ray findings include vertebral fractures (VFs), scoliosis, deformities, and low bone mass, confirmed by low BMD on DXA. Material bone density on biopsy in osteogenesis imperfecta is, however, high [29], and the low BMD on DXA is only a reflection of the deficit in bone volume and mass (low tissue density), rather than a problem with bone mineralization. Genetic confirmation of the condition is not routinely sought when there is a typical family history of autosomal-dominant inheritance [30], as genetic confirmation remains expensive and currently would not change medical management.

In addition, advances in genetics have identified a number of gene defects causing early-onset osteoporosis. Mutations in PLS3, which encodes plastin 3, a bone regulatory protein, were reported in five families with early-onset X-linked osteoporosis with axial and appendicular fractures developing during childhood. Although the exact mechanism remains unknown, osteoporosis is proposed to occur secondary to defects in mechanosensing in the osteocytes, resulting in effects on bone remodeling [31].

Other forms of primary early-onset osteoporosis involve the WNT signaling pathway, which is essential for normal skeletal homeostasis by inducing osteoblast proliferation and differentia-

tion. Defects in this complex signaling pathway predominantly affect bone formation [32]. Low-density lipoprotein receptor-related protein 5 (LRP5), a co-receptor of WNT located on the osteoblast membrane, is the most widely studied. Biallelic mutations in LRP5 cause osteoporosis-pseudoglioma syndrome (OPPG), a very rare condition characterized by generalized osteoporosis and ocular involvement [33]. Heterozygous LRP5 mutations cause early-onset osteoporosis [34]. More recently, WNT1 mutations, which affect canonical WNT signaling, have been identified to cause early-onset osteoporosis in the heterozygous state and osteogenesis imperfecta in the biallelic state [35]. Several other components of the WNT signaling pathway [33], including LGR4 [36] and WNT16 [37], have also been associated with osteoporosis.

Some other rare genetic conditions (non-OI, non-WNT) associated with primary osteoporosis include cleidocranial dysplasia, Marfan, Ehlers–Danlos, and Hajdu–Cheney syndrome (HCS). Hajdu–Cheney syndrome (HCS) occurs due to NOTCH2 mutations that impair the NOTCH signaling, which is required in the differentiation and functioning of osteoblasts and osteoclasts [38]. Due to rapid advances in genetics, even the most recent list of osteoporotic conditions will never be exhaustive [39, 40].

Lastly, for several years, idiopathic juvenile osteoporosis (IJO) has been included among forms of pediatric osteoporosis, where etiology could not be recognized [41]. With the discovery of the new genetic conditions explaining many more cases of primary osteoporosis previously labeled as idiopathic juvenile osteoporosis, this diagnosis is becoming increasingly rare. Idiopathic juvenile osteoporosis (IJO) affects both sexes equally [42] and typically presents before puberty with difficulty in walking, back pain, and vertebral fractures. Decreased BMD, especially in the spine, is associated with evidence of reduced bone turnover on bone histomorphometry [43]. Although spontaneous resolution of symptoms occurs in most children, only partial resolution of lumbar spine BMD was recorded [40].

Secondary Osteoporosis in Children

Secondary causes of osteoporosis in children are much more common. Secondary osteoporosis ensues chronic systemic illnesses in children due to either the effects of the disease process on the skeleton or their treatment. With advances in medical knowledge leading to improved survival rates and long-term outcomes, complications such as secondary osteoporosis are on the rise in these children.

The impact of specific conditions on bone health has been extensively reviewed [27, 44–46]. During the course of chronic disorders, several factors may interact to induce osteoporosis other than direct bone detrimental effects of the disease or its treatment, such as prolonged immobilization, reduced time spent outdoor, and possibly consequent vitamin D deficiency, hypogonadism, and poor nutrition. Furthermore, inflammatory systemic diseases are characterized by increased levels of proinflammatory cytokines (such as tumor necrosis factor alpha, interleukin-1, and interleukin-6), which uncouple bone remodeling cycle, interfering with bone mass acquisition [2].

Childhood rheumatic diseases are associated with reduced BMD and increased risk of vertebral and nonvertebral fractures. This association is robust for juvenile idiopathic arthritis, whereas studies on juvenile systemic lupus erythematosus or juvenile dermatomyositis are more limited [47]. Glucocorticoid-associated osteoporosis is a frequent complication of childhood systemic inflammatory diseases and the most common form of secondary osteoporosis. Glucocorticoids are physiologically involved in normal bone development because of their regulation of osteoblast differentiation, probably by Wnt/b-catenin pathway and TSC22D3 [48]. On the contrary, glucocorticoid treatment directly alters bone remodeling, increasing bone resorption and decreasing bone formation, and indirectly affecting muscle tissue. Finally, glucocorticoids affect calcium homeostasis by increasing its urinary excretion and reducing gastrointestinal absorption [49]. Inhaled corticosteroids may also impact skeletal growth and bone accrual [50], particu-

larly during the first 1–2 years of treatment [51] and in children exposed before 6 years of age [52].

In contrast to extremity bones, vertebrae contain a higher proportion of trabecular bone, which is more metabolically active than cortical bone and thus more exposed to the osteotoxic effect of drugs such as glucocorticoids. Not all vertebrae are equally vulnerable, with most fractures in children located in the upper thoracic (T6/7) and lumbar spine (L1/2) [53].

Clinical Signs and Risk Factors for Osteoporosis in Children

Regardless of the etiology, the diagnosis of osteoporosis in childhood is strictly based on clinical manifestations of bone fragility. This is in concordance with the current diagnostic recommendations, which emphasize that a definition of osteoporosis in children should not be based only on DXA. In the past, DXA was the gold standard to evaluate bone health in children; currently, DXA results should be considered only when associated with an accurate clinical work-up. In 2019, the International Society for Clinical Densitometry (ISCD) [17] recommended that the diagnosis of osteoporosis in children and adolescents should not be made on the basis of densitometric criteria alone. Osteoporosis can be diagnosed in the presence of at least one vertebral compression fracture not related to local disease or high-energy trauma (regardless of densitometry measurements) or in the presence of both reduced bone mass [bone mineral content (BMC) or BMD ≤2 Z-score, taking account for bone dimensions] and a clinically significant fracture history (≥2 long-bone fractures before 10 years of age or ≥ 3 long-bone fractures during the 10–19-year period).

Children with symptomatic osteoporosis typically present with a history of recurrent low-impact fractures or moderate-to-severe backache. Asymptomatic osteoporosis is increasingly being detected through surveillance for vertebral fractures in at-risk children, such as those on high-dose glucocorticoid (GC) therapy, or through incidental osteopenia found on X-ray. While primary osteoporosis mainly occurs in an otherwise healthy child due to an underlying genetic condition, with a typical family history, secondary osteoporosis occurs as a result of chronic illness or its treatment. Therefore, to avoid unnecessary investigations, fracture history assessed by questionnaire should be confirmed evaluating medical documentation [43].

Manifestations of Vertebral Fractures
Vertebral fractures often go undetected in children for two main reasons. First, vertebral fractures can be asymptomatic [54–59], even in the face of moderate-to-severe collapse [54]. Secondly, routine surveillance with a periodic spine X-ray has not historically been signaled as an important component of osteoporosis monitoring. However, the recent ISCD position statement [60] proposed that monitoring beyond BMD is needed in at-risk children since the diagnosis of osteoporosis in children with at least one vertebral fractures no longer requires BMD criteria [18]. Furthermore, the position statement acknowledges that BMD Z-scores above −2 standard deviations (SD) do not preclude increased vertebral and nonvertebral fracture risk.

Predictors of Fractures in Children at High Risk

In recent years, there has been an effort to delineate disease-specific risk factors for osteoporosis through natural history studies by assessing the precise relationship between various illness-related factors and fractures, as well as the relationship between measurable indicators of bone health and fractures, such as BMD and back pain. These studies were reviewed in an article published by Ward et al. [40] and have provided robust results that fine-tune the clinician's ability to identify the at-risk child. Predictors of fractures in children at high risk can be stratified into vertebral and nonvertebral fractures.

Predictors of Vertebral Fractures

Review of the literature revealed a number of clinically useful predictors including glucocorticoids, leukemia, previous vertebral fracture, and underlying disease activity (Fig. 26.1).

First is the exposure to glucocorticoids that was reported as a consistent predictor of both prevalent and incident vertebral fractures. Both cumulative and average daily doses as well as glucocorticoids dose intensity ("pulse therapy") in children with leukemia [61] were predictive of vertebral fractures. Second, leukemia studies have shown that prevalent vertebral fractures around the time of initiating glucocorticoids are highly predictive of future fractures, a phenomenon referred to in adults as "the vertebral fracture cascade" [57, 61]. Third, it was found that the presence of even mild (grade 1) vertebral fractures independently predicts future fractures, highlighting the importance of identifying early signs of vertebral collapse [57]. While back pain predicted prevalent vertebral fractures, in two studies of children with glucocorticoid-treated leukemia and rheumatic disorders [21, 23], pain did not predict new vertebral fractures [61, 62]. This raises the conclusion that a lack of back pain does not rule out the presence of vertebral fractures in at-risk children. The fact that prevalent vertebral fractures around the time of glucocorticoid initiation predict future vertebral fractures attract the attention to the clinical importance of assessing the skeletal phenotype early in the child's disease course. Fourth, in children with glucocorticoid-treated rheumatic disorders, discrete clinical features in the first year were also independent predictors of future vertebral fractures, including increases in disease activity scores in the first 12 months of glucocorticoid therapy as well as increases in body mass index and decreases in lumbar spine BMD Z-scores, both tend to occur in the first 6 months of glucocorticoid therapy [62]. In children with solid organ transplantation, older age was also a consistent predictor of increased vertebral fractures risk [63–66].

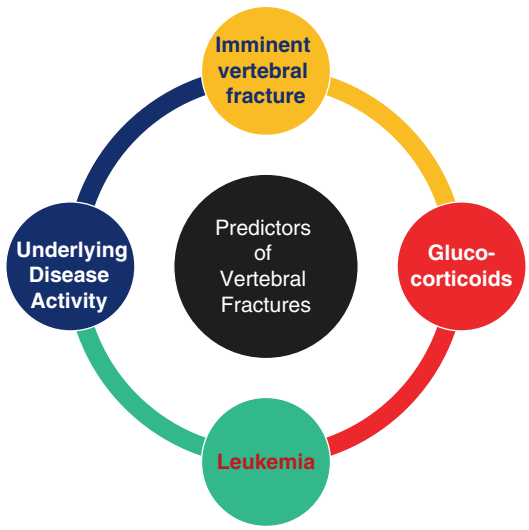


Fig. 26.1 Predictors of vertebral fractures in children: imminent vertebral fracture, glucocorticoids (cumulative, average daily dose/ pulse therapy/ inhalation), leukemia (vertebral fracture cascade, disease activity status

Predictors of Nonvertebral Fractures

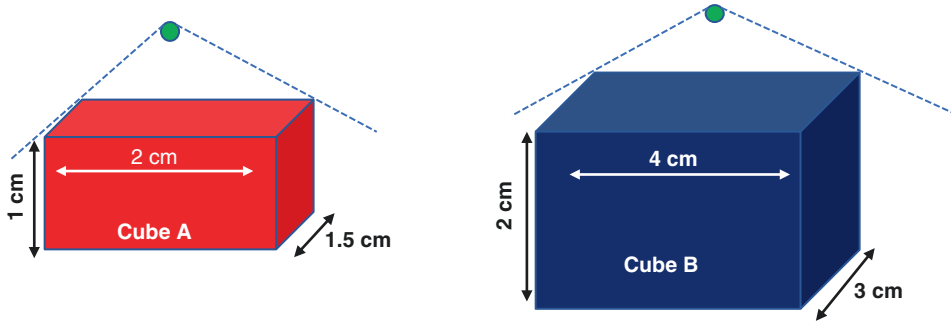
Assessment for the predictors of nonvertebral fractures in children with chronic illnesses revealed that loss of ambulation, anticonvulsant medication, and reductions in BMD at various skeletal sites are among the most consistent predictors of nonvertebral fractures in this setting. An important observation making use of lateral distal femur BMD, a frequent site of fracture in children with neuromuscular disorders, is that every 1 SD reduction in BMD Z-score at this site was associated with a 15% increase in lower extremity fractures [67].

Assessment of Bone Mass and Structure

The diagnosis of childhood osteoporosis is essentially based on the presence of fragility fractures. However, a dual-energy X-ray absorptiometry (DXA) is recommended to ensure a complete assessment of bone health and for monitoring response to therapy. To measure bone mass in children, dual-energy X-ray absorptiometry

(DXA) remains the technique of choice for its high reproducibility, availability, and for being relatively inexpensive. In addition, it is characterized by its low radiation exposure. The preferred sites for measuring bone mineral content are lumbar spine (LS) and total body less head, and measures are recorded in grams or areal BMD (in g/cm^2) [68]. BMD values for children are expressed as age- and sex-specific SD scores (Z-scores), but they also depend on body size, ethnicity, pubertal staging, and skeletal maturity. As a result of DXA's two-dimensional measurement, BMD can be grossly underestimated in children with short stature with a size below the third percentile [69, 70]. Hence, in children with short stature, BMD requires adjustment for height or bone volume such as bone mineral apparent density (BMAD, in g/cm^3) to avoid gross overestimation of osteoporosis [71]. BMAD is the most accurate method to predict vertebral fractures (Fig. 26.2) [72]. Despite its pitfalls, DXA is recommended as a monitoring tool in children with chronic disease, who are at a risk of developing osteoporosis and those who are already on treatment to guide future management [73]. An alternate technique used in children with spinal deformity or contractures is the lateral femur DXA scan [74]. A large cross-sectional study demonstrated an association of increased fracture risk (6–15%) with every 1 SD reduction in distal femur BMD [75].

Though vertebral fractures in children can present with backache, yet often they are asymptomatic. While they are a significant cause of morbidity, they are also an important indicator of future incident vertebral fractures in both chil-



	Cube A	Cube B
Area	2 cm^2	8 cm^2
Volume	3 cm^3	24 cm^3
Area^1.5	2.8 cm^3	22.6 cm^3
Mineral content	3 gm	24 g
Volumetric BMD	1 gm/cm^3	1 gm/cm^3
Areal BMD	1.5 gm/cm^2	3 gm/cm^2
BMAD	1.1 gm/cm^3	1.1 gm/cm^3

Fig. 26.2 The DXA technique analyzes the attenuation of X-rays as they pass through an area of the body. The method cannot detect the depth of the bone that is being measured, and thus is actually an "areal" density in g/cm^2 rather than a "volumetric" or Archimedean density in g/cm^3. As bones grow, the volume increases at a faster rate than the area, so the areal bone density will increase even if the volumetric density remains stable. Vertebrae are not simple cubes, but complex shapes. When measuring bone with DXA, the depth is not known. The depth of a single vertebra can be estimated as the square root of the area, which is the basis for calculating volumetric BMD. The formula is

BMC/area^1.5 (where area^1.5 is the area times the square root of the area).

BMAD probably does not predict fractures in postmenopausal women any better than areal BMD, so it is not necessary to use BMAD clinically for ordinary-sized adults. But in subjects shorter than 5 feet (150 cm), the areal BMD can be very misleading, and BMAD would be the best measure.

dren [76, 77] and adults [78]. Children also have the unique ability of bone reshaping due to their growth potential. Given their importance in the diagnosis of osteoporosis, and that they can be asymptomatic and go undetected, assessment of vertebral morphometry is essential. The lateral spine X-ray currently is the most commonly used imaging technique to evaluate vertebral fractures in children though radiation exposure is high. The Genant semiquantitative method is a technique used to grade vertebral fractures in adults [79], with good reproducibility in children [80]. The newest generation of DXA scanners allows vertebral fractures assessment (VFA) to be performed on lateral scanning. Although radiation doses vary with different scan modes in comparison to spine X-rays [81]. Vertebral fractures assessment (VFA) uses only a fraction (~1%) of radiation exposure and compares with the daily dose of natural background radiation [82]. Although vertebral fractures assessment (VFA) may not have the spatial resolution of lateral spine X-rays [83], the image quality on the new DXA scanners appears promising.

Quantitative computed tomography (QCT) and peripheral QCT (pQCT), in contrast to DXA scanning, have the advantage of measuring cortical geometry and volumetric densities of both trabecular and cortical bone; thus, they provide information not attainable through DXA. Using pQCT in children with cerebral palsy demonstrated smaller and thinner bones rather than lower cortical BMD [84]. pQCT also identified that cortical thickness, and not density, is the main bone variable affected by growth hormone deficiency and treatment [85]. Reproducibility and positioning remain a problem with pQCT. It is specifically useful for children with spinal deformities, contractures, or metallic implants, whereas DXA imaging can prove challenging in these children. The newest technique is high-resolution pQCT, which has the spatial resolution to measure trabecular geometry and microarchitectural changes resulting from treatment. However, it is an expensive, high-irradiation dose limited to imaging extremities and currently mainly used for research purposes [86].

Another method used to measure peripheral bone geometry and density is digital X-ray radiogrammetry, which estimates BMD by hand radiographs in children [87]. However, this technique, as well as quantitative ultrasound and magnetic resonance imaging, is less commonly used in clinical practice since validation studies establishing their association with vertebral fractures or nonvertebral fractures are missing.

Trans-iliac bone biopsy with tetracycline labeling provides the ultimate, invasive diagnostic information on bone material properties, bone formation, and resorption activities, as well as histomorphometry. Biopsies are useful in establishing the diagnosis and defining bone tissue characteristics and metabolic activity in some cases such as idiopathic juvenile osteoporosis (IJO) [43, 88]. However, it is used infrequently as a treatment monitoring tool in children since it requires general anesthesia, and response to therapy, in most cases, can be adequately assessed using imaging or fracture history. As such, biopsies are limited to highly specialized centers and research.

Mobility, Muscle, and Functional Tests

Increasing emphasis is being placed on improving functional outcomes, muscle strength, and mobility in children with osteoporosis. There are various functional tests used, for example, the 6-min walk test [89], Bruininks–Oseretsky Test of Motor Proficiency [90], gross motor function measure [91], Childhood Health Assessment Questionnaire score [92], and the widely used faces pain scale [93]. Specific muscle force and power tests include the chair-rise test, mechanography (legs) [94, 95], and grip strength testing by dynamometry [96]. Since these tests measure different functional variables, selection depends on disease-specific or case-specific deficits and protocols need to be established.

DXA Scan Technical Aspects

Principles of Operation DXA technique relies on the differential absorption of X-rays of two different energy levels to distinguish tissues of different radiographic density. At low energy (30–50 keV), bone attenuation is greater than soft tissue attenuation, whereas at high energy (greater than 70 keV), bone attenuation is similar to soft tissue attenuation. Utilizing this data and a mathematical algorithm, bone mass, soft tissue mass, and bone mineral content can be quantified. DXA quantifies (in grams) the BMD and BMC at various body sites.

Unlike other density measurements, however, the DXA-derived BMD is not a true volumetric measure as it is based on the two-dimensional X-ray projected area of a three-dimensional structure (i.e., areal BMD). The third dimension, depth, is not directly measured because it is in the same direction of the X-ray. This fact contributes to inherent error in the DXA process (Fig. 26.2) [97].

In addition, growth of individual bones over time is not uniform in three dimensions. Consequently, inherent error caused by serial measurements of aBMD in the growing pediatric skeleton makes comparison of follow-up with baseline DXA studies more challenging to interpret in pediatric patients.

DXA Performance Positioning the patient and selecting regions of interest (ROI) require precision by the technologist performing the scan and careful evaluation by the radiologist interpreting DXA results [97, 98]. The ISCD Official Position for DXA performed on children and adolescents (males and females 5–19 years) indicates that, when technically feasible, the lumbar spine and whole-body (WB) aBMD and BMC should be performed as these measures are the most accurate and reproducible skeletal sites for performing aBMD and BMC [17].

The lumbar spine should be straight and centered in the image, with the last rib pair and the upper sacrum visualized. The ROIs are generated automatically using edge detection software and are selected for the L1 to L4 vertebral segments. Artifact, including enteric tubes, orthopedic hardware, and jewelry, should be excluded from the image if possible as artifact contributes to false elevation especially of aBMD numeric results and Z-score for any ROI that includes such objects.

In contrast, the BMC value is not felt to be as affected by the presence of artifacts. If the artifact cannot be removed and obscures the spine, one vertebral body can be excluded and aBMD of the lumbar spine is still considered a reliable measure. If evaluation of the spine is not feasible because of extensive orthopedic hardware or patient positioning issues, DXA of the forearm or distal femur may be performed and serve as a surrogate measure of aBMD [17].

Though lumbar spine and whole-body aBMD and BMC are considered the gold standard measures for initial assessment and follow-up of bone density, the current ISCD position prefers total body less head (TBLH) aBMD or BMC. Using this technique, the calvarium is excluded from whole-body measures due to (1) the high contribution of the relatively static head to whole-body aBMD and BMC during growth of the remainder of the axial and appendicular skeleton and (2) the importance of the postcranial skeleton in fracture risk assessment. In growing children, the hip is not a reliable site for measurement of aBMD given the significant variability in skeletal development and lack of reproducible ROIs [17, 99].

DXA Technicalities, Interpretation, and Reporting in Children and Adolescents

The ISCD 2019 [17] official position outlined its recommendations for the assessment of BMD outcome and its interpretation in children and adolescents with disease that may affect the skeleton, which include the following:

- DXA measurement is part of a comprehensive skeletal health assessment in patients with increased risk of fracture.
- In patients with primary bone disease, or at risk for secondary bone disease, a DXA should

be performed when the patient may benefit from interventions to decrease their elevated risk of a clinically significant fracture, and the DXA results will influence that management.
- The posterior–anterior (PA) spine and total body less head (TBLH) are the preferred skeletal sites for performing BMC and areal BMD measurements in most pediatric subjects. Other sites may be useful depending on the clinical need.
- Soft tissue measures in conjunction with whole-body scans may be helpful in evaluating patients with chronic conditions associated with malnutrition or with muscle and skeletal deficits.
- Proximal femur DXA measurements can be used, if reference data are available, for assessing children with reduced weight bearing and mechanical loading of the lower extremities or in children at risk for bone fragility who would benefit from continuity of DXA measurements through the transition into adulthood.
- DXA measurements at the 33% radius (also called 1/3 radius) may be used clinically in ambulatory children who cannot be scanned at other skeletal sites, provided adequate reference data are available.
- Lateral distal femur (LDF) DXA measurements, if reference data are available, correlate well with increased lower extremity fragility fracture risk in nonambulatory children.
- Lateral distal femur (LDF) DXA can
  - Assess BMD in children when the presence of nonremovable artifacts (orthopedic hardware, tubes), positioning difficulties, abnormal skeletal morphometry, or severe scoliosis with torsion interferes with DXA acquisition at other anatomical sites.
  - Monitor the effects of changes of weight-bearing in nonambulatory children.
- Precision assessment at each skeletal measurement site should be calculated in a sample representative of the patient population being evaluated.
- If a follow-up DXA scan is indicated, the minimum interval between scans is 6–12 months.
- In children with short stature or growth delay, spine and TBLH BMC and areal BMD results should be adjusted. For the spine, adjust using either BMAD or the height Z-score. For TBLH, adjust using the height Z-score.
- An appropriate reference data set must include a sample of healthy representatives of the general population sufficiently large to capture variability in bone measures that takes into consideration gender, age, and race/ethnicity.
- When upgrading densitometer instrumentation or software, it is essential to use reference data valid for the hardware and software technological updates.
- Baseline DXA reports should contain the following information:
  - DXA manufacturer, model, and software version
  - Referring physician
  - Patient age, gender, race ethnicity, weight, and height
  - Relevant medical history including previous fractures
  - Indication for study
  - Tanner stage or bone age results if available
  - Technical quality
  - BMC and areal BMD + BMC and/or areal BMD Z-score
  - Source of reference data for Z-score calculation
  - Adjustments made for growth and interpretation
  - Recommendations for the necessity and timing of the next DXA study are optional
- Serial DXA reports should include the same information as for baseline testing. Additionally, indications for follow-up scan, technical comparability of studies, changes in height and weight, and change in BMC and areal BMD Z-scores should be reported.
- Terminology:
  - T-scores should not appear in pediatric DXA reports.
  - The term "osteopenia" should not appear in pediatric DXA reports.
  - The term "osteoporosis" should not appear in pediatric DXA reports without a clinically significant fracture history.
  - "Low bone mineral mass or bone mineral density" is the preferred term for pediatric

DXA reports when BMC or areal BMD Z-scores are less than or equal to −2.0 SD.

Vertebral Fracture Assessment (VFA) in Pediatric Patients

- DXA VFA may be used as a substitute for spine radiography in the identification of symptomatic and asymptomatic vertebral fracture.
- The Genant semiquantitative method should be used for vertebral fracture assessment (VFA) in children.
- Following VFA, additional spine imaging should be considered in the following circumstances:
  - Vertebrae that are technically unevaluable by vertebral fracture assessment (i.e., not sufficiently visible), provided the detection of a vertebral fracture would change clinical management.
  - Assessment of a single, Genant grade 1 vertebral fracture if confirmation of a grade 1 vertebral fracture alone would change clinical management.
  - Radiographic findings that are not typical for an osteoporotic vertebral fracture (e.g., suspected destructive inflammatory or malignant processes, congenital malformations, acquired misalignments or dislocations).

Densitometry in Infants and Young Children

- DXA is an appropriate method for clinical densitometry of infants and young children.
- DXA lumbar spine measurements are feasible and can provide reproducible measures of BMC and aBMD for infants and young children 0–5 years of age.
- DXA whole-body measurements are feasible and can provide reproducible measures of BMC and aBMD for children ≥3 years of age.
- DXA whole-body BMC measurements for children <3 years of age are of limited clinical utility due to feasibility and lack of normative data. Areal BMD should not be utilized routinely due to difficulty of inappropriate positioning.
- Forearm and femur measurements are technically feasible in infants and young children, but there is insufficient information regarding methodology, reproducibility, and reference data for these measurement sites to be clinically useful at this time.
- In infants and children below 5 years of age, the impact of growth delay on the interpretation of the DXA results should be considered, but it is not quantifiable presently.

Table 26.2 shows the ISCD recommendations regarding the DXA nomenclature and the preferred number of decimal digits.

When Osteoporosis Should Be Suspected?

Factors that contribute to osteoporosis in children and adolescents can be either genetic or in association with another systemic disorders. Lifestyle factors can also contribute to bone thinning. In children suffering from chronic diseases or receiving medications able to exert negative impact on bones particularly if administered for a prolonged period of time, several factors can enhance bone resorption and decrease bone formation converging with net result of increased bone fragility [2,

Table 26.2 The ISCD 2019 official position statements [17] regarding DXA nomenclature and the preferred number of decimal digits

DXA nomenclature		
DXA – not DEXA		
T-score – not T score, t-score, or t score		
Z-score – not Z score, z-score, or z score		
DXA	*Decimal digits*	*Preferred number of decimal digits for DXA reporting*
BMD	Three digits	Example, 0.927 g/cm^2
T-score	One digit	Example, −2.3
Z-score	One digit	Example, 1.7
BMC	Two digits	Example, 31.76 g
Area	Two digits	Example, 43.25 cm^2
% reference database:	Integer	Example, 82%

100]. For this reason, bone health must be assessed at baseline and during follow-up, adopting adequate preventive measures.

There is no universal consensus regarding when and how to assess bone health for all of the pathologies involved. However, there are some clinical guidelines for different pediatric disorders that were reviewed in a recent article [101] and shown in Table 26.3. BMD in patients with chronic diseases should be monitored

Table 26.3 Framework for BMD assessment in chronic medical conditions or long-term therapy precipitating for secondary osteoporosis in children

Disease/ treatment	BMD assessment
Glucocorticoids therapy	Baseline DXA evaluation in patients with prolonged systemic GCs exposure exceeding ≥0.15 mg/kg daily for ≥3 months. Repeat on an annual basis including VFA or lateral radiograph if Z-score < −2 and with ongoing glucocorticoids exposure [102].
Diabetes mellitus	DXA if Low BMD-specific risk factors Increased daily insulin doses Impaired renal function Fracture history [103]
Juvenile idiopathic arthritis (JIA)	< 6 years: DXA in the presence of fragility fractures. > 6 years: DXA if not presenting rapid remission of JIA or in need of high doses of GCs [104].
Systemic lupus erythematosus	DXA evaluation in patients with prolonged systemic GCs exposure exceeding ≥0.15 mg/kg daily for ≥3 months. Repeat on an annual basis if Z-score ≤ −2 [102].
Celiac disease	DXA if No adequate dietary adherence Irregular menstruation Anemia Other risk factors for fractures [103]
Cerebral palsy	Difficult lumbar spine X-ray interpretation in cases of severe scoliosis. Total body or distal femur DXA (area with higher fracture risk) only if there are fragility fractures [105].
Duchenne muscular dystrophy	Baseline DXA and annual monitoring. Lateral spine x-ray: Baseline On GCs treatment: repeat every 1–2 years. Not on GCs treatment: repeat every 2–3 years. If back pain or ≥ 0, 5 SD decline in spine BMD Z score on serial measurements over 12-month period: repeat. Refer to osteoporosis specialist following the first fracture [106].
Rett syndrome	Baseline DXA and serial controls according to individual risk [107].
Epilepsy	Consider DXA for epileptic patients receiving antiepileptic drugs for a prolonged period [108].
Thalassemia	DXA every 2 years from adolescence [109].
Inflammatory/systemic disease	Consider DXA for patients receiving high doses of GCs [103].
Neoplasms	Baseline DXA 2 years after completing chemotherapy with osteotoxic drugs; e.g., MTX, GCs, or hematopoietic cells transplantation; or secondary effects that favor osteoporosis development (growth hormone deficiency, hypogonadism, etc.). DXA follow-up based on the results of baseline DXA and persistent risk factors [110].
Cystic fibrosis	DXA in children ≥ age 8 if Weight < 90% ideal weight FEV1 < 50% Delayed puberty High doses of GCs > 90 days per year At 18, all of them [111].
Anorexia nervosa	DXA in patients with amenorrhea for more than 6 months [108].

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based on the existing guidelines for each disorder. In addition, special attention must be paid to patients suffering from chronic diseases and receiving treatment that may favor the development of osteoporosis; for example, glucocorticoids (GCs), chemotherapy, or antiepileptic drugs.

Laboratory Tests

The diagnosis of secondary osteoporosis is usually made after the initial diagnosis of the underlying disease, which causes it, is made. However, in some cases, it may be the first manifestation of the underlying disease. Although most of the disorders included in the differential diagnosis can be inferred by means of a thorough medical history review and physical examination, some pathologies, for example, phosphocalcic metabolism alterations, hypothyroidism, or some types of leukemia, can be paucisymptomatic and require complementary tests for accurate diagnosis [2]. For this reason, it is recommended to perform some extra laboratory testing when assessing a child with suspected or established diagnosis of secondary osteoporosis (Table 26.4) [27, 112].

Bone turnover markers are specific substances released into the bloodstream during bone formation or resorption that reflect bone metabolic activity at a given time. Examples are amino-terminal propeptides from type 1 procollagen (P1NP) and carboxy-terminal telopeptides (CTx), which have been proposed to be used as reference markers to evaluate formation and resorption, respectively [113, 114]. These can be measured in the blood and urine [115], although for children it is preferable to determine them in plasma [116, 117]. In adults, they have been shown to be useful for monitoring treatment in patients with osteoporosis [118]. In children, however, such interpretation is much more complex [119], although they can help in monitoring antiresorptive therapy compliance and measuring its effectiveness [99].

Table 26.4 Basic lab tests for children with secondary osteoporosis as well as analytical determinations to make based on clinical suspicion

Basic diagnostic laboratory tests	
Lab test	Tests to be assessed
Blood count	Full blood count
Blood chemistry	Calcium, ionized calcium, phosphorus, magnesium, total proteins, creatinine, urea, glucose, 25-hydroxyvitamin D3, PTH, TSH, free T4
24-hour urine chemistry	Calcium, phosphorus, creatinine, tubular Phosphorus reabsorption, sodium
Urine screening	Ca/creatinine[a]
Bone turnover makers	Total alkaline phosphatase
Tests carried out based on clinical suspicion	
Immunoglobulins	
Anti-transglutaminase IgA antibodies	
Cortisol	
Prolactin	
FSH, LH, testosterone	
Homocysteine	
Genetic studies (genes related to osteogenesis imperfecta and disorders characterized by bone fragility)	

[a]Sample from a single urination, preferably first one in the morning

Making the Diagnosis of Osteoporosis in Children

In 2019, the International Society for Clinical Densitometry (ISCD) released a position statement to guide physicians in assessing bone health in children, interpreting densitometric data, and making the diagnosis of osteoporosis in children [17]. Fracture history should be regarded as indicative for osteoporosis in the case of one or more vertebral fractures, in the absence of local disease or high-energy trauma. In such children and adolescents, measuring BMD adds to the overall assessment of bone health. In the absence of vertebral compression (crush) fractures, the diagnosis of osteoporosis is indicated by the presence of both a clinically significant fracture history and BMD Z-score ≤ -2.0. A clinically

significant fracture history is one or more of the following: (1) two or more long-bone fractures by age 10 years and (2) three or more long-bone fractures at any age up to age 19 years.

Therefore, DXA is still necessary to make a diagnosis of osteoporosis in otherwise healthy children with history of long-bone fractures. In these children, a low BMD or BMC Z-score of −2.0 or lower is a mandatory criterion for making a diagnosis of osteoporosis due to the high frequency of long-bone fracture in healthy children. However, a BMC/BMD Z-score > −2.0 does not preclude the possibility of skeletal fragility and increased fracture risk.

Low back pain has shown low sensitivity in children with vertebral fracture; therefore, in children known to be at risk of fracture, active surveillance is required. Lateral thoracolumbar spine radiograph with vertebral assessment by Genant semiquantitative method is the most common imaging modality to assess spine health. However, this modality is associated with a high dose of ionizing radiation; to reduce exposure, vertebral fracture analysis (VFA) by DXA has been proposed as noted earlier in this chapter.

Bone Health Monitoring in at-Risk Children

The ultimate goal of monitoring is to identify high-risk patients for intervention that will prevent the first fracture. However, lack of available data to support such primary prevention has instead led to monitoring that identifies early rather than late signs of osteoporosis, followed by bone-active treatment in those with limited potential for spontaneous recovery (including vertebral body reshaping). This is in line with a secondary prevention approach, which seeks to mitigate the progression of the osteoporosis following identification in its earlier stages [40].

Two important observations have shifted monitoring away from a BMD-centric to a more functional approach: (1) the use of a BMD Z-score threshold to identify a child is problematic due to variability in the Z-scores generated by the different available normative databases [120–122], and (2) asymptomatic vertebral fracture (VF) can occur at BMD Z-scores > − 2, thereby requiring imaging surveillance for vertebral fracture detection. Other functional outcomes that should also be tracked during monitoring including history of nonvertebral fracture, growth, pubertal status, pain, mobility, muscle strength, and the potential for spontaneous recovery (vertebral body reshaping and bone density restitution). BMD remains a vital part of the bone health monitoring approach but as an adjuvant tool to chart the child's BMD trajectory, thereby signaling a child who is losing ground and therefore at increased risk for fractures, or who is showing signs of recovery following a transient bone health threat (potentially obviating the need for osteoporosis treatment).

Patients expected to be glucocorticoid-treated for ≥3 months should be considered for a baseline spine radiograph [or high-quality dual-energy X-ray absorptiometry (DXA)-based vertebral fracture assessment (VFA), if available] at the time of glucocorticoids initiation. Three months or more is the recommended cutoff time since the earliest incident vertebral fracture reported after glucocorticoids initiation in children is at 4 months [59]. Children meeting the criteria for baseline spine imaging should also undergo a follow-up radiograph at 12 months since this is the time point with the highest annual incidence of vertebral fracture in many glucocorticoids-treated children [59, 61]. Annual to biannual imaging for vertebral fracture is advised thereafter for those with ongoing glucocorticoids exposure.

Among children with other risk factors for bone fragility apart from glucocorticoids exposure, the same principles apply; that is, the patient should be assessed for both nonvertebral fracture and vertebral fracture since glucocorticoids-naive children with mobility issues and genetic bone fragility can also develop vertebral fracture [123]. In youth with impaired mobility due to cerebral palsy and congenital myopathies, a spine radiograph is recommended at the latest by about 6–8 years of age and then at intervals thereafter until the end of growth, or sooner in the presence of back pain. Monitoring is recommended to start by this time since treatment should be initiated

before there is insufficient residual growth potential for vertebral body reshaping.

Since BMD is useful as a serial measurement to assist the clinician in understanding the child's overall bone health trajectory and in making logical decisions about the need for ongoing monitoring, discharge from bone health care or intervention, it is recommended that a BMD is carried out at least as frequently as spine radiographs according to the above guidelines, with assessments every 6 months in those children at greatest risk [17].

Monitoring of Vertebral Fractures

The most widely used tool for the assessment of vertebral fracture (VF) in both children and adults is the Genant semiquantitative method [124, 125]. According to the Genant method, the definition of a VF is ≥20% loss in vertebral height ratio regardless of the VF morphology. Vertebral fractures are subjectively graded by trained readers according to the magnitude of the reduction in vertebral body height ratios, without direct measurement. Vertebral height ratios are generated when the anterior vertebral height is compared with the posterior height (for an anterior wedge fracture), middle height to the posterior height (biconcave fracture), and posterior height to the posterior height of adjacent vertebral bodies (crush fracture) (Figs. 26.3 and 26.4). The Genant scores correspond to the following reductions in height ratios: grade 0 (normal), <20%; grade 1 fracture (mild), ≥20 to 25%; grade 2 fracture (moderate), >25 to 40%; and grade 3 fracture (severe), >40%. Overall, the Genant semiquantitative method is preferred over quantitative (six-point) vertebral morphometry [126] since it is faster and takes into consideration the expertise of an experienced reader. In addition, the Genant scoring system permits calculation of the Spine Deformity Index (SDI), the sum of the Genant grades along the length of the spine [40]. The SDI is a global index of spine

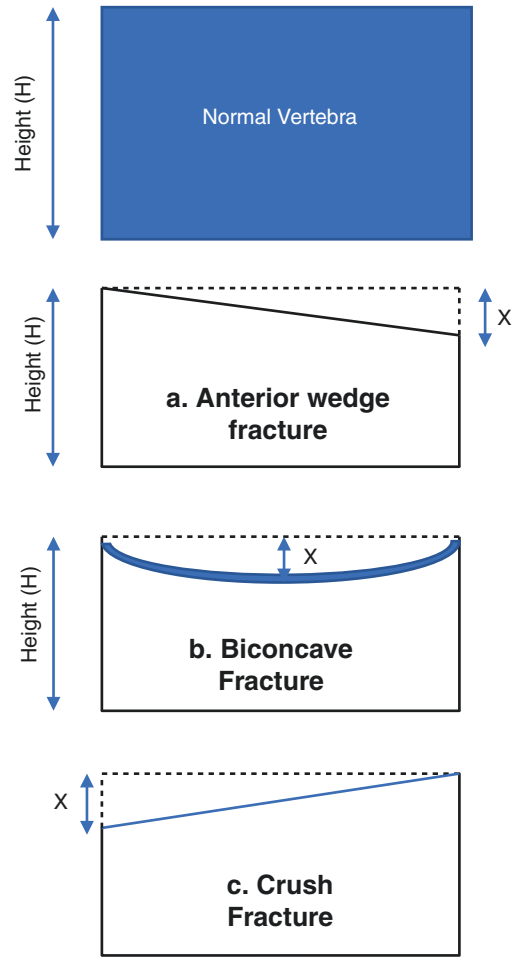

Fig. 26.3 Genant semiquantitative assessment: loss of the vertebral body height is visually estimated as a ratio of a reference vertebral body height for each of the three locations on a vertebral body, anterior, middle, and posterior. (**a**) The loss of anterior vertebral body height designated X is assessed in relation to the posterior height of the same vertebral body designated H. (**b**) Loss of middle vertebral body height is similarly evaluated in comparison to the posterior vertebral height of the same vertebral body. (**c**) Loss of posterior vertebral body height is assessed in comparison to the posterior body of the vertebra above and below. In the case of T4 and L4, only one adjacent vertebra is available as the complete assessment is from T4 to L4. The Genant method defines VF according to the following reduction in height ratios: grade 0 (normal) ≤20%; grade 1 fracture (mild) >20% to 25%; grade 2 fracture (moderate) >25% to 40%; grade 3 fracture (severe) >40% [59, 61]

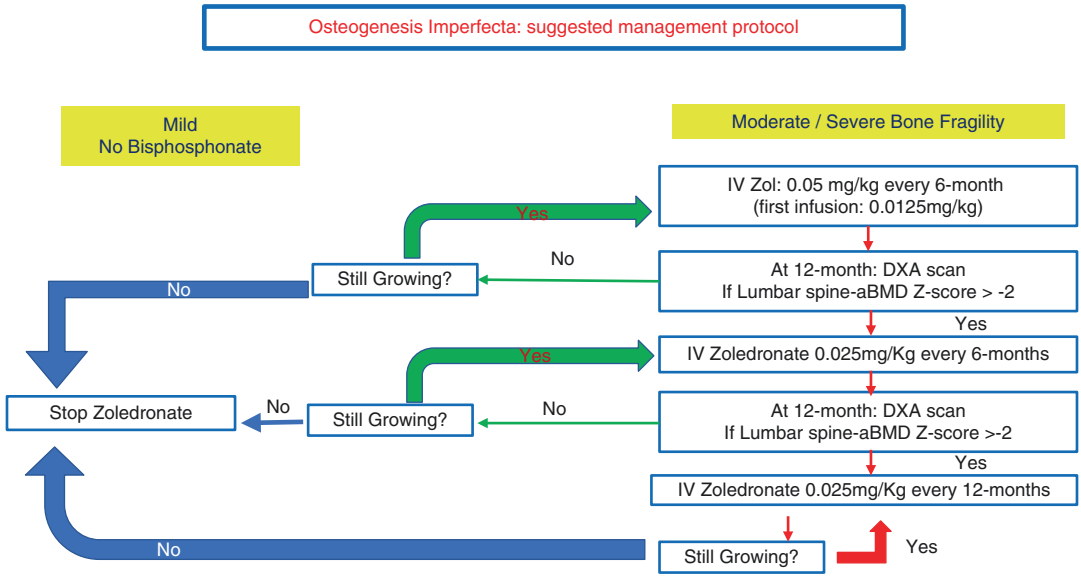

Fig. 26.4 Suggested algorithm for the management of osteogenesis imperfecta

morbidity that is useful clinically and can be used as a continuous outcome variable in research studies [127]. The kappa statistics for intra- and interobserver agreement are similar for children compared to adults using the Genant semiquantitative method [79, 124, 128].

To date, the most common imaging tool for vertebral fracture (VF) detection in childhood is lateral thoracolumbar spine radiographs. In view of the high radiation exposure from spine radiographs but nevertheless critical need for vertebral fracture (VF) assessments as part of bone health evaluations, nonradiographic imaging techniques have been developed which use the scoring methods described above. The use of DXA to diagnose vertebral fracture, known as vertebral fracture assessment (VFA), is carried out using images captured on a lateral spine view. Vertebral fracture assessment is attractive as an assessment tool given its minimal radiation and the fact that fan-beam technology facilitates the capture of the entire spine on a single image without divergent beam issues. Newer DXA machines have a rotating "C-arm," which obviates the need to reposition the patient from the supine to lateral position. However, in general, image quality varies significantly depending on the densitometer [129].

Spontaneous Recovery from Osteoporosis in the Absence of Osteoporosis Therapy

The pediatric skeleton is a dynamic structure with the distinct capability not only to reclaim BMD lost during transient bone health affection but to reshape fractured vertebral bodies through the process of skeletal modeling. Both indices are important measures of recovery in children, either spontaneously or following osteoporosis therapy (e.g., bisphosphonate treatment). Vertebral body reshaping appears to be growth-mediated since it has never been unequivocally reported in adults [130].

Vertebral body reshaping is a clinical phenomenon that is unique to children compared to adults. Restoration of normal vertebral dimensions (vertebral body reshaping) is a growth-dependent phenomenon that results from endochondral bone formation (growth of the vertebral body in height) and periosteal opposition (growth of the vertebral body in width). Therefore, it is extremely important to recognize those children with the potential for vertebral body reshaping. Vertebral body reshaping has been consistently described in children with osteogenesis imperfecta undergoing bisphospho-

nate therapy [131]; however, bisphosphonate-independent reshaping in children with transient threats to bone health and vertebral collapse (e.g., post-glucocorticoids cessation of children with rheumatic disorders) has been reported [40]. Reshaping of the fractured vertebrae was reported also during leukemia chemotherapy (i.e., during high-dose glucocorticoids therapy) (which has been attributed to the saltatory pattern of glucocorticoids exposure with current treatment protocols. Therefore, it has been suggested that bisphosphonate therapy does not directly bring about reshaping but rather has a permissive effect by optimizing BMD in order to prevent further collapse. However, it has to be noted that vertebral reshaping occurs only when bisphosphonate therapy is administered to patients during the growth phase [129].

Vertebral body reshaping after vertebral fracture is a frequently overlooked treatment goal. Furthermore, this phenomenon underscores the critical importance of treating signs of vertebral collapse earlier rather than later, so that treatment can be administered as far in advance of epiphyseal closure as possible [133].

The Management of Osteoporosis in Children

Goals of Treatment

Osteoporosis and fractures in children can lead to significant morbidity and reduce quality of life. The primary goals of management of osteoporosis are prevention of fractures including vertebral fractures and scoliosis as well as improvement in the child's function, mobility, and pain. The inclusion of improvement in function, mobility, and speedy rehabilitation as outcomes treatment measures represents a new era of osteogenesis imperfecta (OI) and pediatric osteoporosis management [134]. Rare diseases like osteogenesis Imperfecta require multidisciplinary teams in tertiary centers, consisting of pediatric bone specialists, orthopedic surgeons, geneticists, physiotherapists, occupational therapists, social workers, and nurse specialists. They are essential to facilitate timely rodding surgery to prevent worsening disability due to recurrent lower limb fractures, provide novel walking aids and ways to improve independence and mobility, as well as make timely decisions to start and stop bone-active therapy.

Another treatment goal in children is improvement in vertebral shape. Vertebral fractures cause back pain, kyphosis, immobility, and height loss. Children are different from adults as growth and puberty are continuously elongating, widening, and strengthening their bones. Specific for children is the ability for reshaping of fractured vertebrae [131, 132, 135, 136], a phenomenon explained by continuous bone formation during halted resorption. Reshaping of the fractured vertebrae may occur in association with bisphosphonate therapy or spontaneously in secondary osteoporotic conditions during remission. Therefore, it is important to better understand the factors associated with spontaneous healing to avoid unnecessary treatment [137].

General Measures for Optimization of Bone Health

First-line measures to optimize bone health can be stratified into three main categories: nutrition, physical activity, and treatment of the underlying condition, as well as its associated comorbidities [138–144]. The most well-described nutritional factors for bone health are vitamin D and calcium; however, a number of other nutrients also play a role in bone metabolism, including protein, potassium, magnesium, copper, iron, fluoride, zinc, and vitamins A, C, and K. Children with chronic illnesses are at particular risk for vitamin D deficiency due to limited sun exposure, malabsorption, and dietary restrictions. Youth with eating disorders (such as anorexia nervosa) or malabsorption (short gut syndromes, celiac disease, Crohn's and exocrine pancreatic disorders) can present with extensive nutritional compromise including lack of essential dietary proteins, fats, fat-soluble vitamins, and mineral ions requiring the expertise of dieticians and gastroenterologists specializing in the underlying

disease and childhood nutrition [145]. Secular trends in dietary habits also appear to have an adverse effect on bone health, with high intake of sugar-sweetened drinks associated with an increased fracture risk [143].

Calcium and Vitamin D Supplementation

Calcium and vitamin D supplementation has not shown any clinically significant effect on BMD in studies performed in healthy children [146]. In contrast, some studies have reported a favorable effect in children with chronic diseases that favor osteoporosis such as cerebral palsy [132]. On the other hand, no side effects have been reported [105, 147]. Thus, although there are no studies that assess the effect of supplementation on the incidence of fractures, calcium supplementation is considered advisable in children and adolescents with low BMD or osteoporosis, especially in those patients with a low dietary intake.

Likewise, ensuring proper vitamin D3 intake (400–600 IU/day) is recommended in order to maintain the plasma levels of 25-hydroxyvitamin D3 higher than 50 nmol/l (20 ng/dL). The optimal intake for children with disorders that may interfere with intestinal absorption or modify calcium metabolism remains unknown [41]. Thus, initially, supplementation should be prescribed with respect to these recommendations and subsequently be modified according to plasma 25-hydroxyvitamin D3, intact parathormone (iPTH) [intact PTH (iPTH) is the biologically active form of parathyroid hormone and is secreted when the calcium level is low], and calciuria, which should be monitored every 6–12 months [99].

Bisphosphonates

Bisphosphonates are synthetic analogues of pyrophosphate and widely used in the management of both primary and secondary osteoporosis. They selectively concentrate in skeleton areas where high remodeling rates are located [148]. Their primary effect is to inactivate osteoclasts. With bone resorption inhibited, bone formation and growth continue, resulting in cortical and trabecular bone thickening, leading to wider, denser, and stronger bones. They are hydrophilic drugs with low intestinal absorption (< 1%) and high distribution volumes that are excreted in urine. Thus, dosages must be adjusted according to glomerular filtrate. Moreover, they are characterized by a very slow elimination from bone tissue and remain in the body for years after treatment [148].

Knowledge on the mid- and long-term safety of these drugs is constantly increasing. Thus, some authors recommend their use as long as osteoporotic criteria are met, particularly in those patients with long bones and vertebral fractures and who exhibit poor potential for spontaneous recovery (age at puberty, risk factor persistence, etc.) [149].

To date, bisphosphonates have only been prescribed as a secondary prevention measure, meaning that once the first fracture occurs. Their use is intended to prevent the appearance of new fragility fractures. Research studies revealed that they confer a positive effect on BMD [150–153], and there is increasing knowledge regarding their long-term safety [2]. On the other hand, if the peak bone mass reached at the end of the growth stage is not optimal, it is more likely that the children will develop osteoporosis at later stages of life. On the basis of the above data, a recent expert panel consensus [99] recommends that clinicians consider treatment with bisphosphonates for those patients without osteoporosis, but low BMD in early puberty, with low Z-scores. In any case, bisphosphonates are used off label in childhood osteoporosis, so informed consent must be obtained when they are prescribed.

Various bisphosphonate preparations are available for either oral or parenteral administration. Intravenous pamidronate is still most widely used in children despite the lack of randomized controlled trials and consensus regarding dosage, duration of treatment, and limited information on long-term safety. The original pamidronate study recommended a dose of 0.5–1 mg/kg per day administered over 3 days every 3 months [154–

156]. More recently, shorter, as well as low-dose pamidronate, protocols [157, 158] have been used. Other intravenous bisphosphonates such as neridronate and zoledronate, which have the benefit of higher potency and less frequent administration compared to pamidronate, have been also assessed for children with osteoporosis. Intravenous infusions of zoledronate (0.025–0.05 mg/kg per day, commonly given over 30 min as a single dose, every 6 months) were reported to be associated with improvement in bone mass and subsequent reduction in fracture risk [159–162]. Similarly, intravenous neridronate (2 mg/kg per day over 30 min every 6 months) improves BMD and reduces fracture rates [163].

Oral bisphosphonates are widely used in adulthood osteoporosis, and some studies have demonstrated that they increase BMD in patients with osteogenesis imperfecta. Nevertheless, in contrast to intravenous bisphosphonates, they lack sufficient potency to induce remodeling after vertebral fracture [164] and are contraindicated in patients with esophagitis risk factors, for example, gastroesophageal reflux or hiatal hernia. Recent studies in children with osteogenesis imperfecta have demonstrated increased BMD using oral risedronate [165] and olpadronate [164]. Oral alendronate increased BMD in children with moderate to severe osteogenesis imperfecta, but no change in fracture risk was identified [166]. Therefore, intravenous bisphosphonates are preferred for pediatric osteoporosis, and oral bisphosphonates are only used for patients with mild forms of osteoporosis, without vertebral fractures [165], and in those who are particularly needle phobic or refuse IV bisphosphonate treatment, or when intravenous administration is contraindicated for any reason, or during the treatment maintenance phase [160].

Table 26.5 shows doses and dosing intervals for the most commonly used bisphosphonates in pediatrics [160]. However, it has to be noted that the optimal treatment duration is not clearly defined and is currently based on expert recommendations [165]. It is advised to discontinue or progressively decrease bisphosphonates dosing for those patients who have not presented fractures during the preceding year and who have attained a Z-score higher than −2 [99].

Table 26.5 Doses and dosing intervals for the most commonly used bisphosphonates in pediatrics

Medication	Route of administration	Dose
Pamidronate (second generation)	Intravenous (dilute in 100–250 ml physiological saline solution, in 3–4 hours)	< 1 year: 0. 5 mg/kg every 2 months 1–2 years: 0. 25–0. 5 mg/kg/day 3 days every 3 months 2–3 years: 0.375–0.75 mg/kg/day 3 days every 3 months > 3 years: 0. 5–1 mg/kg/day 3 days every 4 months Maximum dose: 60 mg/dose and 11. 5 mg/kg/year
Neridronate (third generation)	Intravenous (dilute in 200–250 ml physiological saline solution, in 3 hours	1–2 mg/kg/day every 3–4 months
Zolendronate (third generation)	Intravenous (dilute in 50 ml physiological saline solution, in 30–45 min)	0.0125–0.05 mg/kg every 6–12 months (maximum dose 4 mg)
Alendronate (second generation)	Oral	1–2 mg/kg/week < 40 kg: 5 mg/day or 35 mg/week > 40 kg: 10 mg/day or 70 mg/week Maximum dose: 70 mg/week
Risedronate (third generation)	Oral	15 mg/week (< 40 kg); 30 mg/week (> 40 kg) Maximum dose: 30 mg/week

The common side effects reported with bisphosphonates include the typical acute-phase reaction following the first dose, which occur in about 85% of the children. This is characterized by fever, malaise, diarrhea, nausea, and myalgia [167]. It usually occurs within 72 hours of the infusion but rarely with subsequent doses. Antiphlogistics (anti-inflammatory therapy) [168] as well as oral steroid [169] cover following the first bisphosphonate infusion may reduce the extent of first phase reaction. Transient hypocalcemia, hypophosphatemia, and a rise in C-reactive protein may be observed but are rarely

of clinical significance. However, correction of preexisting vitamin D deficiency prior to commencing bisphosphonate therapy and supplementation of calcium before and after the first infusion is recommended [148]. While the benefits of bisphosphonate therapy are undisputed, potential late effects of long-term, continuous bisphosphonate treatment remain a concern. The antiresorptive effect of bisphosphonate therapy shuts down remodeling, therefore inhibiting normal bone repair with a risk of increased bone stiffness, microcracks, delayed healing of osteotomies in children [170], and atypical femoral fractures in adults [171]. Bisphosphonates also interfere with the growth plate, causing horizontal lines of unresorbed, calcified hypertrophic chondrocytes to move into the metaphyses of long bones with every infusion, and also impair normal metaphyseal inwaisting, leading to abnormally wide and undertubulated long-bone metaphyses [172]. Given these concerns on potential "late effects of bisphosphonate therapy in childhood," more evidence is needed to assess whether "treatment holidays," switching from treatment to maintenance intravenous regimens with less frequent cycles, or oral bisphosphonate may be safer or beneficial to avoid oversuppression of remodeling.

Side effects currently only described in adults include osteonecrosis of the jaw, often seen in metastatic bone disease [173], and renal failure [174], in particular with more potent bisphosphonate. However, to date there are no such reports in children or osteogenesis imperfecta patients of any age [175]. Although the use of bisphosphonates in pregnancy is not recommended, reviews on the unintentional use have not demonstrated serious adverse effects [176–178].

What About Nonosteogenesis Imperfecta Primary and Secondary Osteoporosis?

While osteogenesis imperfecta is routinely managed with bisphosphonate use, the evidence of this treatment in children with nonosteogenesis imperfecta primary, or secondary osteoporosis, in particular those with low-bone turnover, is very sparse. Low-bone formation/turnover conditions, such as immobility-induced osteoporosis [Duchenne muscular dystrophy (DMD) or cerebral palsy] or osteoporosis-pseudoglioma syndrome (OPPG), would be expected to respond less to bisphosphonate therapy than high-turnover conditions, such as acute lymphocytic leukemia (ALL), Hajdu–Cheney syndrome (HCS), or osteogenesis imperfecta. A study in children with Duchenne muscular dystrophy (DMD) treated with bisphosphonate demonstrated improvements in back pain and vertebral height in 100% and 63% of boys, respectively. Although no worsening of vertebral fractures occurred, new incident vertebral fractures were documented in two of the seven patients, all mild and asymptomatic [132]. Bone formation is also impaired in osteoporosis-pseudoglioma syndrome (OPPG), and although response to bisphosphonate therapy is recognized [179], anabolic therapy is advised for such children to improve bone formation [180].

Is There a Room for Individualized Treatment Approach?

A number of important signaling pathways that modulate bone mass have led to novel drug developments in recent years. Denosumab is a human, monoclonal antibody administered subcutaneously that targets RANKL to prevent the activation of RANK, thus inhibiting bone resorption and increasing bone strength at both trabecular and cortical sites without directly interacting with bone surfaces (see Chap. 21). Denosumab is used in different indications in childhood without being approved in this age group at all. Dose and interval of treatment differ significantly [181]. Children with neoplastic disorders like giant cell tumors or giant cell granulomas were treated with 120 mg denosumab monthly [182, 183]. Children with osteoporosis due to impaired muscle function with cerebral palsy were treated with low doses of 10 mg of denosumab. A boy with spinal muscular atrophy was treated with a dose of 60 mg [184, 185]. In patients with a localized

high-turnover osteoporosis and destruction of the skeleton by cystic lesions, denosumab was also used to decrease bone turnover. In children with fibrous dysplasia, aneurysmatic bone cysts, and juvenile Paget disease, denosumab had been administered in doses ranging from 0.5 mg/kg/day up to 70 mg in intervals from monthly to every 7 months [186–188].

For patients with osteogenesis imperfecta, a first prospective trial was performed (NCT01799798) with denosumab in children with osteogenesis imperfecta, revealing a high efficacy of denosumab in suppression of osteoclastic activity and increasing bone mineral density and mobility [189]. In the meantime, a few reports have been published showing short-time side effects in the calcium metabolism (suspected as rebound phenomenon) in adults and children. Another study [190] was carried out to assess whether denosumab treatment can be performed in an individualized concept, meaning that the treatment schedule was individualized depending on the urinary DPD/creatinine excretion course. Recovery of osteoclastic activity was assessed by biweekly measurement of urinary deoxypyridinoline/creatinine ratio (DPD/creatinine) in spot urine. Increases to the DPD/creatinine level before the last denosumab injection were defined as a recovery of osteoclastic activity and therefore end of bone resorption suppression by the agent. Denosumab was administered with 1 mg per kg body weight subcutaneously. Additionally, every patient received postinjection weight adjusted oral calcium and vitamin D supplementation:

- 15 kg body weight day 0–14 post injection: 2 × 250 mg/ day calcium, day 15–28 post injection 1 × 250 mg /day calcium, day 0–28 post injection 500 IU vitamin D
- 15–30 kg body weight day 0–14 post injection: 2 × 500 mg/ day calcium, day 15–28 post injection: 1 × 500 mg /day calcium, day 0–28 post injection: 500 IU vitamin D
- 30 kg body weight day 0–14 post injection: 2 × 1000 mg/ day calcium, day 15–28 post injection: 1 × 1000 mg /day calcium, day 0–28 post injection: 1000 IU vitamin D.

Adopting this protocol, denosumab dose intervals could be extended in the mean from 12 weeks previously to 20.3 weeks. Though during follow-up the areal bone mineral density decreased in patients with a prolonged interval, this was not associated with any clinical impairments of mobility or vertebral shape. Results of the study revealed that the mean relative change of lumbar aBMD was −6.4%. Lumbar spine aBMD Z-scores decreased from −1.01 ± 2.61 (mean ± SD) to −1.91 ± 2.12 (p = 0.015). Mobility changed but not significantly (p = 0.08). No severe side effects occurred.

Many reports about calcium homoeostasis in patients treated with denosumab have been published recently. The risk of hypocalcemia during the first 2–4 weeks after injection could be compensated by oral calcium substitution. Recently, a rebound hypercalcemia after denosumab effect ceased has become a reason of concern [191–193]. Therefore, the serum calcium homoeostasis needs to be carefully monitored during denosumab therapy course to better assess the risk of calcifications in children and adolescents treated with denosumab.

Novel Therapies

Apart from antiresorptive therapy, there is a gap to be filled in terms of management of osteoporosis in children. Anabolic treatment options for pediatric bone disorders are urgently needed, in particular for low-bone turnover conditions. Anabolic agents such as synthetic parathyroid hormone (teriparatide) used in adults to directly stimulate bone formation [194] are currently contraindicated in children due to the risk of osteosarcoma reported in rodent models [195]. Also, antibodies against inhibitors of the WNT signaling pathway (sclerostin and dickkopf-related protein 1) look promising [196], though so far no data regarding its use in children is available. Growth hormone is another anabolic agent, known to increase cortical thickness and improve muscle mass [196]. When growth hormone is combined with bisphosphonate treatment in children with severe osteogenesis

imperfecta, greater BMD and height can be achieved compared to bisphosphonate therapy alone. However, no difference in fracture incidence was reported [85]. Larger and well-designed multicenter trials are required to confirm these beneficial effects.

Finally, excessive transforming growth factor-β (TGF-β) signaling has been implicated in the pathogenesis of both CRTAP recessive and type I collagen-dominant osteogenesis imperfecta; anti-TGF antibody rescues the phenotype in both forms of the disease, garnering interest in other high-bone turnover osteoporotic states [40, 197].

Treatment Considerations in Specific Conditions

Osteogenesis Imperfecta

In osteogenesis imperfecta and potentially other genetic forms of bone fragility, where the degree of bone fragility can be so profound so as to cause in utero fractures or fractures in infancy and early childhood, medical therapy alone may be insufficient to restore normal mobility.

In such cases, intramedullary rodding is necessary to straighten lower (and sometimes upper) limb deformities, prevent fractures, and foster mobility, in combination with bisphosphonate treatment plus physio- and occupational therapy. In severe cases, bisphosphonate therapy is often required before surgical rodding can be carried out so that there is sufficient bone to permit effective hardware insertion. As well, teeth and craniofacial abnormalities (including dentinogenesis imperfecta, basilar invagination, and jaw abnormalities) require the input of specialized dentists and surgeons such that overall a multidisciplinary team is required to care for the child with osteogenesis imperfecta, particularly in the moderate and severe forms [40]. Figure 26.5 shows a suggested protocol for the medical management of osteogenesis imperfecta.

Glucocorticoids-Induced Osteoporosis

Patients treated with systemic glucocorticoids (GCs) lose bone mass more markedly during the first 3–6 months of treatment, mainly trabecular bone [198]. This loss depends on the dose and treatment duration [199, 200]. Although lower doses are less harmful than higher doses, there appears to be no unequivocally safe dose since fracture risks have been reported to persist with prednisone (or equivalent) doses of 2.5–7.5 mg/day [198]. Thus, as in other patients with osteoporosis risk factors, monitoring BMD and vertebral fractures occurrence is advisable. In the absence of clear data on the optimal time for a DXA in this group, it has been recommended to perform a DXA during the first 6 months of treatment and repeating it every 9–12 months if treatment continues.

Regarding vertebral fracture screening, some studies reported an incidence rate of around 10% during the first year, with nearly 50% of such cases being asymptomatic [201, 202]. For this reason, it is advisable to assess these patients using imaging technique at the beginning of treatment, and thereafter annually while glucocorticoids are maintained.

The Spanish Rheumatology Society Consensus [203] holds that the prevention of glucocorticoid-induced osteoporosis (GIOP) must begin as early as possible for all patients receiving doses higher than 5 mg/day of prednisone (or equivalent) for more than 3 months. Preventive actions include prescribing the lowest possible dose of glucocorticoids to control the underlying disease, as well as encouraging physical exercise, avoiding toxic products, such as tobacco and alcohol, and ensuring a balanced diet with the required intake of calcium and vitamin D [203, 204]. A recent systemic review concluded that calcium and vitamin D supplementation should be started with the same dose recommended for healthy children in all children on glucocorticoids, particularly when treatment is expected to last more than 3 months, as a preventive action against gluco-

corticoid-induced osteoporosis (GIOP) development [205]. It has also been advised to maintain this supplementation for 3 months after discontinuation of glucocorticoids treatment since its effect on bone continues even after treatment has been halted. Nevertheless, no studies have determined an optimal period of supplementation. This same review recommends the use of bisphosphonates for preventive purposes [205], despite the lack of any comprehensive data. However, the use of bisphosphonates in the absence of fragility fractures remains a matter of controversy. Nevertheless, its effectiveness is proven when glucocorticoid-induced osteoporosis (GIOP) has been established; that is, when pathological fractures are clearly evident [206].

Most studies suggest that an inhaled glucocorticoids dose lower than the equivalent of 800 mcg/day of budesonide has only a minimum effect on fracture risk, while higher doses are associated with an accelerated decrease in BMD and a higher risk of fractures. In these patients, although nonpharmacological preven-

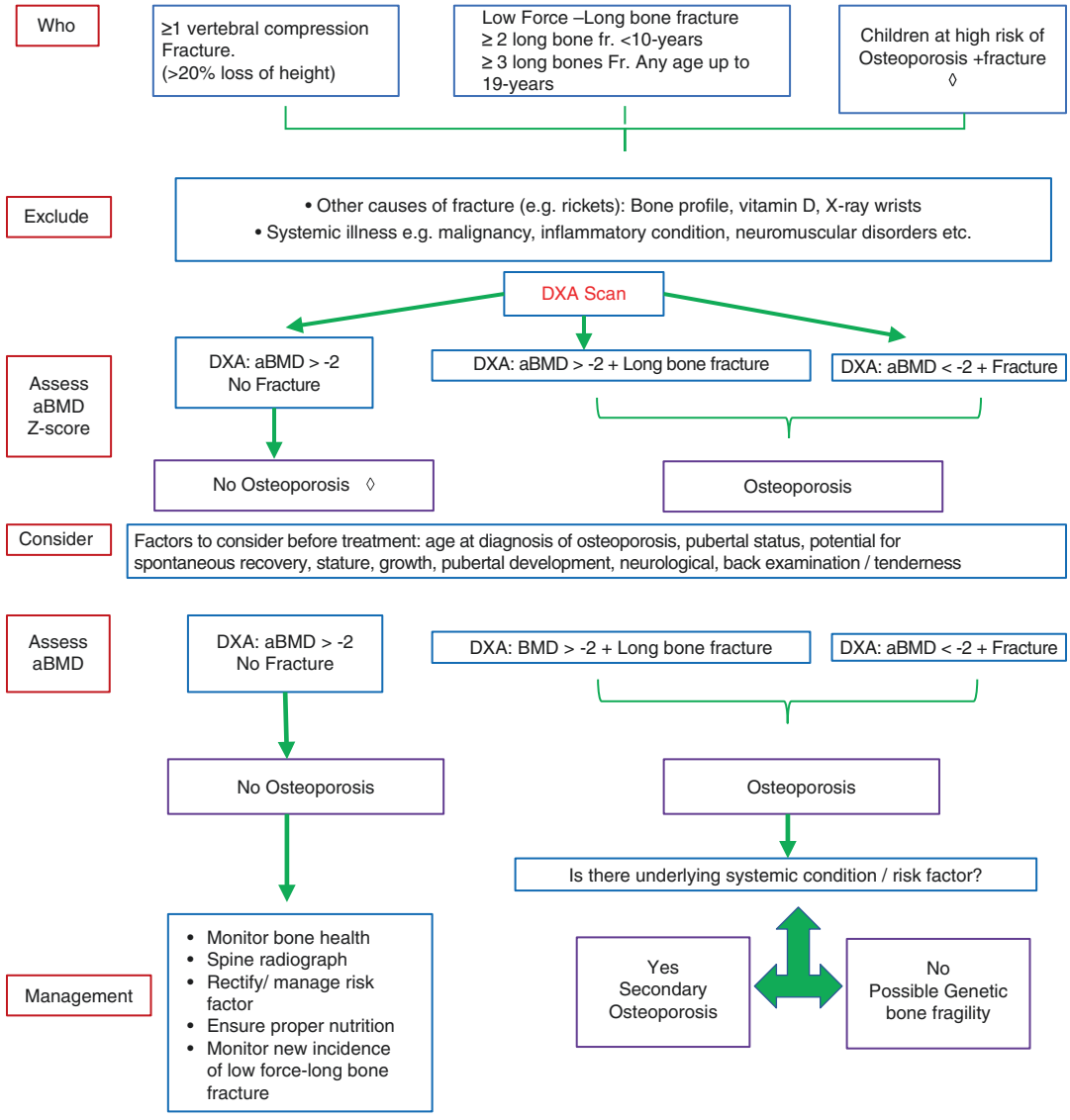

Fig. 26.5 Osteoporosis diagnosis, monitoring, and treatment algorithm for children with osteoporosis

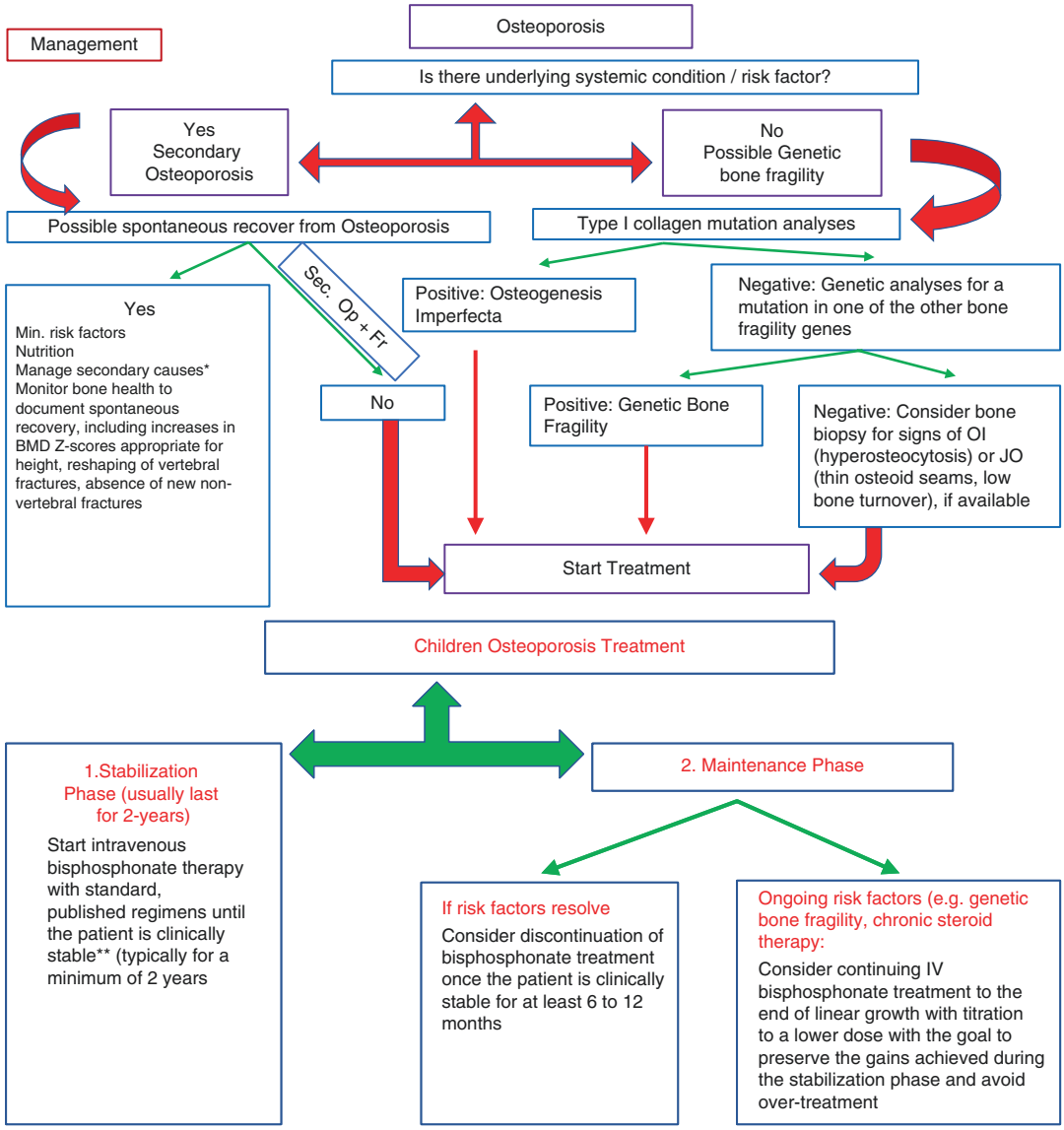

Fig. 26.5 (continued)

tive actions are justified [204, 207, 208], it is not advisable to routinely carry out such procedures as lateral spine X-rays or DXAs unless these patients have other risk factors [207–209]. Furthermore, the role of calcium and vitamin D supplementation in patients prescribed inhaled glucocorticoids (GCs) has not yet been established, although some groups recommend supplementation for higher-risk populations [210].

Anorexia Nervosa

In this condition of severe low weight, the historical occurrence of nonvertebral fractures has been reported at 31% in girls compared to 19% in healthy controls [211], while the prevalence of vertebral fractures is as low as 2.5% [212]. It has long been established that the best strategy to improve bone density is to gain weight and restore normal menstrual function [213]. Oral

estrogen–progesterone combinations are not effective in adults or adolescents with anorexia nervosa, and transdermal testosterone replacement is ineffective in adult women. Physiological estrogen replacement as transdermal estradiol with cyclic progesterone does increase bone mineral accrual in teens with anorexia, approaching that of normal weight controls.

The American College of Sports Medicine has recommended that oral contraceptives be considered in amenorrheic athletics over 16 years of age, but only if BMD is declining despite sufficient weight gain [214]. A study of risedronate revealed increased spine and hip BMD in adult women with anorexia nervosa; however, a controlled study of oral alendronate in teens showed no effect on lumbar spine and hip BMD compared to placebo [215]. To date, there have been no controlled trials assessing the effect of IV bisphosphonate therapy on the incidence of vertebral and nonvertebral fractures, on vertebral body reshaping following prevalent vertebral fractures, or on BMD in adolescent anorexia nervosa. Given the synergistic effects of bisphosphonates and linear growth, such a trial is warranted in young patients with anorexia nervosa who are still growing.

Epilepsy and Antiepileptic Drug Therapy

Individuals with epilepsy are at a twofold higher risk of sustaining fractures, which is thought to occur either due to an increased risk of fall or treatment with certain antiepileptic drugs (AEDs) [216]. However, the incidence and prevalence of vertebral fractures in children with epilepsy on AED are yet to be established. Older cytochrome P450-inducing AEDs such as phenytoin, phenobarbital, and carbamazepine are associated with low-bone mass and vitamin D deficiency, resulting in increased fracture risk. However, the newer AEDs with minimum or no enzyme-inducing effects have demonstrated a better safety profile on bone metabolism [217]. Immobility and neurological conditions that increase the risk of fall as well as comorbidities limit the interpretation of human studies assessing the effect of AEDs on bone.

Many more rare conditions cause secondary osteoporosis including inherited metabolic conditions such as glycogen storage disease, galactosemia, Gaucher's disease, Menkes disease, protein intolerance, and homocystinuria. Mechanisms of bone loss for these conditions have not been studied in detail.

Consider Puberty and Nutrition

In the care of chronically ill children, hypogonadism, pubertal delay, and low calorie intake are frequently overlooked aspects, though they can lead to the development of secondary osteoporosis and require specific treatment. The timing and dosing of sex hormone replacement in children with hypogonadism are important for optimum bone mass accrual during puberty. In addition, improving weight gain by optimizing calorie intake is especially important in children with delayed pubertal maturation secondary to anorexia nervosa [218] as well as other chronic illnesses [219].

Improving Muscle Strength, Mobility, and Rehabilitation

Lack of locomotion, due to either recurrent fractures in children with osteogenesis imperfecta or chronic illnesses, reduces mobility, muscle force, and subsequently bone strength. Based on studies in adults [220], high-frequency low-amplitude whole-body vibration (WBV) is being developed as a nondrug therapy to increase muscle force and mobility in children. A randomized study in mice with osteogenesis imperfecta showed improved cortical and trabecular bone with whole-body vibration (WBV) [221]. An observational study in children with osteogenesis imperfecta (OI) demonstrated improved ground reaction force, balance, and mobility [222]. Small randomized clinical trials conducted in children with cerebral palsy, receiving approximately 9 min/day of whole-body vibration (WBV), five

times a week, demonstrated greater walking speed with no bone effect [223] or improvement in tibial bone density [224] or cortical bone thickness [225]. Whole-body vibration (WBV) appears a promising intervention that can be used as a preventative measure or an adjunct to therapeutic intervention, at the least for rehabilitation, since secondary loss of function and mobility is common in osteogenesis imperfecta and other disabling conditions. However, larger long-term studies are required.

Osteoporosis Diagnosis and Treatment Algorithm

To be able to assess, diagnose, and achieve appropriate monitoring of the bone health status of children at risk of sustaining fractures attributed to osteoporosis, clinical, radiological, and analytical parameters should be observed and recorded regularly. Below is a suggested algorithm for children's management in standard practice.

Initial Assessment

At initial assessment as well as at each monitoring visit, the treating health-care professional should take a fracture history and advise patients to report to their health-care provider any fractures that occur in between visits. Bone and back pain assessments are also part of the annual monitoring protocol. Back or bone pain that is reported between clinic visits should be assessed by plain radiographs to assess the possibility of fracture. Assessing the number of fragility fractures and pain episodes is important. In terms of densitometry, though variations in Z-scores are relevant, the optimal frequency for DXA performance is insufficiently defined [103]. It has been recommended to repeat DXA after 1 year, and then every 1–2 years thereafter according to the patient's trajectory, with a minimum interval between checks of 6–12 months.

As far as vertebral fracture, it is crucial to perform a radiological assessment of the vertebra since they are frequently asymptomatic and can appear even in patients with Z-scores higher than −2 [40]. Moreover, their evolution can lead to changes in the management approach or type of treatment advised [149]. There are no studies that have definitively determined how often vertebral fracture(s) should be monitored, although some authors propose lateral spine X-rays on an annual or biannual basis [40]. In fact, the frequency should be individualized and tailored according to the patient's risk factors, with a minimum period of 6 months and a maximum period of 2 years. Furthermore, no studies or guidelines have established the optimal periodicity for assessing phosphocalcic metabolism. To handle this, it has been recommended to make an analytical determination on an annual basis [99].

Osteoporosis is present once a child with risk factors for low-trauma bone fragility demonstrates clinically significant fracture(s) that matches the definition of pediatric osteoporosis outlined earlier in the chapter [17]. The patient should be referred to a clinician with specific expertise in managing pediatric osteoporosis if this has not already been done.

Treatment: Stabilization Phase

The current standard of care for treating osteoporosis in childhood is intravenous (IV) bisphosphonate therapy (pamidronate, zoledronic acid, or neridronate) [40, 226]. Using oral bisphosphonate therapy during the pediatric years is not advised because of data arising from controlled trials in osteogenesis imperfecta; the published controlled trials in which authors quantified vertebral body height clearly revealed increased vertebral heights in youth with osteogenesis imperfecta who were treated with IV bisphosphonate therapy [227–229]. In contrast, none of the controlled studies of oral bisphosphonate studies revealed a positive effect on vertebral height [230–232]. In addition, it is well known that the oral bioavailability of oral bisphosphonates is low [233, 234].

IV therapy should be given at standard, published doses, as outlined in Table 26.5 [40, 155,

227, 235]. A clinician with relevant expertise should administer these agents to ensure the appropriate side effect management and that contraindications, such as renal disease, are considered. While bisphosphonate therapy is administered, in some centers, on an inpatient basis, the treatment can also be safely delivered in outpatient settings provided an on-call physician is available to the patient in the week after each infusion. Given the possibility of fever and vomiting with the first infusion, glucocorticoid stress-dosing recommendations must be provided [236].

Bisphosphonates are contraindicated in patients with poor renal function (estimated glomerular filtration rate < 35 mL per minute). The US Food and Drug Administration updated the label for zoledronic acid, stating that it is also contraindicated in patients with acute renal impairment and that patients should be screened for renal insufficiency before initiating treatment. Monitoring for other side effects reported in adults on long-term bisphosphonate therapy (including osteonecrosis of the jaw and atypical femur fractures) is also necessary and underscores the importance of monitoring bisphosphonate therapy under care of an osteoporosis treatment expert. A full discussion of appropriate doses, potential side effects, and steps to ensure patient safety on bisphosphonate therapy should also be discussed with the patients [226, 237].

Regarding the calcium and vitamin D supplementation, since the optimal intake for children and adolescents suffering from chronic diseases is unknown [41], doses should be modified according to the level of calciuria and plasma levels of 25-hydroxyvitamin D3 as well as intact parathormone (iPTH). The optimal frequency for monitoring these parameters is unknown [238], although some authors advocate that determinations should be made every 3–12 months [238, 239]. It is advised that levels of 25-hydroxyvitamin D3 should be determined every 6–12 months, or 3–6 months after a dose change. Furthermore, an annual determination of calciuria is recommended. A renal ultrasound should be conducted to rule out nephrocalcinosis in the event of increased calciuria or when urine collection is not possible [99].

Concerning the children treated with bisphosphonates, there are no studies that have determined an optimal frequency for analytical checks. However, it is advisable to carry out monitorization prior to each infusion for patients receiving intravenous bisphosphonates, and every 6 months for patients taking bisphosphonates orally [99]. Table 26.6 includes a list of treatment outcomes showing how to identify clinical stability in children with pediatric osteoporosis who received medical management.

Table 26.6 A list of treatment outcomes showing how to identify clinical stability in children with pediatric osteoporosis who received medical management

Subjective treatment outcomes	Objective treatment outcomes
In symptomatic patients, treatment usually results in pain remittance within 2–6 weeks Improvement of bone and back pain Improvement in mobility	In case of vertebral fracture, healing and subsequent bone remodeling should be visible at X-ray a few months after drug administration Eventual reshaping of vertebral fracture Absence of new vertebral fracture in previously normal vertebral bodies Absence of additional loss of vertebral height at sites of previous fractures Absence of new nonvertebral fractures To stabilize the BMD Z-score trajectory of the patient at the follow-up DXA scan
Clinical stability: If the patient achieved Absence of new VF in previously normal vertebral bodies and absence of further loss of vertebral height at sites of previous fractures Stable healed vertebral fracture/reshaping of vertebral fractures Absence of new nonvertebral fractures Absence of bone and back pain Improved mobility Stable aBMD or increase in spine BMD Z-score appropriate for height (z score or > −2 SD)	

Maintenance Phase and Discontinuation of Osteoporosis Therapy

Once the patient is clinically stable (Table 26.6), consideration should be given to continuing IV therapy but at a lower dose [38]. The goal of this approach is to preserve the clinical gains achieved during the stabilization phase while avoiding overtreatment. Vertebral body reshaping after vertebral fracture is a frequently overlooked treatment goal, one that occurs only when bisphosphonate therapy is administered to patients during the growth phase. This phenomenon underscores the critical importance of treating signs of vertebral collapse earlier rather than later, so that treatment can be administered as far in advance of epiphyseal closure as possible.

The duration of maintenance therapy depends on the patient's bone health status (whether clinically stable or not) and whether the risk factor, for example, glucocorticoid therapy is ongoing. When bisphosphonate therapy is discontinued during the growth phase, the newly formed bone adjacent to the growth plate (i.e., the treatment-naive bone) is once again low density, creating a stress riser between the treated and treatment-naïve bone. Metaphyseal fractures have been observed at the interface between the treated and untreated bone in children after treatment is discontinued [240]. This observation has led to the general recommendation in children that bisphosphonate therapy should be continued at least until the end of final height in those with persistent or permanent risk factors for osteoporosis [241] [including glucocorticoid therapy and myopathy as in Duchenne muscular dystrophy (DMD) and, as a minimum, even beyond final adult height if the patient is not yet clinically stable].

No studies have been used to address which BMD increment or cutoff is associated with a clinically acceptable decrease in fracture rates that would categorize the patient as stable once achieving final adult height. In the absence of such data, it is recommended that the areal BMD Z-score should stabilize (if previously on the decline) or increase beyond the precision of the measurement, and furthermore, the areal BMD Z-score should approximate the patient's height Z-score.25 Another approach is to aim for a BMD Z-score > −2.0 [242].

If a patient deteriorates after treatment is discontinued (i.e., presents with a new vertebral fracture, worsening of existing vertebral fracture, or a low-trauma extremity fracture after adult height attainment and after bisphosphonate cessation), then reinitiation of treatment is indicated. At present, the benefits and risks of drug holidays (periods of bisphosphonate discontinuation) in pediatric osteoporosis remain uncertain. However, if the child's bone status remains stable, considering drug holiday, similar to that adopted in adults, might be well-thought-out. Further research is required to determine the optimal efficacy and safety with these long-term bisphosphonate approaches [133].

In conclusion, osteoporosis in children is a new and evolving area, with certain unique diagnostic and clinical challenges. Recently, there has been an increased awareness of osteoporosis in children, both as a primary problem due to genetic mutations and enzyme deficiencies and also as secondary to various diseases, medications, and lifestyle issues. In 2019, the ISCD has released its definition and approach to interpret the DXA scan and osteoporosis. Clinical experience with bisphosphonates in pediatric patients is growing, with benefits to quality of life demonstrated in osteogenesis imperfecta. Increased awareness among pediatricians is important to identify patients at risk of developing osteoporosis.

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Atypical Femur Fractures

27

Yasser El Miedany

Introduction

Low-energy femur fractures in patients receiving alendronate were first described in 2005 [1], followed by two case series in 2007 [2] and 2008 [3] reporting strong associations with alendronate. Since then, many articles have been published on atypical femur fractures (AFFs). The American Society for Bone and Mineral Research Task Force on AFFs analyzed 310 published cases in 2010 [4]. This was followed by a second report from the American Society for Bone and Mineral Research (ASBMR) Task Force in 2013, reviewing all the studies published between 2010 and 2013 [5].

Atypical femoral fractures, also known as bisphosphonate-related proximal femoral fractures, are an example of insufficiency fractures. Although the direct causative link remains somewhat controversial, it was reported as an uncommon complication of long-term use of bisphosphonates [6]. Atypical femoral fractures are stress or insufficiency fractures occurring in the femoral shaft, which may occur either unilateral or bilateral. The occurrence of atypical femur fractures has been described and linked to a negative side effect of antiresorptive therapy [7]. Considering the large population benefiting from this pharmacotherapy, the incidence of this fracture entity is rather low [8]. However, the difficult diagnosis caused by initially mild symptoms and slight radiological changes combined with a problematic therapy drives the need for guidelines to be established. The handling of the condition represents a challenge to the orthopedic surgeon not only regarding the surgical approach and the kind of osteosynthesis but also the short as well as the long-term patient's medical management, which should aim for avoidance of bone remodeling oversuppression [9]. Although the first encouraging steps have been made toward an evidence-based therapy [10], the results must be interpreted with caution, considering the rareness of such an event [11].

This chapter will provide the definition of AFF, terminology, and the difference between fatigue fracture, fragility fracture, insufficiency fracture, and atypical fracture. The chapter will expand to discuss epidemiology and pathogenesis of AFF, clinical features and diagnosis of atypical femur fractures, as well as management.

Definition

In the first ASBMR Task Force report [4], a provisional definition of AFF was published, with a subsequent update in 2014 [5]. These definitions have been used in studies for separating AFF from other fractures below the lesser trochanter

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Table 27.1 Comparison between the original and revised American Society for Bone and Mineral Research (ASBMR) atypical femur fracture case definition

Original	Revised (changes from 2010 are in underlined italicized font)
Major features	
The fracture located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare	*The fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare*
Associated with no trauma or minimal trauma, as in a fall from a standing height or less	Associated with no trauma or minimal trauma, as in a fall from a standing height or less
Transverse or short oblique configuration	*Fracture line originates at the lateral cortex and is substantially transverse in orientation, although it may become oblique as it progresses medially across the femur*
Noncomminuted	Noncomminuted or minimally comminuted
Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures only involve lateral cortex	Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures only involve lateral cortex
	Localized periosteal or endosteal thickening of lateral cortex at the fracture site ("beaking or flaring")
Minor features	
Localized periosteal reaction of lateral cortex ("beaking or flaring")	Generalized increase in cortical thickness of the *femoral diaphysis*
Generalized increase in cortical thickness of the diaphysis	Unilateral or bilateral prodromal symptoms such as pain
Prodromal symptoms, such as dull or aching pain in groin or thigh	Bilateral incomplete or complete femoral diaphysis fractures
Bilateral fractures and symptoms	Delayed *fracture* healing
Delayed healing	

of the femur. In comparison to the original definition, the newer one continues to require that the fracture must be located just below the lesser trochanter and above the supracondylar flare, but this is no longer listed as part of the definition. Instead, the fracture must have four of five of the major features (Table 27.1). Minor features (Table 27.1) may or may not be present. In the original definition, the lateral cortex periosteal reaction was considered a minor feature. In the newer definition, the lateral cortex reaction, resulting in so-called beaking or flaring, is now considered a major feature.

Several studies have addressed the effect of the new ASBMR criteria on the diagnosis of AFF. In one review, implementing the newer ASBMR definition resulted in a decrease of about 50% of fractures no longer meeting the definition of AFF [12]. The most common reason for this was the change in the description of the fracture orientation. By the earlier definition, AFF had to have a transverse or short oblique configuration. In the newer definition, a major feature was "the fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur" (Fig. 27.1).

With regard to imaging techniques for diagnosis of AFFs, Critchlow et al. assessed the sensitivity and specificity of each radiographic criterion to identify an AFF [13]. Four independent experts representing different medical specialties within Kaiser Permanente Southern California compared radiographs from 55 AFFs and 39 non-AFFs. The most sensitive features distinguishing AFFs from non-AFFs were the lateral cortex transverse fracture pattern (mean 93.6%, range 85.5–98.2%), medial cortex transverse or oblique fracture pattern (mean 84.1%, range 72.7–98.2%), and minimal or noncomminution (mean 93.2%, range 89.1–98.2%). Specificity was greatest for lateral cortex transverse fracture pattern (mean 95.5%, range 92.3–97.4%). Luangkittikong and Unnanuntana [14] reported similar prevalence of AFFs with both criteria and that localized periosteal thickening of the lateral cortex was the most specific finding for bisphosphonates exposure in those with AFFs. In a study by LeBlanc and colleagues, two independent expert physicians applied the 2013 definition to radiographs previously categorized as AFFs by the 2010 definition [12]. The approximate 50% decrease in the number of fractures that met the 2013 than the 2010 ASBMR case definition (37

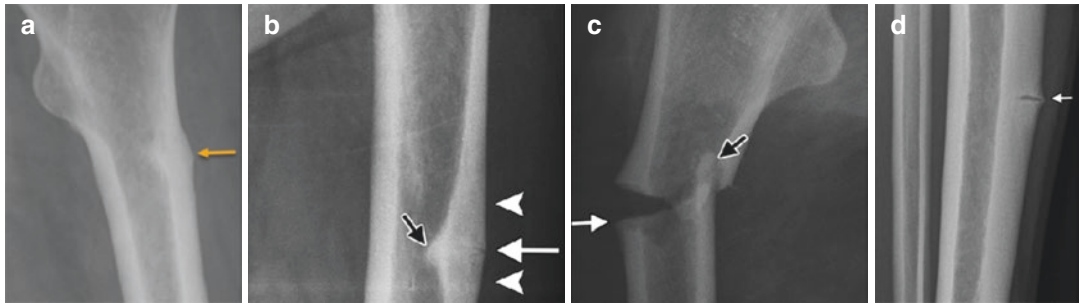

Fig. 27.1 Spectrum of radiographic abnormalities seen with atypical femoral fractures in three patients. (**a**) Plain X-ray left hip and femur anteroposterior, 64-year-old woman, showing enlargement of incomplete fracture and periosteal or endosteal thickening (arrow) of the lateral cortex ("beaking") of the femoral diaphysis, which is consistent with an atypical femoral stress reaction. (**b**) X-ray left hip, 66-year-old woman, AP view showing a transversely oriented fracture (white arrow) of the lateral cortex of the femoral diaphysis with associated endosteal beaking (black arrow) and adjacent cortical thickening (arrowheads), findings that are consistent with incomplete atypical femoral fracture. (**c**) X-ray right hip, 60-year-old woman, AP view, showing a noncomminuted fracture of the femoral diaphysis consistent with a complete atypical fracture. The fracture is substantially transverse (white arrow) in the lateral cortex but becomes more oblique with a medial spike as the fracture propagates medially (black arrow). Associated endosteal and periosteal beaking with thickening of the lateral cortex suggests that this complete fracture originated in the lateral cortex. (**d**) Plain X-ray right leg anteroposterior, 58-year-old women, showing stress fracture of the tibia bone

vs. 74) was primarily due to the more precise specification of transverse configuration. Twelve shaft fractures were reclassified as AFFs due to modification of comminution and periosteal/endosteal thickening criteria. In our opinion, radiographic studies that use the revised ASBMR case definition will capture the phenomenon more accurately [15].

Terminology

The overlap of various terminology words used to describe traumatic fractures may cause some confusion. This includes stress, fatigue, insufficiency, fragility, atypical, and pathological fractures, which can be an impediment to understanding, reporting, and grading these injuries [16, 17]. Stress fractures, in the broadest sense of the term, can be divided into fatigue fractures and insufficiency fractures. In clinical practice, fatigue fractures and insufficiency fractures lie along a spectrum, and in some cases, it can be difficult to differentiate between the two. However, understanding the biological and radiographic differences can lead to a better understanding of the underlying pathophysiology.

A fatigue fracture is a focal failure of normal bone caused by repetitive applied stress [16, 18, 19]. Fatigue fractures commonly occur when the patient engages in increased frequency, duration, or intensity of activity, such as when military recruits sustain "march fractures" of the metatarsal bones [20].

In comparison, an insufficiency fracture is a focal failure of abnormally weakened bone caused by repetitive applied stress [16–19]. The term fragility fracture likewise signifies a fracture in abnormally weakened bone; however, the term is often used in the setting of an isolated mechanical loading event rather than repetitive applied stress, and it applies most commonly in a patient with osteoporosis [21–49]. In clinical practice, the terms fragility and insufficiency are often used interchangeably with reference to osteoporotic fractures because, in many cases, it is not possible to distinguish the chronicity and magnitude of loading, resulting in fracture in diffusely weakened osteoporotic bone.

Although osteoporosis is by far the most common underlying metabolic disturbance resulting in fracture [17, 22], insufficiency fractures may arise from a variety of disorders that influence the ability of bone to withstand normal loading

forces, including disorders of bone mineral homeostasis (e.g., osteoporosis, hyperparathyroidism, diabetes mellitus, osteomalacia), bone remodeling (e.g., Paget disease, osteopetrosis, other sclerosing bone dysplasias), collagen formation (e.g., osteogenesis imperfecta, Marfan syndrome), the adverse effects of pharmaceuticals (e.g., glucocorticoid drugs, chemotherapeutic agents), and prior radiation therapy [19, 22–27]. However, in the absence of a known history of metabolic bone disease, differentiation between fatigue and insufficiency fractures is often arbitrary, and it is not always clear how to distinguish normal from abnormal bone.

Atypical femoral fractures occur in the lateral cortex of the femoral diaphysis (Fig. 27.2) and can be seen in patients undergoing long-term therapy with bisphosphonate medications. In distinction to stress and insufficiency fractures, where the terminology is somewhat imprecise, atypical femoral fractures are explicitly defined, and terminology should follow the established guidelines of the American Society for Bone and Mineral Research (ASBMR) [23, 25]. The imaging appearance of these fractures is similar to that of stress (fatigue) fractures; however, they should be considered as a form of insufficiency fracture because the bone can be excessively brittle and weakened.

The term pathological fracture generally is reserved for fractures through a focal neoplasm, which may be either benign or malignant [19, 26, 27], although this definition is also inconsistently applied, and pathological fracture through osteomyelitis has been described in the literature [28, 29]. This is in contradistinction to a fracture of a region of metabolic bone disease—whether diffuse, such as with osteopetrosis, or focal, such as with Paget disease—which generally should be referred to as an insufficiency fracture [30, 31] (Table 27.2).

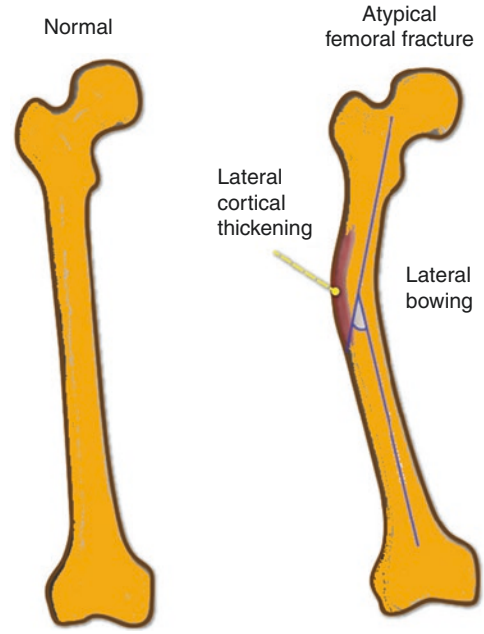

Fig. 27.2 Atypical femur fracture. Illustration showing the morphology of the femur and site of atypical femur fracture. Location of the atypical femur fracture in the femoral diaphysis as defined by the ASBMR: distal to the lesser trochanter—proximal to the supracondylar flare. (Quoted from Starr et al. [15] under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/)

Table 27.2 Characteristics of different types of stress fractures in contrast with pathological fracture

Stress fracture				Pathological fracture
Fatigue fracture	Fragility fracture	Insufficiency fracture	Atypical fracture	
Focal failure of a normal bone caused by repetitive applied stress Example: March fractures	Focal failure of abnormally weakened bone Isolate mechanical loading Example: Osteoporosis fracture	Focal failure of abnormally weakened bone Caused by repetitive applied stress Examples: bone remodeling disorders, collagen formation, drug induced (please see text)	Focal failure of abnormally weakened bone Occurs in the lateral context of the femoral diaphysis Usually in patients on long term bisphosphonate therapy *Has definition criteria	Fracture through focal neoplasm (benign/malignant) May occur though osteomyelitis

Epidemiology

In the second ASBMR Task Force report, AFF incidence was very low, ranging from 50 to 130 cases per 100,000 patient-years [31]. Their frequency was increased in patients on BPs, with a direct relationship between duration of BP exposure and risk of AFF [6, 31–40]. There was a significant association between glucocorticoid use and AFFs [31, 32, 35, 37, 39, 40]. Affected patients were approximately a decade younger than controls, a finding substantiated by a recent systematic review of 14 studies, in which 10 papers used the 2010 and 4 used the 2013 ASBMR definition [41]. The overall incidence of AFFs was low ranging from 3.0 to 9.8 per 100,000 person-years [41], the highest rate in a retrospective Norwegian fracture registry study that included periprosthetic fractures [42], which were specifically excluded in both ASBMR Task Force definitions. Other epidemiological studies have addressed relationships between AFF, BP use, and factors that may predispose certain patient populations to heightened risk. Most continue to report that AFF incidence is low, particularly compared to incidence of ordinary hip fractures [43–45].

AFFs in Osteoporosis Patients Treated with Denosumab

AFFs have been reported in osteoporosis patients receiving denosumab. While the majority of reports document extensive prior bisphosphonates exposure, as reviewed by Seiga et al. in 2016 [46] and reported by Ramchand et al. [47], AFFs have been reported in patients on denosumab with brief prior bisphosphonates exposure [48]. In the FREEDOM Trial open-label extension, two participants developed AFFs (0.8 per 10,000 participant-years), one after 7 years of denosumab exposure and one after 3 years of denosumab exposure [49].

AFFs in Osteoporosis Patients Treated with Romosozumab

Romosozumab is a monoclonal antibody that increases bone formation by binding to and inhibiting sclerostin and also decreases bone resorption. In the Fracture Study of Postmenopausal Women with Osteoporosis (FRAME), 1 of 3521 participants in the romosozumab group had an AFF after 3.5 months of exposure; that individual had a history of prodromal pain at the fracture site prior to enrollment [50]. In the Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) study, 4093 postmenopausal women with osteoporosis and a fragility fracture were randomly assigned to monthly romosozumab or weekly oral alendronate for 12 months followed by open-label alendronate for another 12 months [51]. There were no AFFs during the initial 12 months in either group; in the second 12 months, two AFFs occurred in the romosozumab to alendronate group (< 0.1%) and four AFFs in the alendronate to alendronate group (0.2%).

AFF in Autoimmune Disease and Steroid Therapy

Autoimmune disease and glucocorticoid use, established risk factors for osteoporotic fracture, have both been linked to AFF [45]. In 125 Japanese patients (90% women) with long-standing autoimmune disease taking BPs and glucocorticoids, Sato et al. reported that localized periosteal thickening of the lateral cortex ("beaking") was present in 8.0% (15 femora, 10 patients) and new beaking developed in 10.3% (21 femora, 12 patients) over 2 years. A complete AFF at the beaking site occurred in one patient. Factors significantly associated with beaking included >4 years of BP therapy, longer duration of BP therapy (6.1 vs. 5.0 years), age 40–60 years, and diabetes [52]. They measured the height of the beaking reaction in 20 femora (12 patients), characterizing it as pointed or arched [53].

Beaking was considered "severe" if associated with pain, a complete AFF, or an incomplete AFF with a visible fracture line; the periosteal reaction was higher and more commonly pointed in the severe form.

AFFs in Cancer Patients Treated with Bisphosphonates and/or Denosumab

Edwards et al. retrospectively assessed the incidence of and risk factors for AFF in cancer patients followed at the MD Anderson Cancer Center over a 10-year period, both treated with oral and low-dose IV BPs for osteoporosis and with high-dose pamidronate and zoledronic acid for metastatic cancer [54]. As only AFFs that came to clinical attention were assessed, no absolute incidence rate was reported. Among 10,587 BP users, there were 23 AFFs compared to 2 AFF cases among 300,553 patients who did not receive BPs (OR 355.58; 95% CI, 84.1–1501.4, $p < 0.0001$). In cancer patients treated for osteoporosis, six AFFs occurred in patients on alendronate for a mean of 84 months and two AFFs occurred in patients on ibandronate for a mean of 36 months.

Compared to other bisphosphonates, the OR of an AFF was higher in patients treated with alendronate for osteoporosis (5.54; 95% CI; 1.60–19.112) and zoledronic acid was associated with a lower OR (0.34; 95% CI; 0.12–0.97). The authors hypothesized that the lower rate of AFFs in zoledronic acid users was because the drug concentrates in skeletal metastases and is less available to other skeletal sites [54]. However, there was a marked difference in duration of exposure between those treated with BPs for osteoporosis (84 and 36 months for alendronate and ibandronate, respectively) and those treated with zoledronic acid for metastatic cancer (5 and 14 months for zoledronic acid and pamidronate, respectively). Duration of exposure is an important risk factor for AFFs as time is required for suppressed remodeling to cause changes in bone material properties (collagen and mineralization) that may predispose to microcrack initiation and propagation [55].

Denosumab is used to treat metastatic skeletal disease and multiple myeloma at higher doses and with greater frequency than for osteoporosis (120 mg monthly vs. 60 mg twice yearly). Tateiwa et al. reported two AFF patients with metastatic breast cancer; one took BPs for 11 years before starting denosumab and one took only bisphosphonates [56]. In both, tomosynthesis, an older three-dimensional imaging technique that permits acquisition of higher-resolution images than conventional radiographs with lower radiation exposure than computed tomography, identified fracture lines within the area of cortical thickening that were not visible on radiographs [56]. Austin et al. reported two patients who sustained AFFs after receiving denosumab for metastatic cancer for 2 and 3.5 years without prior BP therapy [57]. Both experienced prodromal thigh pain, and in both, the fractures were initially attributed to skeletal metastases; neither patient had histological evidence of malignancy at the fracture site [57]. Yang et al. reviewed records of 253 patients at their cancer center who received at least 12 doses of denosumab for metastatic bone disease. During a median follow-up of 27 months, they identified one patient with a complete AFF (incidence 0.4%; 95% CI 0.1–2.2%) who received 70 doses of IV BP before receiving 28 monthly doses of denosumab [40]. They also reviewed all available radiographs in a subset of 66 patients with at least 21 monthly doses of denosumab; 2 patients had diffuse cortical thickening of the femoral diaphysis and localized periosteal reaction of lateral femoral cortex (incidence 4.5%; 95% CI 1.6–12.5%), confirmed on bone scan and magnetic resonance imaging [58]. These papers raise concern that clinical and subclinical presentations of AFF may be attributed to metastases and missed in cancer patients.

Periprosthetic AFFs

Two recent studies addressed periprosthetic fractures, which were excluded in the 2010 and

the 2013 ASBMR Task Force case definitions because they are associated with a known risk of femoral fractures. A retrospective Norwegian study of all patients greater than or equal to 65 years old treated at a single institution between 2004 and 2011 for subtrochanteric and diaphyseal fractures included patients with and without implants [59]. Of 217 fracture patients with evaluable radiographs, 17 fractures in 16 women were designated atypical by unspecified criteria. Their catchment area included 21,630 women aged ≥65 years, of whom 2214 were treated with BPs. AFF incidence was 9.8 (95% CI 5.2–14.5) per 100,000 person-years and 79.0 (95% CI 37.8–120.3) per 100,000 person-years in those receiving BPs. However, 8 of 17 fractures occurred close to implanted metal [9]. A more recent 10-year retrospective study of 15 North American centers defined characteristics of 196 patients with AFFs receiving long-term (> 2 years) BPs in whom the AFF was periprosthetic (PAFF, n = 21) or not periprosthetic (AFF, n = 175) [60]. Only periprosthetic fractures with atypical features (lateral cortical beaking or hypertrophy, transverse lucency in the lateral cortex, transverse orientation of the fracture in the lateral cortex, minimal comminution) were included. PAFFs took longer to heal and had higher mortality and significantly more complications. Compared to the literature, several features common to patients with ordinary periprosthetic fractures (history of revision surgery, infection, total hip replacement for previous low-energy hip fracture with/without femoral loosening) were not present in BP-treated patients with PAFFs. Prodromal pain was common in PAFF patients, but no data were presented [60]. While the ASBMR case definition for AFFs excluded periprosthetic fractures, emerging data suggest that they may occur. Physicians should be alert to the radiographic and clinical features and consider immediate cessation of BP therapy, imaging of the contralateral limb, protected weight-bearing, and close monitoring for signs of complete AFF or surgical fixation to stabilize the femur.

Pathogenesis of AFF

The fact that AFFs have been reported in patients never exposed to antiresorptive therapies such as bisphosphonates or denosumab, and the heterogeneity in bone histomorphometry found in AFF patients, it can be concluded that severe suppression of bone turnover is not a constant finding in patients with AFF. Several possibilities have been raised that the clinician should be aware of them. These include the following.

Stress or Insufficiency Fracture

The second ASBMR Task Force [5] considered AFFs to be stress or insufficiency fractures that develop over time (as manifested by prodromal pain) and appear to start in locations of stress on the lateral femur. Bisphosphonates may alter the ability to heal such fractures, most likely attributed to prolonged suppression of bone remodeling. Long duration of bisphosphonates therapy may lead to osteon homogeneity with respect to tissue age and mineralization. In susceptible individuals, repetitive loading of the femur may lead to accumulation of microcracks within the cortex. Intracortical fracture repair, normally accomplished by targeted osteoclastic resorption of microcracks, which tends to aggregate in actively remodeling bone, is inhibited by bisphosphonates, thus leading to microcrack aggregation and propagation.

Hip Geometry and AFF

Some investigators have suggested that the geometry of the femur may play a role in the pathogenesis of AFF. Specifically, femoral anatomy, which may influence the position of maximal tensile stresses on the lateral femoral cortex. This suggestion was based on the propensity for AFFs to be bilateral and in the same location on ipsilateral and contralateral sides and the finding that anterior and lateral bowing were correlated with tensile stress adjacent to the fracture site [61].

Since the publication of the 2013 ASBMR Task Force [5], several reports were published supporting this concept. Saita et al. evaluated weight-bearing radiographs of 10 patients with 14 AFFs [62]. AFF locations were similar in those with bilateral fractures; the standing femorotibial angle (Fig. 27.3) was significantly larger (more varus) in those with diaphyseal than subtrochanteric fractures and larger than those with ordinary femoral fractures [62]. In other studies, femoral neck-shaft angle was smaller in AFF patients than healthy controls in other studies, also suggesting that more varus proximal femoral geometry predisposes toward AFF [63–65]. A femoral neck-shaft angle cutoff of <128.3° had a sensitivity of 69% and a specificity of 63% to predict AFF [65], although not observed in a Singaporean Chinese cohort [66].

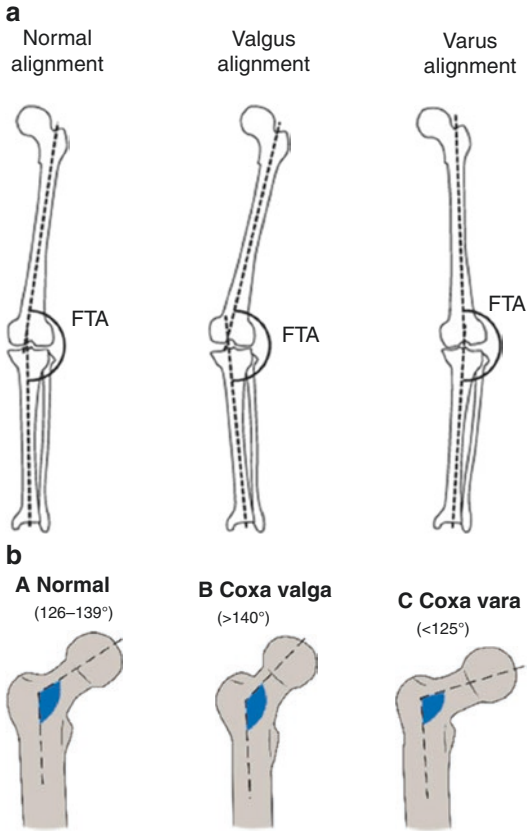

Fig. 27.3 (**a**) Femorotibial angle: the femorotibial angle (FTA) is the lateral angle between the axis of the femoral shaft and that of the tibial shaft. An increased FTA is called varus alignment while a decreased FTA is called valgus alignment. (**b**) Femur neck-shaft angle: a decreased femur neck-shaft angle is called coxa vara or varus alignment. An increased neck-shaft angle is called coxa valga or valgus alignment. (**c**) Femoral bowing angle: femoral bowing angle is the line that best describes the midpoint of the endosteal canal of the femoral diaphysis drawn in the proximal and the distal quarters. (Quoted from Starr et al. [15] under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/)

In their article, Starr and her colleagues [15] concluded that there is increasing evidence that the presence of a more varus femorotibial angle and lateral femoral bowing influences mechanical forces on the lower limb and the region of maximal tensile loading on the lateral femoral cortex, whereas the subtrochanteric AFF patients are more likely to have smaller femoral neck-shaft angles. Such biomechanical factors may account for the more proximal location of such fractures in individuals with more varus femorotibial angles.

Genetic Predisposition

The first evidence for a genetic influence on AFFs was reported by Roca-Ayats et al. [67]. Whole-exome sequencing in three sisters with AFFs and long-term bisphosphonate therapy revealed a novel p.Asp188Tyr substitution in the enzyme geranylgeranyl pyrophosphate synthase Asp188Tyr located in the genomic position g.235505746G → T on chromosome 1 (GRCh37/hg19). This mutation in GGPS1 affects a site within the enzyme that is inhibited by bisphosphonates, and this enzyme is key in the mevalonate pathway. This mutation would be expected to reduce enzyme activity and could predispose to AFF [67]. In a genome-wide search for nonsynonymous variants in coding region between 13 AFF patients with and 286 controls without AFFs, 21 genetic variants were more common in the AFF group [68–70]. Many cases had two or more at-risk variants, suggesting that the risk for AFFs may be polygenic and result from accumulation of at-risk genetic variants [71]. However, AFFs have been reported in bisphosphonate-naïve patients, in patients using other antiresorp-

tives [46], and in other genetic conditions with suppressed bone turnover [69, 70] or defective mineralization [71, 72].

Other Medications: Glucocorticoids, Proton Pump Inhibitors

Long-term use of both glucocorticoids and proton pump inhibitors has been linked to a variety of side effects, which also are related to bone metabolism. Proton pump inhibitor intake changes resorption and may lead to different forms of malnutrition, which has been associated with an increased general risk of fractures [73]. Furthermore, several studies also associated AFF risk with proton pump inhibitors (PPI) use [74]. However, there was no correlation with fracture location [75]. Similarly, long-term use of glucocorticoids is known to cause osteoporosis. Recommendations include treating with calcium and vitamin D plus an additional osteoporosis medication (oral bisphosphonate preferred) in adults at moderate-to-high fracture risk [76].

Since therefore the intake of bisphosphonates is frequently combined with glucocorticoids, the isolated influence of glucocorticoids is still under discussion. However, the importance of both medications in relation to the occurrence of AFF was rated by the ASBMR as high, so it was included in the definition as one of the minor criteria [77, 78].

Bone Material Properties in Patients with AFFs

Bones are exposed to a variety of mechanical forces, including compressive, tensile, bending, shearing, and torsional forces (24). The immediate response of bone or any other structural material to mechanical forces is determined according to the interplay of two primary factors—the ability of the material to absorb a mechanical load (stress) and the ability to deform under those forces without failure (strain) (Fig. 27.4). At low load levels, a bone readily deforms within its elastic range, and the bone returns to its original shape and structure when the load is released. As mechanical load increases, the bone deforms beyond its elastic range (into the plastic range) and microcracks are formed. A fracture occurs when there is accumulation of microcracks outpacing the body's capacity for repair (e.g., stress, fatigue, or insufficiency fracture), when there is a single force exceeding the failure load of the bone (e.g., traumatic fracture), or when there is a combination of these two [30].

Spontaneous or low-trauma fractures of the femur bone are unusual. Femur is rich in cortical bone and physiologically adapted to withstand large, repetitive forces. Although antiresorptive therapies increase bone mineral content, prolonged exposure may cause some changes in cortical bone material properties with potentially deleterious effects on bone strength. These effects may vary according to the bisphosphonates medication class. In a four-point bending study of femur bones from osteoporotic sheep exposed to raloxifene, alendronate, zoledronate, or teriparatide for 1 year, alendronate was associated with reduced fatigue life (fewer cycles of stress before failure) and lower modulus loss at failure (reduced tendency for a material to bend) [79].

Biopsies of the proximal femoral cortex were compared among five groups of postmenopausal women undergoing surgery for fracture or total hip arthroplasty: bisphosphonate-treated with AFF, bisphosphonate-treated with ordinary osteoporotic fractures, bisphosphonate-treated without fractures, bisphosphonate-naïve with typical osteoporotic fractures, and bisphosphonate-naïve without fractures [55]. By vibrational spectroscopy and nanoindentation, the **b**isphosphonate-treated AFF group had higher tissue mineral content and more mature collagen (characteristics associated with bone that is harder and more brittle) than bisphosphonate-treated women with ordinary osteoporotic fractures. In addition, bisphosphonate-treated patients had increased propensity for crack initiation and decreased deflection of crack paths at osteon borders. This study showed that normal mechanisms by which bones dissipate energy and retard crack propagation were impaired by bisphosphonates; together

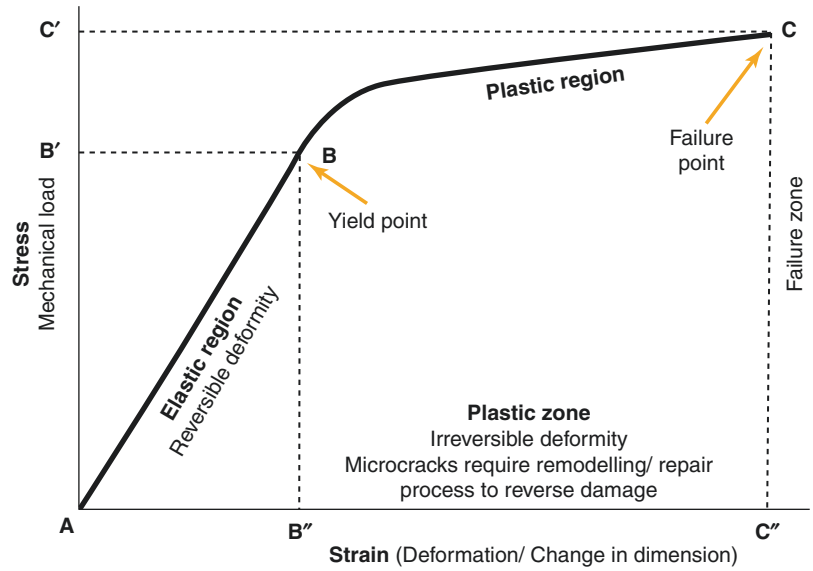

Fig. 27.4 Stress–strain curve**.** The yield point represents the mechanical load required to cause irreversible plastic deformation of a material. In bone, multidirectional forces above the yield point result in microcracks that initiate the bone remodeling and repair cascade. A stress fracture occurs when the rate of microcrack formation exceeds the repair capacity of the bone. The failure point represents the mechanical load required for gross failure of the material. In bones, this is the force required to produce an acute traumatic fracture

with increased uniformity of mineralization, this could lower resistance to fracture and explain the transverse fracture morphology seen in AFFs.

In contrast, bone microarchitecture does not appear to influence AFF pathogenesis. Zanchetta et al. used high-resolution peripheral quantitative computed tomography (HR-pQCT) to evaluate microarchitecture among BP-treated AFF, BP-treated and BP-naïve patients without AFFs [80], finding no difference in any volumetric or microarchitectural index. However, as HR-pQCT measures bone microarchitecture at the radius and tibia, it could miss local changes in the femur.

Mechanisms of Impaired Fracture Healing in AFF

Normally, bone microcracks heal by targeted remodeling in which osteoclasts resorb damaged tissue and osteoblasts form new bone. Suppression of remodeling, typical of bisphosphonate-treated patients, has been documented in AFF patients by bone turnover markers, iliac crest biopsies, and fracture site biopsies [5, 6, 59]. Schilcher et al. performed micro-computed tomography (CT), infrared spectroscopy, and histomorphometry on cortical biopsies including the fracture line in eight patients, four with complete AFFs, and four with incomplete AFFs [81]. In the incomplete AFFs, the fracture gap varied from 150 to 200 μm wide and contained amorphous, nonmineralized, acellular necrotic material. Bone adjacent to the fracture gap demonstrated evidence of remodeling with osteoclasts, resorption cavities, and woven bone, with no evidence of remodeling or callus within the gap [81]. The investigators hypothesized that local strains related to low-impact activities such as walking prevented cell survival and delayed healing [81, 82]. Radiographic new bone deposition with bridging was observed within resected cortical deficits in all cases, within the expected time frame for cortical bone [83].

Atypical Fractures in Other Bones

Atypical insufficiency fractures have been linked mainly to the femur bone. On the contrary, atypi-

cal fractures of other bones are much less common. There are only few case reports available that describe insufficiency fractures occurring in other bones. Atypical fracture of the tibia bone is the most commonly reported fracture. Fractures of the tibial diaphysis [84–86] and metaphysis [87, 88] of patients on long-term bisphosphonate therapy were published as case reports. The diagnostic guidelines outlined by the American Society for Bone and Mineral Research (ASBMR) delineate the criteria for atypical insufficiency fractures [89, 90]. However, this definition is strictly limited to femoral fractures and is not designed for fractures in alternative sites. Most of the atypical fractures reported in other bones apart from the femur meet all major and multiple minor ASBMR criteria for atypical fractures. In one study, key features include presenting with bilateral transverse, noncomminuted tibial fractures following no trauma, with delayed fracture healing and prodromal pain for several months leading up to the fracture [91].

Furthermore, there have been published reports of nontraumatic fractures of bones other than the tibia, in patients on long-term bisphosphonate therapy for osteoporosis, including the fibula [92] and ulna/radius [93]. Thus, the clinician needs to be aware of such possibilities as atypical fractures potentially associated with antiresorptive therapy can occur in weight-bearing long bones other than the femur.

Clinical Features and Diagnosis of Atypical Femur Fractures

Avoiding AFF by identifying patients at risk of developing AFF (Fig. 27.5), optimizing osteoporosis management, and recognizing impending fractures are challenging and require a high index of suspicion for any patient with a history of osteoporosis, especially, but not exclusively, if currently or recently treated with bisphosphonates (AFF has also been reported in patients who have discontinued bisphosphonates years prior to the fracture [31]) or other prophylactic medication and complaining of thigh or groin pain, even if they received treatment for only a brief period. When suspicious of incomplete AFF, careful radiographic exploration for features suggestive of impending fractures on hip and pelvic radiographs should occur. In patients with a complete fracture, the contralateral side should also be radiographed and carefully inspected for transverse fracture lines in lateral cortex, beaking, and other characteristic signs of atypical femoral fracture since 40% or more have bilateral involvement [94–96]. The sensitivity and specificity for these signs are generally high, especially for transverse fracture lines, lack of comminution, and localized periosteal or endosteal thickening of the lateral cortex (“beaking”) [97].

In cases with normal radiographs on the contralateral side, but where there is still clinical suspicion, computed tomography (CT) should be considered since fracture lines, not visible on radiographs, might be diagnosed. Lee et al. [98] have shown that patients with a subsequent AFF have a thicker lateral cortex in the subtrochanteric region of the femur on CT before the fracture event than bisphosphonate users who did not sustain a femoral fracture and than bisphosphonate-naïve patients. Thus, CT might be used for the early detection of AFF in long-term bisphosphonate users. Periosteal and endosteal edema can be visible using magnetic resonance imaging (MRI) and might also be indicative of an impending fracture and might be used in conservative follow-up of impending fractures [99].

Management of Atypical Femoral Fractures

Early Detection of AFFs

Extended femur scanning by DXA has been suggested as a tool for screening the patients for atypical femur fractures [100]. When prolonged treatment with antiosteoporotic medication is necessary, it is reassuring for physicians and patients to assess the patient for the possibility of an incomplete AFF. DXA has the advantage of being able to detect incomplete AFF in patients

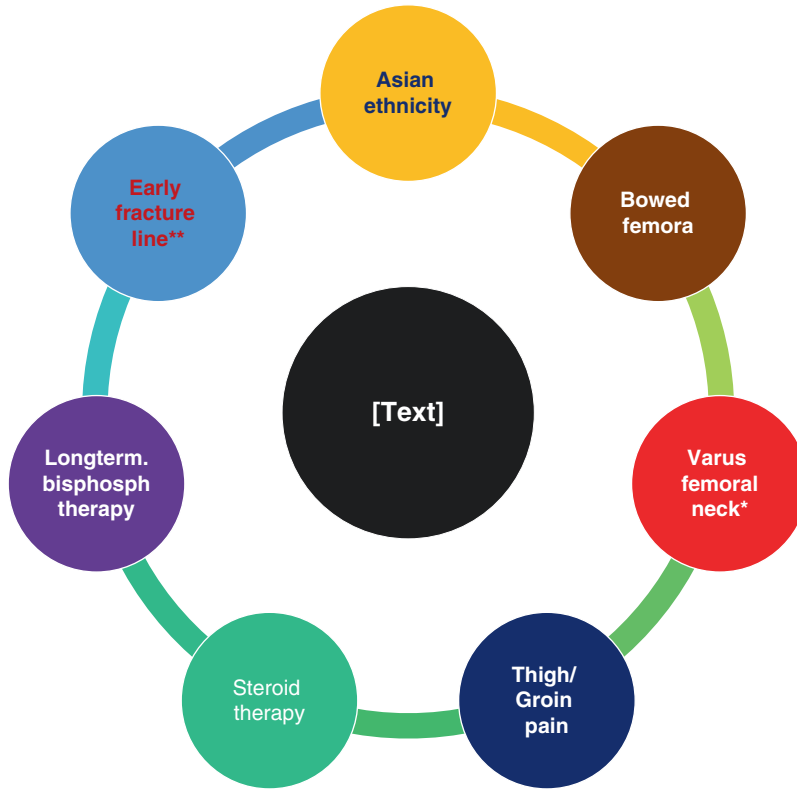

Fig. 27.5 Potential indicators of patients at risk for AFF (in addition to antiresorptive drugs). *Varus femoral neck/shaft angle. **Signs of early fracture line or periosteal reaction on image of femur

on antiresorptive treatment with negligible radiation exposure and without additional costs when DXA is performed for follow-up evaluation. Therefore, extended femur scans by DXA could be considered a clinically relevant screening method because early identification of AFFs has therapeutic consequences.

Between October 2011 and January 2013, 257 patients over age 50 who had been on bisphosphonates for over 5 years had a dual-energy X-ray absorptiometry (DXA) scan of the femur scan with the region of interest (ROI) extended distally from 15.3 to 22 cm. Cortical beaking was detected in 19 (7.4%); all had follow-up radiographs and seven (2.7%) had radiographic evidence of incomplete AFFs [101]. A subsequent study by the same investigators used single-energy (SE) DXA technology to image the entire femur between May 2013 and September 2014; none of 173 patients on bisphosphonates for over 5 years had cortical beaking, suggesting declining prevalence of AFFs possibly due to contemporaneous declines in bisphosphonates prescribing from 2009 through 2014 [102]. Between 2006 and 2014, Van de Laarschot et al. performed bilateral extended femur scans in 282 patients on long-term bisphosphonates [103]. Ten incomplete AFFs were diagnosed in nine patients (3.2%); one was a false positive and two patients did not have follow-up X-rays of the femur. Khosla et al., in a perspective published in the *Journal of Bone and Mineral Research*, noted that SE DXA is a promising new technology that can detect localized periosteal reactions and may be useful to monitor patients who require long-term BPs for impending AFFs [104].

Extended femur scans can easily be implemented as a screening tool for incomplete AFFs when a follow-up DXA is performed for therapeutic evaluation and they should not be limited to symptomatic patients. The exposure to irradiation should not represent a negative point. DXA has the advantage of utilizing very low irradiation exposure dose compared with conventional radiography [105, 106]. It is estimated that the effective radiation dose of a unilateral dual-energy

extended femur scan with a maximum length of 33.6 cm is ~0.37 μSv compared with ~10 μSv of one anteroposterior X-ray of the femur [107].

The extended DXA scans of the femur are carried out with the region of interest (ROI) extended distally from 15.3 to 22 cm to depict the lesser trochanter down to the supracondylar flare. Femur scans should be assessed for beaking (also called flaring), which is defined as localized periosteal or endosteal thickening of the lateral cortex, by visual inspection. If beaking was visible on DXA and evaluation of previous X-rays or other medical images did not explain this abnormality, an additional X-ray of the femur should be ordered to confirm the presence of incomplete AFF. Incidental findings such as irregularities of the medial cortex should be reported as well because they may lead to additional diagnostics. The patient's medical records should be checked for the occurrence of a complete or incomplete AFF in the past based on the available clinical correspondence and/or radiographs of the femora [100].

However, it should be kept in mind that prospective studies on the natural course of established incomplete AFFs are lacking and that it is also unknown if and how soon AFFs still may develop when there is absence of beaking at this moment. Furthermore, AFF by extended femur scan will necessitate decision-making for preventive surgery versus conservative treatment. In a recent study by Min and colleagues, a novel scoring system was proposed to predict the occurrence of a complete fracture among patients with incomplete AFF [108]. A score of 9 or higher indicates a high risk of an impending complete fracture and warrants prophylactic fixation.

Prophylactic Treatment

Impending fractures, as defined by the ASBMR, have an elevated risk of progressing to a complete fracture as high as 28.3% within 6 months after diagnosis. Subtrochanteric location, functional pain, and a radiolucent line of more than 50% of the lateral cortex were identified as risk factors for occurrence of a complete fracture [108]. Prophylactic surgical treatment with cephalomedullary nail seems to be effective, particularly in those with extensive cortical defects and pain and/or marrow edema on magnetic resonance imaging (MRI), which are predisposed to delayed or nonunion or to progress to complete AFFs without surgical intervention [109]. It also seems that fractures heal faster when treated surgically with a consequent shorter hospital stay. Progression to complete fracture and pain refractory to nonsurgical treatment reduce the success rate of nonsurgical treatment of incomplete fractures to approximately 50% [110].

The ASBMR recommends that patients with incomplete fractures and no pain, or those with periosteal thickening but no cortical lucency, should limit weight-bearing and avoid vigorous activity. Reduced activity should be continued until there is no bone edema detected on an MRI or no increased activity detected on a bone scan [6].

In the study carried out by Min and colleagues [108], a practical scoring system was developed to identify impending complete fracture among incomplete atypical femoral fractures. The proposed scoring system (Table 27.3) appeared accurate, reliable, and valid. The system can be useful to determine how to treat incomplete atypical femoral fractures. In planning the treatment of incomplete atypical femoral fracture, the problem lies in accurately distinguishing between nonpending fractures that can be treated without surgery and impending fractures that require prophylactic fixation. Results of the study revealed that a score of 7 is suggestive (probability of fracture, 8%) of an impending fracture, whereas a score of 8 is diagnostic (probability of fracture, 15%). When a score of 9 or more is obtained, the probability of fracture warrants prophylactic fixation. Conversely, incomplete atypical femoral fracture with a score of 7 or less may be treated conservatively. Patients who had painless incomplete AFF should be informed that pain might be a prodromal symptom for the progression to a complete fracture, and follow-up evaluations should be done frequently. During the follow-up, physicians should recalculate the proposed scor-

Table 27.3 Scoring system to predict the occurrence of a complete fracture among patients with incomplete AFF [108]

	Score		
Variable	1	2	3
Site	Others	Diaphyseal	Subtrochanteric
Pain	None	Mild	Functional
Contralateral	Complete	Incomplete	Intact
Radiolucent	Focal change	<1/2 of diameter of the involved femur	≥1/2 of diameter of the involved femur

ing system according to the changes of pain intensity and radiographic feature.

Management of Patients After Atypical Femur Fractures

The literature suggests that surgical treatment of AFF is more complex than that of typical femoral fractures, healing time is prolonged, and reduction and surgical technique is more demanding, leaving little room for error. Surgically, cephalomedullary nailing is the preferred method for surgical fixation of complete and incomplete AFF [111]. However, plate fixation and other methods may come into consideration depending on fracture location. For patients with bowed femurs, an alternative nail entry site may be necessary [112], and for these patients, lateral fixation has been suggested as an alternative [113]. It should be kept in mind that a greater percentage of fractures treated with plate fixation (31.3%) require revision surgery than fractures treated with intramedullary nailing (12.9%) [114]. In any event, surgery should be followed by a rehabilitation program.

Several studies show increased healing time for AFF. Lee et al. 48 showed that only 63% of 46 fractures healed within 6 months, but 95.7% subsequently healed without any further surgery. Egol et al. [115] reported 98% healing within 12 months of surgical treatment, almost two-thirds returned to self-reported baseline function. The same study also found that malreduction was associated with delayed healing. Other studies have not been able to achieve the same high healing rate. A review by Koh et al. [114] including 733 patients with 834 fractures showed an overall healing rate of 85% and a revision rate of 12.6%.

Lim et al. [116] tested 46 variables for association with healing time longer than 6 months or nonunion. High BMI and subtrochanteric fracture location were significantly associated with delayed healing time, but these factors are not controllable. More interesting was that delayed union or nonunion was significantly associated with postoperative gaps at the fracture site, primarily at the lateral or anterior cortex. Failing to restore the anatomical neck-shaft angle, when reducing and fixing AFF, has also been shown to cause significant longer healing time [117]. In cases of excessive bowing, anatomical reduction might require special techniques or implants [118]. Iatrogenic intraoperative fractures and implant failures are also more frequent compared with typical femur fractures [119].

Medical Management of AFF

For patients with AFF in either form, a stress reaction, stress fracture, incomplete or complete subtrochanteric or femoral shaft fracture, bisphosphate, or other potent antiresorptive agents should be discontinued. Dietary calcium and vitamin D status should be assessed, and adequate supplementation prescribed [6]. Simple fixation without optimizing bone metabolic profile and stopping any possible influencing factors may prevent healing [120] and even cause failure in these cases [121]. Whether the antiresorptive agents should be discontinued permanently or could be resumed after a "drug holiday" of 3–5 years is unknown [122].

Teriparatide (TPTD), a recombinant parathyroid hormone (PTH), has been suggested as a possible option of treatment of AFF, particularly for patients with incomplete AFF who have not undergone surgery. It has also the potential to

enhance bone healing in patients with delayed healing or nonunion and is, in theory, a good option for supplement treatment in patients with bisphosphonate-associated AFF since bone turnover is suppressed in these cases. However, the response to teriparatide has been variable (24), and while anecdotal evidence of the beneficial effect exists, there are also anecdotal case reports of teriparatide failure to prevent AFF [121]. In an open-label study, Watts and co-workers [122] performed iliac crest bone biopsies and clinical assessment in 14 patients treated with teriparatide for 2 years. Five had incomplete fractures (two bilateral), six had unilateral complete fractures, one had bilateral complete fracture, and two presented with complete unilateral fracture but developed a contralateral fracture during teriparatide therapy. Spine BMD was increased in most patients and stable in the remainder. In the hip, bone density remained stable throughout the teriparatide treatment. Therefore, teriparatide's role in the treatment of AFF is still unknown and should not be used routinely.

The use of low-intensity pulsed ultrasound (LIPUS) [123] and bone marrow aspirate concentrate [124] has been reported in small retrospective series and case–control series, but evidence is still too limited to conclude any beneficial effect.

Time for a New Treatment Paradigm

Over the past two decades, bisphosphonates have booked their place as the first option for osteoporosis treatment. With the introduction of the inexpensive generic oral bisphosphonate therapy, it has become the standard of care. Gaining more experience with the safety profile of bisphosphonates and link between AFF and long duration of bisphosphonates therapy, there were suggestions for a new approach of osteoporosis management. In the DATA-SWITCH study [125], teriparatide for 2 years followed by denosumab for 2 years led to much better bone response than denosumab for 2 years followed by teriparatide for 2 years. Suggestions to use teriparatide (as well as abaloparatide) as first-line therapy have faced two main hurdles: (1) they are administered as subcutaneous injections on a daily basis and (2) they are much more expensive than oral bisphosphonates. Even in glucocorticoid-induced osteoporosis, for which a study [126] showed fewer fractures in patients treated with teriparatide than with alendronate, the American College of Rheumatology still recommends oral bisphosphonates as the first treatment option. However, with the introduction of generic less expensive form of teriparatide, and the introduction of the recently licensed dual-action romosozumab, further changes in the treatment paradigm are expected.

The inclusion of the absolute fracture risk in the treatment pathways paved the way for new approaches to identify high-risk patients who most likely would require relatively longer-term therapy. For these patients starting with an anabolic agent first, would be the best option. Increasing bone mass and improving microarchitecture with an anabolic medication before starting a bisphosphonate might change the risk for fracture when the patient is reassessed 5 years after antiresorptive therapy. With this paradigm, it is likely that more patients will be eligible for a drug holiday. In the 2-year VERO study [127], teriparatide-treated postmenopausal women had fewer morphometric and clinical vertebral fractures than women treated with risedronate, providing more support to the use of anabolic therapy for osteoporosis. If AFF is related to the duration of bisphosphonate exposure, as has been shown by some [128] but not all [129] studies, then lowering fracture risk for some patients by this 7-year plan (2 years anabolic therapy followed by 5 years of bisphosphonate treatment) might lower the AFF risk. After the drug holiday, another course of anabolic therapy (perhaps 1 year) could then be followed by reinstitution of bisphosphonate treatment. While a plan such as this has some theoretical appeal, there may be a potential to implement it among the treatment recommendations in the coming few years.

In conclusion, though AFF remains a rare complication in comparison to the osteoporotic fractures prevented by antiresorptive therapy, AFF represents a challenge to health-care profes-

sionals treating osteoporosis. The ASBMR has been defined as "the fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur." Though linked to long-term bisphosphonate therapy, it occurred also in association with other medications. Greater understanding of the biological and genetic pathogenesis of AFF may permit a more precise approach to assessing individual risk before starting antiresorptive therapy. Recent development of single-energy DXA scan technology that can detect incipient cortical "beaking" may permit monitoring of patients on long-term antiresorptive therapy for incomplete AFFs prior to fracture. Until newer methods to treat osteoporosis are developed, creative management strategies, avoidance of treatment for those at low risk, as well as careful monitoring of treated patients are the only tools currently available to minimize the incidence of AFF.

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28 Pregnancy, Lactation, and Bone Health

Yasser El Miedany

Introduction

During pregnancy and lactation, female physiology must adapt to meet the added nutritional demands of the fetus and neonate. In fact, both pregnancy and lactation impose significant stress on maternal calcium homeostasis, consequently resulting in substantial changes in the calcium store of the body, that is, bone mineral [1]. During pregnancy, the baby growing in its mother's womb needs plenty of calcium to develop its skeleton. This need is especially great during the last 3 months of pregnancy. If the mother does not get enough calcium, her baby will draw what it needs from the mother's bones. Similarly, breastfeeding affects the mothers' bones too. Studies have shown that, during breastfeeding, women often lose 3–5% of their bone mass, although they recover it rapidly after weaning [2]. This bone loss may be caused by the milk's calcium content, which is drawn from the mother's bones. However, the amount of calcium the mother needs depends on the amount of breast milk produced and how long breastfeeding continues. Women also may lose bone mass during breastfeeding because they are producing less estrogen, which is the hormone that protects bones [3].

Teenage mothers may be at especially high risk for bone loss both during pregnancy and breast feeding, as well as for osteoporosis later in life [4]. In contrast to older women, teenage mothers are still in the phase of building much of their own total bone mass. The unborn baby's need to develop its skeleton may compete with the young mother's need for calcium to build her own bones, compromising her ability to achieve optimal bone mass that will help protect her from osteoporosis later in life. To minimize any bone loss, pregnant and breastfeeding teens should be especially careful to get enough calcium during pregnancy and breastfeeding. On the other hand, the combination of breastfeeding and delaying pregnancy until the majority of bone mass has been acquired appears to have a protective effect on bones [2].

This chapter will try to answer several questions related to the impact of pregnancy and lactation on the women's bone health, including the following questions: How much is the calcium demand during pregnancy and lactation? What are the body adaptations that take place during pregnancy and lactation to meet these added demands? What are the biochemical and hormonal changes that happen to facilitate these adaptations and its impact on the mineral and skeletal metabolism? What are the physiological changes that take place in bones to support these extra calcium needs? What impact do these adaptations have on the bone mineral density? And

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lastly, what are the long-term consequences of pregnancy and lactation on the women's skeletal health?

The Calcium Demand During Pregnancy and Lactation

The fetal requirement for mineral, which the pregnant woman must supply, has been determined by measuring the bone metabolism during (calcium and bone metabolism) ash weight and mineral content of fetal cadavers between 24 weeks and term. Multiple studies have demonstrated that the average full-term fetus has30 g calcium [5–13], 20 g phosphorus [11–13], and 0.80 g magnesium 7, 11–13]. However, fetal mineral content is not obtained at a constant rate during pregnancy; instead, at least 80% of the calcium, phosphorus, and magnesium present in a human term fetus is accreted during the third trimester [5–12]. This corresponds to a mean calcium transfer rate of 100–150 mg/kg per day [5–11], which, for an average-sized fetus, is 60 mg/day at week 24 and 300–350 mg/day between the 35th and 40th week of gestation [11]. Similarly, the rate of phosphorus transport is 40 mg/day at week 24 and increases to 200 mg/day over the last 5 weeks of gestation [2, 11]. The rate of magnesium transfer increases more modestly from 1.8 to 5.0–7.5 mg/day over the last 5 weeks [11]. When expressed as hourly rates, during the third trimester the fetal demand for calcium and phosphorus represents between 5% and 10% of the amounts present in the mother's plasma [6, 8]. This means that the fetal demand for calcium and phosphorus has the potential to provoke maternal hypocalcemia and hypophosphatemia.

The neonatal requirement for mineral, which may be supplied through breastfeeding, has largely been inferred from several approaches. A general consensus is that average milk output and its average calcium content are more robust indicators of the average neonatal requirement for calcium [14]. The Institute of Medicine used these calculations to determine the estimated average requirement (EAR) for calcium intake and concluded that breastfeeding requires that an average of 200 mg calcium be provided daily through milk to a singleton during the first 6 months. From this intake, the neonatal skeleton is expected to accrete ~100 mg of calcium daily [14]. However, the output of milk on an individual basis is determined by the suckling demands of the neonate and can certainly markedly exceed these values. Women who nurse twins and triplets can have, respectively, more than double and triple the milk output of women nursing singletons [15, 16]. Individual cases of women nursing singletons have documented milk output of up to 2.4–3.1 liters per day that was sustained for more than 12 months of lactation [17, 18]. The composition of milk is similar between women with average and high outputs [15, 16], and so producing more milk will cause greater maternal losses of calcium. Between 6 and 12 months of age, more infant nutrition comes from solid food despite continued breastfeeding. Fewer studies have examined this time frame, so the data are less robust. The average calcium content of human milk is somewhat lower at 200 mg/l [19], and the intake is less at 600 ml/day [20], which means that the infant has an estimated calcium intake of 120 mg/day from human milk. An additional 140 mg/day of calcium is estimated to come from solid foods to bring the total infant calcium intake to ~260 mg/day [14].

Overall, these studies indicate that pregnant women do not provide much calcium or other minerals to their fetuses until the third trimester, when the peak rate of calcium transfer exceeds 300 mg/day on average. Data for lactating women and their babies are more variable, but suggest that the average calcium requirement is more modest, at ~200 mg daily during the first 6 months, and ~120 mg daily during the second 6 months. All of these values, from 300 mg daily during the third trimester to 120 mg daily during late lactation, may seem achievable given the normal intake of calcium and normal efficiency of intestinal calcium absorption. However, fractional calcium absorption is normally ~25% of intake in healthy adults who consume adequate calcium [21]. If normal efficiency of intestinal calcium absorption were relied upon, pregnant women would have to consume an extra 1200 mg/

day during the third trimester, whereas lactating women would have to consume an extra 800 mg daily during the first 6 months and 480 mg daily during the second 6 months.

Body Adaptation During Pregnancy and Lactation

Pregnancy: The main objective of calcium adjustments during pregnancy is to enable the adequate transplacental transfer of 30 g of calcium required for the successful mineralization of the fetal skeleton. Eighty percent of that amount is transferred during the third trimester when placental calcium transport averages 110–120 mg/kg per day [22]. The fetus enjoys a status of persistent hypercalcemia, where a calcium placental pump maintains a gradient irrespective of the calcium status in the mother (Fig. 28.1). This means that insufficiencies in the adjusting machinery in the mother will entail decalcification at her skeleton, something that may be a universal phenomenon at the third trimester, when the transfer of calcium increases drastically.

The physiological maternal adaptation in the metabolism of calcium results from the implication of different regulators. Interestingly, the fetus collaborates in most of them, with placenta being an important contributor. Modern analytical techniques and sophisticated animal models have provided some advances in the field, although several obscured areas remain. A clear picture of the specific role of each of the potentially concerned agents is elusive, but some key responsibilities have come into focus [23].

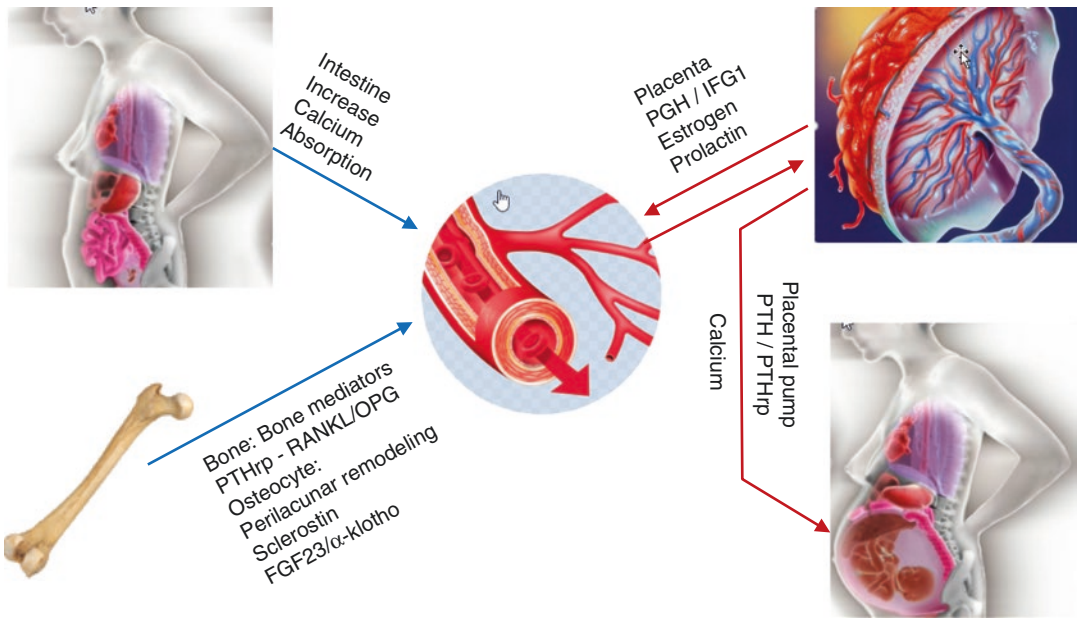

Fig. 28.1 Adequate transfer of calcium to the fetal skeleton is ensured by changes in both the mother and the fetoplacental unit. The mother is the main source of the calcium transferred to the fetus. Three main domains, mother, placenta, and fetus, are shown in the figure. The changes in the maternal domain include an increased intestinal absorption of calcium. More calcium supply is induced by the maternal parathyroid hormone-related-peptide (PTHrp) and by local changes within maternal bone, where receptor activator of nuclear factor kappa B ligand/osteoprotegerin (RANKL/OPG) and osteocytes may participate. The calcium drainage is partly counterbalanced by an increased anabolic process, where IGF1, stimulated by placental growth hormone (PGH), is involved. Other potential agents are estrogen and prolactin. Despite the reactive bone formation process, the bone balance can be negative for the mother. The placental calcium gradient is sustained by the placental pump, where fetal PTH and PTHrp are determinant

Mineral Ions During Pregnancy

Normal pregnancy results in altered levels of calcium [24]. The ionized calcium (the physiologically important fraction of calcium) remains constant throughout pregnancy. In contrast, the total serum calcium (which is the sum of the ionized, complexed and albumin-bound fractions of calcium in the circulation) falls in pregnancy due to a fall in the serum albumin. In clinical practice, the total serum calcium is more commonly measured than the ionized calcium. The commonly observed decrease in total serum calcium should not be mistaken for evidence of "physiological hyperparathyroidism of pregnancy," an erroneous concept that has persisted in some modern texts [25, 26]. The fall in total serum calcium is an unimportant artifact of an unphysiological measurement; the ionized calcium is the relevant measurement and should always be assayed if there is any doubt about the true value of the serum calcium during pregnancy (or at any time). Serum phosphorus levels are also normal during pregnancy.

Intestinal and Renal Handling of Calcium

Intestinal Absorption of Calcium: Several clinical studies have demonstrated that intestinal absorption of calcium is doubled during pregnancy from as early as 12 weeks of gestation (the earliest timepoint studied); this change appears to be a major maternal adaptation to meet the fetal need for calcium. This increase may be largely the result of a 1,25-dihydroxyvitamin D-mediated increase in intestinal calbindin$_{9K}$-D and other proteins; based on evidence from limited animal studies, prolactin and placental lactogen (and possibly other factors) may also mediate part of the increase in intestinal calcium absorption. The increased absorption of calcium early in pregnancy may allow the maternal skeleton to store calcium in advance of the peak fetal demands that occur later in pregnancy [24].

Renal Handling of Calcium: The 24-h urine calcium excretion is increased as early as the 12th week of gestation (the earliest timepoint studied), and the amounted excreted may exceed the normal range. Since fasting urine calcium values are normal or low, the increase in 24-h urine calcium likely reflects the increased intestinal absorption of calcium (absorptive hypercalciuria). The elevated calcitonin levels of pregnancy might also promote renal calcium excretion (Fig. 28.2).

Vitamin D

The concentration of 1–25 (OH)2 vitamin D3 (calcitriol), the active metabolite of vitamin D, increases during pregnancy. The increase, already detected at the first trimester, continues up to term, when it attains levels that are several folds higher than before pregnancy [27, 28]. Maternal kidney, and possibly placenta, decidua, and fetal kidney, provides the necessary 1a-hydroxylase activity. The contribution of the extrarenal sources, however, seems to be of little significance, as suggested by the inappreciable changes in calcitriol reported in an anephric woman during pregnancy [29]. The changes in vitamin D are concomitant with the improvement in the efficiency of the intestinal absorption of calcium, which doubles its capacity. This intestinal adaptation seems to be important in helping the mother to accommodate the fetal demand for calcium.

Parathyroid Hormone

The increased intestinal absorption of calcium has prompted the hypothesis of a possible contribution of PTH. The characteristic hypocalcemia of pregnant women has further contributed to the concept that hyperparathyroidism is an important mechanism fueling the fetal skeleton with calcium sequestered from the mother. However, it is now known that hypocalcemia derives from the physiological hypoalbuminemia of pregnancy,

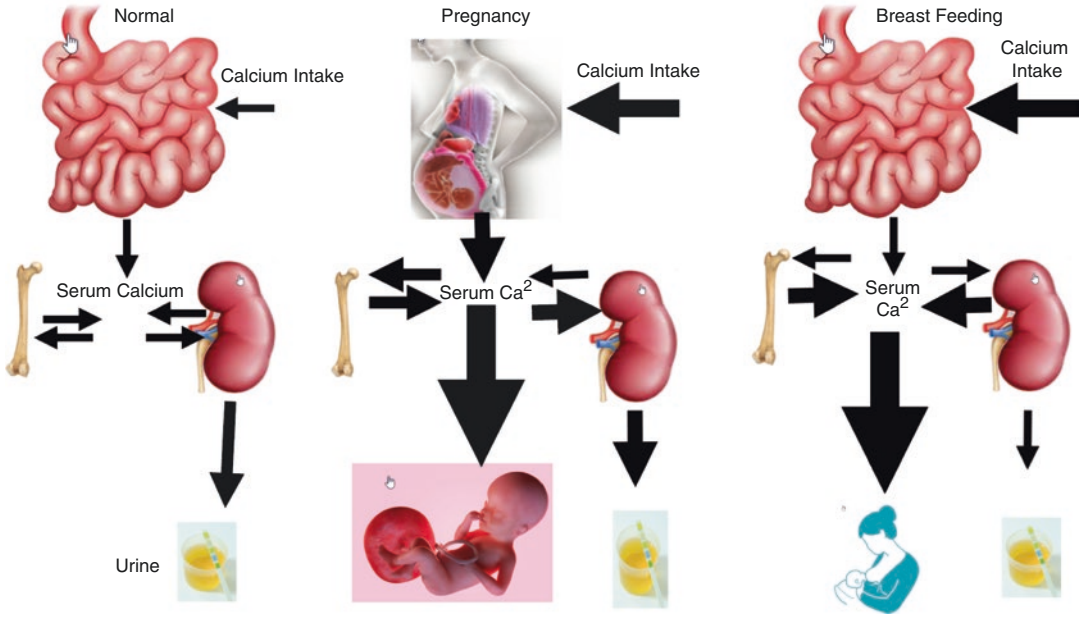

Fig. 28.2 Comparison of the calcium homeostasis in human normal state, pregnancy, and lactation. The thickness of arrows indicates a relative increase or decrease with respect to the normal and nonpregnant state

which coexists with unaltered levels of free calcium, the real reset regulator of PTH levels [30]. Furthermore, there is no change in phosphate levels, and more reliable immunoassays confirm that the circulating PTH level slightly decreases during pregnancy and normalizes at the end of this state [31].

The PTHrp constitutes another potentially important agent, given its significant role in calcium loss from maternal bone during lactation. PTHrp increases during late pregnancy, the sources being both maternal and fetal as breast, decidua, placenta, amnion, umbilical cord, and fetal parathyroid glands have been involved [30]. The details about the role of PTHrp during the end of pregnancy are not totally clear, but pathological hypercalcemia follows when abnormally increased due to disease [32].

The changes in fetal PTH and PTHrp also play an indirect role in the regulation of maternal skeleton. Both PTH and PTHrp participate in maintaining the calcium placental pump, which acts as an active mechanism draining calcium from the mother. The role for the calcium-sensing receptor (CaSR) in setting the balance between PTH and PTHrp within the fetus has been demonstrated in murine models [33]. Genetic models in mice, where a crucial role for PTHrp [34] and the concurrent collaboration of PTH [35] has been shown, confirm the fetal responsibility in orchestrating these adjustments.

IGF1 and Pituitary Growth Hormone (PGH)

Pregnancy also involves changes in the circulating levels of IGF1. The oscillations are small during the first and second trimesters, but then the peptide increases during the third trimester and decreases postpartum [31, 36, 37]. These changes seem to be influenced by active participation of PGH, which gradually replaces the control in the synthesis of IGF1 during the second half of pregnancy [38]. PGH, which should be distinguished from placental lactogen (HPL), is the product of the expression of the GHV (GH2) gene, as opposed to pituitary GH, which is the product of the GHN (GH1) gene [39]. PGH is secreted in the syncytiotrophoblast from the sixth week of pregnancy and gradually replaces pituitary GH during pregnancy [38, 40]. PGH is found only in mater-

nal blood and is supposed to influence the availability of nutrients to the placenta. A prospective clinical study found a significant association between PGH and fetal growth during normal pregnancy [37]. This modulation may be direct, by autocrine or paracrine mechanisms, or indirect, by regulation of IGF1 [41].

Other Regulators

RANKL and Osteoprotegerin (OPG): Both proteins [which belong to the tumor necrosis factor (TNF) superfamily, are produced in bone by osteoblasts] exert a powerful regulatory effect on bone metabolism [42]. RANKL binds to membrane RANK receptors and sets in motion a series of postreceptor events leading to activation, migration, and final differentiation of mature osteoclasts, the bone-resorbing cells [43]. Binding of OPG to RANKL prevents the interaction of RANKL for RANK and limits osteoclastogenesis [44].

Studies investigating the changes in RANKL and osteoprotegerin (OPG) during pregnancy revealed that osteoprotegerin (OPG) levels are stable during pregnancy and only rise at term, when they double in parallel with an apparently paradoxical increase in bone resorption [45, 46]. The rapid postpartum fall in OPG suggests a placental origin, which has been corroborated by the finding of a high concentration of osteoprotegerin in placental membranes [47]. Studies investigating the circulating levels of RANKL revealed parallel changes to those of osteoprotegerin [48, 49]. However, these data require a cautious interpretation because of the methodological problems with current assays for measurement of serum RANKL. Most commercial kits measure free RANKL, which is w1/1000 of the total serum RANKL. This feature explains that some investigators have reported undetectable levels of RANKL in up to 50% of individuals [50]. Moreover, the antibodies may measure different RANKL types of the soluble molecular species of the cytokine [51], a conceivable difficulty given the research profile of the available assays. These limitations are also attained, and may be augmented, when the ratio RANKL/OPG is used instead of RANKL.

Sclerostin and Fibroblast Growth Factor 23: Osteocytes are multifunctional cells with crucial regulatory roles in several mechanisms affecting bone homeostasis [52]. Among their abilities, osteocytes may remove and replace their perilacunar matrix, a concept baptized as "perilacunar remodeling," which has been shown to be regulated by hormonal changes in mice. Lactation is associated with increases in osteocyte lacunar area [53]. The potential participation of this mechanism in the maternal and fetal bone changes during pregnancy is still not fully clear. Sclerostin is an osteocyte-derived protein with a significant capacity for inhibiting the Wnt signaling pathway, a powerful promoter of bone formation. Studies have shown that the inhibition of sclerostin with specific monoclonal antibodies has a noteworthy effect in terms of increase in the bone mass in osteopenic women [54].

Fibroblast Growth Factor 23 (FGF23), mainly expressed in osteoblasts and osteocytes, is another powerful modulator of bone metabolism because of its regulatory potential of phosphate and 1,25-dihydroxyvitamin D3 [55].

There is still sparse information on the possible implication of the Wnt pathway in the development of the fetal skeleton. A Scandinavian study [56] reported that the circulating levels of sclerostin were lower in the mother at the 30–32 weeks of pregnancy than in the umbilical cord at delivery. Interestingly, cord sclerostin, but not maternal sclerostin, was significantly associated with dual-energy X-ray absorptiometry (DXA)-measured total body bone mineral content (BMC) in the newborn. The levels of FGF23 and of α-klotho, the FGF23 obligatory co-receptor, were measured in the same study. While the levels of FGF23 were similar in the maternal and the fetal compartment, those of α-klotho were higher in the umbilical cord plasma. However, neither FGF23 nor α-klotho was associated with fetal BMC [56].

The positive correlation between cord sclerostin and fetal BMC raises many unresolved questions. Sclerostin counteracts the anabolic effects of the Wnt pathway, which should translate into less effective bone formation potential. The possibility that sclerostin might be reactive in the context of a high bone anabolic milieu, as found in the fetus during the third trimester, may be an explanation. Studies in adults exhibiting high bone mass phenotype are consistent with this hypothesis [57]. The progressive elucidation of the complex interplay between regulators of bone metabolism in the fetus will help to understand these findings.

Estrogens and Prolactin: Pregnancy also involves changes in other agents with powerful effects on bone metabolism, such as estrogens and prolactin (PRL), which in both cases are produced in the placenta. Their specific potential in modulating maternal bone metabolism is still unresolved.

Estrogens are known downregulators of bone resorption [58], and therefore, should act to contain the accelerated loss of bone mass. There is no indication suggesting an alternative role for estrogens during pregnancy. The case of prolactin is more complicated. Data from experimental studies have shown that there are prolactin receptors in human osteoblasts and that their activation leads to reduced proliferation and mineralization potential of these cells [59]. Moreover, studies on rats have shown that prolactin directly stimulates osteoblasts to increase the ratio of RANKL to osteoprotegerin [60]. The limiting action of osteoprotegerin (OPG) on the proresorptive potential of RANKL would translate into increased loss of bone mass.

Pathophysiology and Lactation-Associated Osteocytic Osteolysis

One remarkable characteristic of bone microarchitecture is the magnitude of the osteocyte network that lies hidden inside the mineralized matrix. Dendritic osteocytes connect to one another, to blood vessels and to bone surface cells enabling a global communication within bone tissue. Residing in a fluid-filled interstitium of lacunae and canaliculi, osteocytes sense the mechanical load that is being placed upon the skeleton during locomotion [61]. The transmission of the loading information from osteocytes is coupled with the secretion of factors, that is, sclerostin and RANKL, to directly regulate bone matrix turnover by osteoblasts and osteoclasts [62, 63]. In the recently discovered multifunctionality of osteocytes, ranging from phosphate homeostasis to interaction with distant organs, this is just one of many ways through which osteocyte network connectivity contributes to bone health [52].

In addition to their interaction with other bone cells, they interact with their local perilacunar and pericanalicular matrix. Around the 1970s, bone resorption by osteocytes even seemed as important for the provision of calcium as osteoclast-dependent resorption [64]. The process of osteocytic osteolysis may have significant effects on bone physiology. The reversible remodeling of lacunar shapes and network connectivity could not only free calcium from the bone matrix, but could also affect the mechanosensation detected by osteocytes and alter bone turnover. Furthermore, lacunocanalicular adaptations may contribute to local bone quality characteristics and fracture resistance [65].

The enhanced resorption of the maternal skeleton during lactation is further supported by measurements of bone turnover markers, bone structure by high-resolution imaging, bone material properties, and histomorphometric analyses. The classical mechanism of enhanced bone resorption is osteoclast-driven and affects primarily trabecular bone and endocortical surfaces [66, 67]. However, if osteoclast-mediated bone resorption was the sole mechanism at play, then the inactivation of osteoclasts through a bisphosphonate would be expected to fully attenuate the decline in BMD during lactation. Since experimental data showed only a partial blocking of bone loss in lactating mice treated with pamidronate [68, 69], it was hypothesized that an alternative osteolytic mechanism exists.

In lactating mice, a targeted deletion of parathyroid hormone (PTH) receptor 1 (PTHR1) prevented osteocyte-specific remodeling and upregulation of osteoclast markers, whereas treatment with PTH-related peptide (PTHrP) led to the opposite effects, demonstrating the importance of PTHrP signaling through the osteocyte PTHR1 [70]. This is in accordance with the known upregulation of PTHrP into the systemic circulation and into milk during lactation [68, 71–74]. Since PTHR1 signaling also induces the production of receptor activator of NF-κB ligand (RANKL) [75, 76], and osteocytes are major contributors of RANKL production [28, 63], it seems possible that during lactation osteocytes participate in both, a direct remodeling of their environment and a stimulation of osteoclast-mediated resorption through upregulation of RANKL [77]. Conversely, after conditional knockout of the PTHR1 in osteocytes, a low calcium diet translated into an impaired homeostatic calcemic response, that is, hypocalcemia in mice, indicating that osteocytes are involved in mineral mobilization [29, 78]. Further insight into the mechanism through which osteocytes achieve perilacunar remodeling and calcium mobilization was supported by the finding that osteocytes generate a mild acidic environment through expression of the proton pump in an analogous manner to osteoclasts, and that this cell-induced acidification is modulated through PTHrP [79].

Lactation in rodents and humans is physiologically characterized by a surge in prolactin production and a decline in estradiol and progesterone [68, 80, 81]. In a study investigating the impact of estrogen loss on the osteocyte lacunar–canalicular network, Ciani et al. reported an increased solute transport around osteocytes of the proximal tibia of ovariectomized rats probably because of an enhanced lacunar–canalicular porosity [82]. On the other hand, prolactin levels surge during early lactation initiating milk production. In the meantime, prolactin is a known stimulator of PTHrP production [83]; consequently, prolactin is able to exert direct action on bone cells. Seriwatanachai et al. showed that prolactin enhances bone turnover by downregulating osteoprotegerin, while concurrently upregulating RANKL production [84].

Another study identified matrix metalloproteinase 13 (MMP-13) as an essential factor for lactation-induced osteocyte perilacunar remodeling [85]. MMPs are multifunctional proteins, which mainly act as coupling factors of bone remodeling under physiological conditions, whereas their overexpression usually results in enhanced bone resorption and osteolysis [86]. Tang et al. showed that MMP-13 is indispensable for osteocyte perilacunar remodeling and its loss results in compromised bone quality and strength [85].

BMD Changes During Pregnancy and Lactation

There has never been, and is very unlikely to be, a randomized, double-blind, placebo-controlled trial (RCT) demonstrating that pregnancy and lactation influence the BMD level or incidence of fracture. Blinded RCTs, the highest level of "evidence" cannot be performed as neither the investigator nor the participant can be blinded as to pregnancy and lactation. Instead, inferences can be drawn on the basis of retrospective and prospective, observational, cohort studies, and cross-sectional, observational, and case–control studies. As these studies are all subject to the risk of systematic bias, they can never be regarded as hypothesis-testing. They can only be hypothesis-generating, and causality can never be proven. Lack of the highest level of evidence within the evidence-based hierarchy is not proof of lack of efficacy. In fact, implications can be considered based on the highest level of evidence in the literature. There are several challenges when it comes to assessment of BMD changes during pregnancy and lactation, which include the following.

Methodological Problems for Evaluating BMD in Pregnant and Lactating Women

Evaluating the BMD in pregnant and lactating women has attendant problems. By using the current bone mineral density assessment techniques, both weight and soft tissue composition can influence the BMD measurement [87, 88]. If a prospective study finds changes in the BMD, with additional changes in the soft tissue, questions are raised whether the discrepancy in the BMD between the two measures is attributed to actual discrepancies in the BMD or whether it is linked to a discrepancy in the soft tissue composition that may have occurred between the assessments and could have led to the false conclusion that changes in BMD have occurred [87–89].

Weight, lean body mass, and fat content are aspects that are prone to change during both pregnancy and lactation, and consequently represent confounding factors when changes in BMD are being evaluated [90]. Firstly, no consensus exists on how the BMD data should be presented—unadjusted for weight or soft tissue composition [91], adjusted for changes in weight [92], or adjusted for changes in fat and lean body mass separately [88]. Furthermore, the fluid shift that occurs during and just after a pregnancy [93] also influences the BMD estimation. The increase in extracellular fluid, together with the altered distribution of tissue volume resulting from the development of the fetus, and changes in the placental and mammary compartments, makes measurements even more difficult to interpret [94]. The third issue is an ethical one as most of the measuring techniques involve ionizing radiation, and the radiation is expected to reach the fetus. Such measurements should be avoided, leading to baseline measurements in prospective studies being done before conception and after delivery—in many studies, years before and years after the pregnancy in question.

Variation of the Confounding Factors That Can Influence BMD

Calcium is the most prominent mineral of the skeleton. In fact, calcium is vital for the skeleton not only during growth [95], but also during young adulthood [96] and in old age [97]. Furthermore, there is an existing relationship between calcium intake and fracture risk particularly in the elderly [97]. Calcium functions as a threshold nutrient, that is, calcium intake is relevant up to a specific threshold level only, and adding more calcium above this level will not improve BMD [98]. The calcium supply comes into focus during a pregnancy as the pregnant mother is the main and only source to provide the fetus with calcium; this ranges from approximately 50 mg/day at 20 weeks of gestation and rising to 330 mg/day at 35 weeks [99]. Theoretically, for pregnant women, such higher calcium demand represents a load to the skeletal system and is expected to reflect negatively on the BMD; if she relies mainly on her skeletal reserves of the mineral. However, on the other hand, there are physiological mechanisms in place during pregnancy to make up for this demand. This includes increased intestinal calcium absorption as well as reabsorption from the kidney, which usually leads to ample calcium supply that is sufficient for both the mother and the fetus. This view is supported by studies reporting that calcium supplementation in pregnant women with normal or high calcium intake has little or no effect on their BMD [27]. Whereas in pregnant women with low calcium intake, there is some evidence that they may benefit from calcium supplementation [99, 100]. Other dietary components such as protein, magnesium, zinc, copper, iron, fluoride, as well as vitamins D, A, C, and K, are also required for normal bone metabolism. On the other hand, a high intake of caffeine and alcohol exerts a negative impact on BMD [101, 102]. Many women reduce both smoking and alcohol consumption

during pregnancy, and theoretically, this could (if anything) lead to increased maternal BMD.

On another front, earlier published studies reported that during a pregnancy there is an increase in maternal weight and fat content [88, 103]. While the increased weight results in an increased mechanical load on the skeleton, the increased fat content leads to an increased estrogen production. Both of these factors, hypothetically, have a positive anabolic influence on bones and consequently the BMD [104]. Furthermore, the production of estrogens by the placenta, predominantly in the form of estriol (but also estron and estradiol), leads to generally high levels of estrogens [105]. As estrogen is regarded as the most important regulatory hormone for the skeleton, these changes could hypothetically lead to increased BMD.

Lastly, physical activity, which is another important anabolic regulatory factor for BMD in pregnant women, has been considered and assessed [106]. As pregnant ladies often reduce their normal level of physical activity, at least during the latter part of the pregnancy, this could theoretically lead to reduction in BMD.

Collectively, these changes are able to influence BMD; therefore, it is virtually very difficult to predict the final change in BMD that may occur during a pregnancy.

So, Are There Any Changes in BMD During a Pregnancy?

In a cross-sectional case–control study carried out by Karlsson et al. [106], which included 73 women who had just given birth, there was a 7.6% lower lumbar spine BMD and a 3.9% lower total body BMD reported, in comparison to 55 age- and sex-matched controls, after adjustment for differences in soft tissue composition. This was the only published study that took into consideration the soft tissue discrepancies when evaluating the impact of a pregnancy on BMD. Several prospective, controlled, and non-controlled studies were in agreement with the outcome of that study published by Karlsson et al. In a small study carried out by Drinkwater and Chesnut [107], which included six women, there was a 2.4% reduction in femoral neck BMD and a 2.2% reduction in radial shaft BMD. In another study, which included 10 women, Black and colleagues [36] reported a 3.2% reduction in both spine and total hip BMD. In a third study, which included 38 women, More et al. [108] reported a 4.9% reduction in ultra-distal forearm BMD. In a fourth study, which included 5 women, Holmberg-Mattila et al. [109] found a 3.0% reduction in spine BMD, whereas Naylor et al. [110] found a 3.2% reduction in pelvis BMD and a 4.6% reduction in spine BMD in 16 women. In concordance, Ritchie et al. (1998) reported a 9% loss in spine BMD in 14 women.

In summary, only Karlsson et al. [88] and Sowers et al. [91] performed the follow-up measurements close to delivery, 3 days and 15 days after parturition, respectively. The other studies used baseline measurements done up to 12 months before conception and follow-up measurements done up to 12 months after delivery, inevitably including the effect of lactation. Furthermore, only three studies were controlled and only one study adjusted for differences in soft tissue composition when pregnant and non-pregnant women were compared.

In spite of all these methodological problems, it can be concluded that during a pregnancy there is a loss of about 5% of the maternal BMD. It also seems reasonable to conclude that general intervention has little or no effect on this loss, except perhaps in cases where there is a low nutritional intake of calcium reported.

Variation of the Confounding Factors That Can Influence BMD During Lactation

Lactation is associated with dramatic changes in the calcium metabolism. It is estimated that during full breastfeeding, every day, 200 mg calcium is transferred from the mother to the infant; consequently, in one lactation period of 3–6 months, the total calcium transfer through the breast milk is greater than the calcium content transferred across the placenta during the pregnancy period

of 9 months [99]. However, this is balanced by an adaptation process of the maternal absorption of calcium to the required level, and a general calcium supplementation appears to have no or only minor impact on the BMD during lactation.

Studying the effect of increased calcium supply on BMD and bone turnover, it seems that calcium supplementation does not influence the loss of BMD induced by lactation. Randomized, controlled intervention studies of lactating women did not show any effects of an increased calcium supply on bone turnover markers [27, 92, 94]. Similar findings were also reported when the BMD was monitored. In a study involving 274 lactating mothers, Polatti et al. [111] reported that calcium intervention had only transient, without any long-term benefits on BMD. Similarly, Kalkwarf et al. [112] did not find an effect of calcium supplementation on BMD, whereas Prentice et al. [113] stated that during lactation even women with low calcium intake did not benefit from calcium supplementation. On the other hand, even the few studies that reported a positive, though yet small, influence of postpartum calcium intervention have usually reported a beneficial impact similar to that recorded in nonlactating mothers [27, 113, 114].

As far as vitamin D is concerned, there were no studies to indicate that vitamin D requirements are greater in lactating women than in nonlactating ones [115]. Finally, it is difficult to exclude the possibility that the intake of other dietary components, associated with the arrival of a new baby, may have an impact on the mothers' BMD. Many women reduce smoking, coffee, and alcohol intake, and as these nutritionally exert a negative impact on BMD [101, 102], these changes may have an anabolic effect on the BMD.

On another front, after giving birth, there is a decrease in maternal weight and fat content was reported during lactation, which is most obvious during the first weeks after a delivery [116]. Such loss of body weight results in a decreased mechanical load on the skeleton, whereas the reduction of the fat content results in a decreased peripheral estrogen production. Both of these factors may (hypothetically) have a catabolic impact on the BMD [91, 104]. This negative impact on BMD is further accentuated when breastfeeding is started.

According to a review by Kovacs, lactation is associated with significant temporary bone loss and increased bone turnover markers, especially during the exclusive breastfeeding period [2]. High levels of prolactin cause prolonged suppression of the hypothalamic–pituitary–ovarian axis, amenorrhea, and consequent hypoestrogenemia. In addition, other factors, such as higher parathyroid hormone-related protein (PTHrP) serum levels and lower efficiency of calcium intestinal absorption, may contribute to higher bone resorption rate [3]. Prolactin concentrations remain elevated during the first 3–4 months of lactation, and it has been suggested that this high level may have a negative influence on the BMD by suppressing the hypothalamus–pituitary axis [91]. After weaning, estrogen levels return to normal, which should lead to a recovery in BMD—a notion supported in the majority of published studies [92, 117, 118].

In contrast to pregnancy, after delivery, many women gradually increase their level of physical activity, a change that would have a beneficial effect on BMD. However, some women find that after giving birth they lack spare time, and consequently their level of physical activity becomes reduced. Therefore, it remains difficult to draw any general conclusions regarding the effect of physical activity during lactation, and whether active exercise would result in increased BMD.

So, Are There Any Changes in BMD During Lactation?

In the current literature, there are two systematic reviews focused on lactation-related bone loss [118, 119]. However, these studies make no mention to the new methods for bone loss evaluation, including HR-pQCT, hip structural analysis (HSA), and body composition data. Earlier studies revealed that during the first months of lactation assessing biochemical markers of bone resorption and bone formation revealed an elevated bone turnover. However, this decreases

after 6–12 months, even in women who continue to breastfeed [94, 99]. Such variation of the bone biochemical markers gives an indirect evidence that the level of BMD changes during lactation. In a cross-sectional case–control study, carried out by Karlsson et al. [88], 65 breastfeeding women sustained a drop of 4.1% in the lumbar spine BMD and a 2.0% lowering of the femoral neck BMD after 5 months of lactation, after adjustment for differences in soft tissue composition. Interestingly, 12 months after delivery, assessment of the lumbar spine BMD in this cohort showed complete recovery in this cohort, whereas the BMD in the femoral neck showed partial recovery [88].

The results of other prospective, controlled and noncontrolled studies were in agreement with those reported in Karlsson et al. studies [88, 116]. In the work carried out by Drinkwater et al. [107], which included 10 women with 6 months of lactation, the authors reported a 6% reduction in femoral neck BMD. In another work, Affinito and colleagues [121] compared 18 lactating mothers to 36 nonlactating mothers, and the results revealed reduction of 7.5% in lumbar spine BMD and a 5% reduction in distal radius BMD, with an incomplete recovery reported 6 months after weaning. In concordance, in a study that included 40 breastfeeding mothers and 40 age-matched controls, Kent et al. [114] found a 7.1% reduction in the ultradistal radius BMD. The conclusions were supported by the finding of a dose–response relationship that a longer period of lactation is associated with a higher loss in BMD, an outcome that strengthens the suggestion that lactation does lead to a reduction in BMD [108, 122]. It also seems reasonable to conclude that general interventions have little or no effect on BMD loss during lactation, except perhaps calcium supplementation for women with a low nutritional intake of calcium.

The clinically most relevant question that comes to the surface is, does BMD recover after weaning? A transient phase of bone loss with lactation, at a magnitude as reported above, but with a total recovery after 6–18 months of weaning, has been supported in most publications [92, 116]. It has also been suggested that closely spaced pregnancies may be a risk factor for osteoporosis later in life due to additive periods with a loss of BMD in quick succession without appropriate recovery period [121]. However, there have been studies investigating mothers with short intervals between childbirth and lactation periods longitudinally, but all of these studies imply that these women do not risk failure of bone recovery to pre-lactation levels after the last period of lactation [91, 122].

Parity and Bone Long-Term Effects of Pregnancy and Lactation on the BMD

As noted earlier, pregnancy and breastfeeding affect calcium metabolism, and eventually, BMD. Consequently, the vertebral and femur BMD declines owing to high calcium demand and bone resorption during pregnancy. However, compared to women who gave birth to one child, those who gave birth to two or more children experienced less reduction in BMD, indicating that parity might have a protective effect on bones [123–125], whereas others claim that the number of births does not affect the BMD of postmenopausal women because bone loss after pregnancy is restored after delivery [126, 127].

In fact, it is difficult to determine the influence of parity on BMD as it involves a complex interrelationship between factors such as calcium intake during pregnancy, increase in body mass and body fat, and hormonal changes [128, 129]. In general, BMD decreases by about 3% during pregnancy as calcium is lost during fetal development [120]; however, BMD also increases owing to increased mechanical load on the bones from increased weight and body fat during pregnancy, higher bone formation due to placenta lactogen in the early stages of pregnancy, and estrogen influence in the later stages of pregnancy. These effects may offset each other [124], resulting in parity not having a significant impact on the presence of osteoporosis.

As far as lactation is concerned, the protective effects of previous lactation history and parity on bone were demonstrated in some studies. Salari

et al. [120] carried out a systemic review on the influence of pregnancy and lactation on maternal bone health, in which they noted that there is no consensus about the contributory effect of lactation on osteoporosis. Earlier studies were in agreement with this conclusion. Kojima et al. investigated the effect of parity and lactation on BMD in pre- and postmenopausal women in a cross-sectional study. They stated an inverse correlation between total lactation period and BMD in premenopausal women but found no association between them in the postmenopausal women, and they concluded that lactation and parity does not have major effect on BMD later in life [130].

Zhang et al. confirmed the detrimental effect of parity on BMD with no influence of lactation in postmenopausal Chinese women while in premenopausal women none of them caused significant association [131]. Karlsson et al. studied the effect of pregnancy and lactation in 73 women aged 20–44 years and observed significant decrease in spine and body BMD after delivery. In the first 12 months after delivery, the BMD of nonlactating mothers did not significantly change; however, 12 months after delivery, lumbar spine BMD showed significant increment [88]. Meanwhile, higher BMD loss was seen in lactating mothers. They could not find correlation between parity and BMD. Hill et al. .reported the association of >5% increase in BMD of African Caribbean women with parity and lactation in age-adjusted models, but the correlation was not significant [132]. Lenora et al. conducted a cross-sectional study in Sri Lankan women and found no detrimental effect of parity and duration of lactation on BMD in postmenopausal women [133]. In another former study, Chantry et al. indicated the positive association between lactation, age of pregnancy, and bone [4].

Considering lactation duration, it was found that women engaging in 12–24 months of breastfeeding had a higher risk of osteopenia in the femoral neck compared to those breastfeeding for less than 12 months and that those breastfeeding for more than 24 months had a higher risk of osteoporosis in the lumbar spine than did those who breastfed for less than 12 months. On another front, in a study on the effects of breastfeeding for 24 months or more on osteoporosis risk [134], postmenopausal women who breastfed for more than 24 months showed a significantly higher risk of osteoporosis compared to women who did not breastfeed. However, this study showed that there were no differences in risk of osteoporosis between women who breastfed for less than 24 months and those who did not breastfeed.

In conclusion, it seems that parity does not influence the occurrence of osteopenia and osteoporosis in the lumbar spine and femoral neck. It can be asserted that breastfeeding duration influences the occurrence of osteopenia and osteoporosis in the lumbar spine and femoral neck. Therefore, it is important to educate women about bone loss, especially if they breastfeed for more than a year, as well as to provide preventative education, such as on the importance of adequate calcium intake and exercise.

Pregnancy-Related Transient Osteoporosis of the Hip

Transient osteoporosis of the hip (TOH), also known as bone marrow edema syndrome, is a rare skeletal disorder of unknown etiology. It can occur in women and middle-aged men, but most often occurs in previously healthy women during the third trimester of pregnancy. It is essentially a diagnosis of exclusion. A few case reports of transient osteoporosis of pregnancy are now in the literature [135–142]. The patient typically presents with progressively worsening unilateral or bilateral hip pain without any prior history of trauma. The pain is exacerbated by activity, which limits motion of the hip [136]. As such, TOH should be included in the list of differential diagnoses when sudden and progressively worsening hip pain occurs in a pregnant woman in her third trimester. The suggested etiologies include pelvic nerve compression, vascular insufficiency, or changes in fibrinolytic system with pregnancy—though a definite cause remains unknown to this date [143].

The diagnosis of TOH in pregnancy can be made by either plain radiographs or an

MRI. However, MRI is useful for distinguishing between TOH and osteonecrosis, which can present similarly to TOH [144]. MRI typically shows marrow edema involving the entire femoral head and neck, with possible extension into the subtrochanteric region, and commonly associated joint effusion [145]. It shows increased signal intensity on T2-weighted images and a decreased intensity on T1-weighted images [146–148].

Familiarity with pathognomonic MRI features is important to confirm the diagnosis. Radiographic findings may lag behind clinical symptoms by 4–8 weeks. They would typically demonstrate regional demineralization or osteopenia diffusely involving the femoral head and neck with joint space preservation. Osteopenia typically resolves within 9 months of symptom onset [143, 146]. These findings may be confused with avascular necrosis of the femoral head or femoral neck stress fracture. However, diffuse rather than focal involvement of the femoral head or neck helps differentiate these entities from TOH [149].

About 40% of patients may show involvement of other joints other than the hip. This fact may be consistent with our patient's associated pain in knee and ankle, though no imaging studies were done for these areas to confirm our suspicion. Besides, knee pain could be a consequence of postural changes, increase in weight, and increased laxity of ligaments in pregnancy—all of which could contribute to knee pain in pregnancy [144]. Knee pain in pregnancy is not uncommon. The process may regress in one joint but may recur in another [150].

In contrast to osteonecrosis, TOH in pregnancy resolves by 6–8 months postpartum [136]. While there have been case reports of treating patients with bisphosphonates, human data on the safety of bisphosphonates in pregnancy are sparse and anecdotal [144]. Given the favorable prognosis with complete restoration of bone density, treatment is usually supportive and conservative, comprising bed rest and prevention of weightbearing (use of crutches) in order to circumvent femoral fracture, and analgesics for pain control [136, 144, 148, 149]. In a few rare cases, femoral fractures have been known to occur, but the great majority of cases resolve over a period of 6 months on average, without fractures [148–150].

Pregnancy, Lactation, and Risk of Fracture

Bone loss predisposes patients to bone fractures, which may cause disabilities and work loss, and imposes high cost to the society. Based on the impact of pregnancy and lactation on bone mass, different effects can be seen. Some investigations revealed reduced risk of hip fracture due to parity [151–153]. Kauppi et al. confirmed the positive effect of parity on BMD and showed inverse association between risk of hip fracture and parity [154]. The association of nulliparity with hip fracture was confirmed in several studies [155, 156]. Michaëlsson et al. analyzed data from a population-based case–control study in Swedish women and reported a 5% reduction of hip fracture per child, which was influenced by the use of oral contraceptives (OCP) [157]. They observed that oral contraceptives increase the risk of hip fracture with no association between duration of lactation and risk of hip fracture. Also, they found no correlation between body mass index (BMI) and duration of lactation with risk of fracture [157]. Specker et al. considered the effect of parity on bone size and strength as the factors that reduce the risk of hip fracture [158].

Huo et al. observed a 13% reduced risk of hip fracture in association with every 6 months increase in lactation per child in Chinese women [159]. In agreement with this study, Cumming et al. and Kreiger et al. observed the association of reduced risk of hip fracture with duration of lactation per child in a dose-dependent fashion [160, 161]. In a case–control study in Thailand, addition of each child was associated with a 13% reduction of risk of fracture [162] while some studies in Caucasians did not support it [151, 157].

Naves et al. conducted a longitudinal study on Spanish women over 8 years and found pregnancy as an important protective factor for the incidence of Colles' fractures [163]. The results

of the Mallmin et al. study confirm this finding as they showed more Colles' fractures in women who had never been pregnant [164].

Pregnancy, Lactation, and Bone Biomarkers

Because of the teratogenicity of X-ray on pregnant women; measurement of bone biomarkers, offers the investigators the opportunity to monitor changes in the bone metabolism, being a relatively reliable indicators of bone status. Several studies demonstrated high maternal bone turnover, particularly high levels of deoxypyridinoline (DpyD) and bone alkaline phosphatase (BALP) during pregnancy and 12 months postpartum in prospective studies [165, 167]. Osteoprotegerin (OPG), which is a member of the tumor necrosis factor superfamily, acts in counteraction with receptor activator of nuclear factor κB ligand (RANKL) and inhibits osteoclast activity. Production of osteoprotegerin is induced by 17β-estradiol, increases over pregnancy, and decreases during lactation [166, 167]. It has been known that osteoprotegerin is elevated in murine pregnancy, which may protect maternal skeleton [168].

Little is known about the role of osteoprotegerin, which might have placental origin, during pregnancy in human. One study reported no significant change in osteoprotegerin during pregnancy but increased level of osteoprotegerin during labor [166]. Naylor et al. observed significant increase in osteoprotegerin and β cross-linked C-telopeptide of type I collagen (β CTX) at 36 weeks of pregnancy followed by rapid postpartum decline [169]. Their study showed no correlation between change in osteoprotegerin and bone turnover or BMD [169]. Vidal et al. found osteoprotegerin level of human milk to be 1000-fold higher than human serum. This high amount may prevent bone loss later in life [170].

Holmberg-Marttila et al. [171] assessed the postpartum changes in bone turnover markers and found significant postpartum decrease in β cross-linked C-telopeptide of type I collagen (β CTX) (bone resorption marker) and increase in bone alkaline phosphatase (BALP), amino-terminal telopeptide of procollagen (PINP), and osteocalcin (OC) (bone formation markers) as early as 1 month. They indicated the association of higher parity and longer history of lactation with lower bone turnover markers.

Cross-sectional and longitudinal studies indicated a 50% reduction of parathyroid hormone during lactation [172–174]. Also, some studies reported decrease in procollagen I carboxy peptides (PICP) in the first and second trimesters and increase in the last trimester as well as elevation of urine deoxypyridinoline (DpyD) two- to threefold during lactation higher than the third trimester [170, 172–175]. In another longitudinal study, Chan et al. compared BMD and bone biomarkers of lactating and nonlactating Chinese mothers and reported a significant decline in BMD of lactating mothers in the first 6 months, which returned to baseline at 12 months. Serum bone alkaline phosphatase (BALP) was higher in lactating mothers and serum intact parathyroid hormone (iPTH) increased in both groups [176]. In a third study, Carneiro et al. reported higher levels of biochemical bone markers including CTX, N-terminal telopeptide (NTX), bone alkaline phosphatase (BALP), and osteocalcin in lactating mothers. They indicated the distinctive pattern of increased bone turnover in states of rapid bone loss (myeloma, cancer, etc.), which displays uncoupling bone markers versus lactation and osteoblast–osteoclast coupling [177].

Osteoporosis During Pregnancy

The transitory deterioration of maternal bone during pregnancy leads to increased bone fragility. Osteoporosis may indeed occur if concomitant conditions, such as baseline osteopenia, or other predisposing circumstances, are present. Prevalence is unknown because the main diagnostic methods involve radiation, which is usually avoided in pregnant women. Consequently, diagnoses are made at a later stage, often when a final severe outcome, consisting of a clinical fracture, occurs.

Fragility fractures affecting both the spine and the hip, although rare, have been described in the literature [178, 179].

Clinical Presentation

The main clinical symptom is severe and persistent back pain, which usually occurs at the end of pregnancy or early puerperium. The high prevalence of back pain in women during advanced pregnancy explains the poor attention received, and the consequent low number of diagnoses. When suspected, imaging techniques should help in clarifying the diagnosis. Cortical bone may be affected as well. The hip is then the preferred territory as it occurs in the form of the disease so prevalent in older women. Hip fracture may then present as an additional complication [180]. The low prevalence of this form was confirmed by a prospective study in France, which detected three hip fractures in 4900 pregnancies [181].

Consistent with the transitory condition of the process, bone density tends to recover in most, but not all, cases after delivery [182], an observation that may explain the low rate of recurrence in subsequent pregnancies [179, 183, 184]. The interest in detecting women at risk has been hindered by the sparse number of published cases, which has limited the options for detecting risk factors. The rationale of using established clinical risk factors for fragility fracture, or others included in the absolute fracture risk assessment scales [185], may be an option, but it has not been tested. A possible genetic background has been suggested after some reports of familial aggregation [183, 186, 187].

The concrete case of hip fracture may have a mixed origin because transitory processes have been described in the absence of systemic osteoporosis or in nonpregnant women or men at midlife [188]. The term transitory regional osteoporosis has been proposed to denominate these cases, whose pathophysiological mechanisms remain elusive.

Diagnosis

The value of early diagnosis is mainly limited to the decrease in the clinical impact of fragility fractures as the low frequency of the picture limits the options for a consensus on risk profiles in pregnant women. Measurement of BMD with DXA will show either osteopenia or evident osteoporosis, which may be accompanied by vertebral deformities or vertebral collapse. Conventional radiography will confirm the fracture in most cases [189, 190]. DXA scan may be used because the low irradiation does not affect fetal safety and even less at the advanced stage of gestation in which the problem arises [191]. However, the low incidence of this pathology does not support the generalized use of DXA for screening unless there are clear risk factors, which have not been described. Consequently, it is only the good clinical judgment as a consequence of abnormally increased pain at either the back or the joint, which should raise the suspect of a fracture.

The irradiation dose absolutely limits the use of computed tomography, but interest is arising on the use of alternative technologies, such as magnetic resonance (MR), which can be safely used during pregnancy. MRI may be particularly efficacious in detecting vertebral fractures, which may be missed by conventional radiography [192]. Moreover, MRI may help in the diagnosis of the regional forms because the accompanying bone marrow edema may be detected by this technology. Located at the epiphysis and extending into the subchondral bone, edema is often accompanied by joint effusion [193].

Quantitative ultrasound (QUS) is another tool for osteoporosis assessment that could be a safe measure. Different QUS systems measure different bone properties that are not closely related to bone mineral content (BMC) measured by DXA. Broadband ultrasound attenuation (BUA) measurements depend on the trabecular architecture of cancellous bone (qualitative aspects, such as separation and connectivity of trabeculi) explaining why QUS measurements are predictive of fracture risk in

elderly but are poor for monitoring the bone changes in young subjects [194].

Treatment

Once diagnosed, the limited knowledge on the pathophysiology, combined with the absence of randomized controlled trials, strongly limits the availability of solid treatment protocols. Symptomatic treatment, including rest, load reduction, and analgesics, is of help. Despite the frequent bone recovery in the long term, there is interest in the additional benefit that may provide pharmacological compounds with activity on bone metabolism [23].

Bisphosphonates emerge as an attractive option because of their proven efficacy in osteoporosis and other bone diseases. The difficulty derives from two features of these compounds. One consists of the long-time retention in the skeleton, which raises concerns in that even pre-pregnancy administration may involve fetal exposure. The other feature stems from findings in animal studies, which have detected passage of these drugs through the placenta and their deposits in fetal bone [195]. Worries about short- and long-term fetal safety have consequently been raised.

The short experience in humans, however, has not confirmed any fetal anomalies. Two studies have investigated teratogen information services from different world regions to search for pregnancies in which women were taking bisphosphonates shortly before pregnancy or during the first weeks of pregnancy. One study detected 24 pregnancies in which women took alendronate [196], and the other study found 21 women exposed to different types of bisphosphonates [197]. No major anomalies were found in the neonates or after comparison with a control group. These data were corroborated in a systematic search, which detected 51 cases of exposure to different types of bisphosphonates before or during pregnancy. In none of the cases were skeletal abnormalities or other congenital malformations detected in the neonates [198]. More extended exposure, also without apparent impact on the newborn, was found in one isolated case in which the woman was treated daily with alendronate during the whole pregnancy because she was unaware of being pregnant until the beginning of labor [199]. The magnitude of the bone response, with the caution imposed by the low numbers, seems to be sizeable and substantially improves the physiological recovery observed after weaning. Increases of up to 23% in spinal BMD after 2 years of treatment were compared favorably with the 11% observed in untreated women [200]. Despite being so and the lack of adverse fetal effects in the few cases of inadvertent use, the actual consensus is that this treatment should be avoided during pregnancy [197].

The recent use of teriparatide has been followed by a remarkable increase in BMD at both the spine and the hip in a few cases with vertebral fractures diagnosed at postpartum or within the lactation period [201–204].

Orthopedic interventions may have a role as well. Some initial experience with vertebroplasty has shown success in vertebral fractures. Hip fractures, in turn, require the surgical approach option that better suit the particular characteristics of the fracture [205, 206].

Recovery of the Bone Health After Lactation

As noted earlier, pregnancy and lactation-induced osteoporosis (PLIO) is a rare complication related to substantial trabecular bone loss and fragility fractures, mainly spine fractures in the first weeks of lactation and the cortical bone is relatively spared in this period. A recent systematic review [207] revealed that using DXA or SPA showed complete recovery or a tendency to recovery in all skeletal sites evaluated. However, while there was complete spine BMD measurements recovery in all of the studies, there was a trend to recovery in the femoral neck BMD measurements. Considering the lumbar spine BMD measurements comparison between the final (after 12–18 months) and initial (postpartum), this meta-analysis showed a significant mean difference ($p < 0.001$). The weighted mean differ-

ence at spine BMD measurements remained significant among the Latin American ($p < 0.001$), European ($p = 0.02$), and Asian ($p = 0.03$) studies. On the other hand, the comparison among the femoral neck BMD measurements did not show any significant association between the final and initial values ($p = 0.323$).

One QCT study [208] showed transient volumetric spine trabecular loss with complete recovery. On the other hand, an HR-pQCT study [209] demonstrated cortical vBMD, cortical and trabecular thickness reduction in the first 12 months postpartum in women lactating 4 months or longer. Also, the cortical vBMD and trabecular thickness were still lower than baseline values in women lactating 9 months or longer. Another study of the ultradistal tibia and radius [210] revealed an increase of cortical porosity, as well as matrix mineralization deterioration, and fewer trabeculae and greater separation among them.

In conclusion, the results of this systematic review revealed transient trabecular bone loss during breastfeeding with recovery or tendency to recovery after weaning when assessed and monitored by DXA and HRpQCT measurements. However, the cortical bone recovery can be delayed.

This variation has been linked to the pathophysiological mechanisms involved particularly during the lactation period, including hypoestrogenism and longer hypothalamic–pituitary–ovarian axis suppression related to higher prolactin [211], and parathyroid hormone-related protein (PTHrP) serum levels, as well as lower efficiency of gut calcium absorption [212]. The daily rate of calcium transferred from maternal milk to newborn is approximately 200 mg, and higher gut absorption of this ion is one of the most important homeostatic mechanisms to meet fetal needs [213].

However, much of calcium from milk is supplied through bone resorption of maternal skeleton because the intestinal calcium absorption returns to pre-gestational levels while breastfeeding [214]. The PTHrP is a key mediator during lactation because its high concentrations may predict the magnitude and severity of bone loss, regardless of estradiol, intact PTH, and 25-OH-vitamin D serum levels [1, 215]. After returning the menses, there is a tendency to bone loss recovering in the first months of lactation, especially related to estrogen status, which is similar, but not analogous, to its effect during puberty and is opposite to its role after the menopause [216].

The systematic review [207] concluded that the lactation is associated with transient trabecular and cortical bone loss at axial and peripheral skeletal sites, depending on returning regular menses and weaning. In most of the women, a complete bone recovery occurred after lactation. Some microarchitecture deterioration of peripheral sites, such as radius and ultradistal tibia, may occur after prolonged breastfeeding although no hip geometry damage.

Long-Term Effect of Pregnancy and Lactation on Bone Health

Perhaps the most important relevant question from the clinical point of view is whether there is association between the female reproductive history and long-term changes in the BMD, and whether the reduction in BMD described during a pregnancy and lactation is associated with an increased risk of developing osteoporosis and fragility fractures in older age. Few cross-sectional observational or case–control studies have been published that evaluate the long-term effect of multiple pregnancies and lactation on BMD. In a study carried out by Karlsson et al. [88], which involved 39 premenopausal women with a minimum of four pregnancies, and after adjustment for differences in soft tissue composition, results revealed that the BMD of the assessed group was no lower than in 58 age-matched controls with a maximum of two pregnancies. Furthermore, there was no correlation between the total duration of lactation and BMD. A similar conclusion was drawn by Kojima et al. [130], who had included 465 pre- and 713 postmenopausal Japanese women in a cross-sectional study and by Johansson et al. [217] including 70-year-old Swedish women, and in a systematic review [119], including 23 different citations.

In contrast, in a study involving 1855 postmenopausal women, Cure-Cure et al. [218] reported that women with two deliveries or more had a 3% higher total body BMD, an 8% higher femoral neck BMD, and a 4% higher leg BMD than women with no children. This is agreement with the results of several other studies including Forsmo et al. [219], who included 1652 peri- and postmenopausal Norwegian women; Grainge et al. [220], including 580 English women aged 45–61 years; Tuppuvainen et al. [221], including 3126 Finnish women aged 47–56 years; Murphy et al. [222], including 825 English women aged 41–76 years; Sowers et al. [223], including 217 white American women aged 22–54 years; as well as Mariconda et al. [224], including 320 Italian women. These studies concluded that, in general, women with a history of one or several children had 3–5% higher BMD than nulliparous women.

This long-term positive effect of pregnancy and lactation on bone health is supported by assessment of the long-term risk of fracture in these women. Fracture can be considered the only clinically relevant endpoint of BMD deterioration. Alderman et al. [225], including 355 postmenopausal women with a fracture and 562 matched women with no history of fracture, reported that the incidence of hip and forearm fractures was no higher in women who had given birth to four or more children than in women who had not given birth. Also, women who had breastfed for more than 2 years did not have a higher fracture risk than women who had never breastfed. The notion that fracture incidence for women with multiple pregnancies was no different from that of nulliparous women has been supported by several studies [116].

In summary, virtually no study has suggested an association between lactation and fracture risk. It appears that having many children leads to a situation that, if anything, leads to not only a higher BMD, but also a reduced fracture risk. The causality cannot be proven, but the association between number of children and fracture risk may operate through a different mechanism than is detected by BMD as the association remains even after adjusting for differences in BMD in women with no or many children [226, 227].

In conclusion, pregnancy and lactation can have dual effect on bone; beneficial or detrimental. The final net effect of pregnancy and lactation on bone is in general not negative both on the short- as well as long-term aspects. On the short term, bone resorption tends to recover after delivery or weaning of the baby, whereas on the long term, pregnancy and lactation (including the duration of breastfeeding) are not associated with the development of postmenopausal osteoporosis or occurrence of fractures. Care should be given to preexisting medical conditions that might make the woman prone to developing osteoporosis or mechanical stress fractures.

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Part VII

Bone Health as a Comorbidity

Bone Health and Cancer Therapy

29

Yasser El Miedany

Introduction

Developments in systemic cancer therapies and diagnostic approaches have paved the way to consistent improvements in cancer survival; consequently, the sequelae of the long-term cancer management have attracted the attention of the treating health-care professionals as it mandated extra care. Treatment-related adverse effects impact significantly the patients' quality of life as many of them are expected to live for years following the diagnosis and treatment of their illness. In addition, they are also associated with significant impact on the health economy as well as social care.

In 2019, it has been estimated that there are approximately 16 million survivors of cancer in the United States and approximately 32 million worldwide [1]. Survivors of cancer are increasingly in their sixth, seventh, and eighth decades of life. The two largest groups of survivors are women with early-stage breast cancers and men with nonmetastatic prostate cancers. Patients with cancer are at increased risk of developing osteoporosis due to the accelerated loss of bone mineral density as a complication of their treatment. This makes them at higher risk of developing osteoporotic fractures, particularly cancer therapy-induced bone loss is faster and more severe than aging-associated bone loss [2].

Cancer therapies, including hormone therapy, radiation therapy, chemotherapy, and surgical castration, can directly or indirectly damage bone, resulting in loss of bone mass (i.e., osteopenia and osteoporosis) [3]. Furthermore, many cancer patients have additional comorbidities or risk factors for osteopenia or osteoporosis that may predispose them to bone loss [4, 5]. It is the coalescence of survivors of cancer and osteoporosis, a health problem of near-epidemic proportion that forms the underlying rationale for this chapter. This chapter will discuss the unique aspects of cancer therapy-associated bone loss and the interaction between cancer, hormones, and bones. This will be followed by discussing the pathophysiology of cancer treatment-induced bone loss, diagnosis of cancer-induced bone loss, and monitoring of the bone mineral density assessment. The chapter will expand to discuss clinical sequelae and management of cancer therapy-induced bone loss. It will conclude with an algorithm for identification and management of the bone health status in patients receiving cancer therapy.

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Table 29.1 A comparison between normal aging-associated bone loss and cancer therapy-induced bone loss

Normal aging-associated bone loss	% of lumbar spine BMD loss at 1 year	Cancer therapy-induced bone loss	% of lumbar spine BMD loss at 1 year
Men	0.5	Aromatase inhibitor therapy	2.6
Postmenopausal	1.0	Bone marrow transplantation	3.3
Early menopause	2.0	Androgen deprivation therapy	4.6
		Aromatase inhibitor therapy plus gonadotropin-releasing hormone (GnRH)	7.0
		Ovarian failure induced by chemotherapy	7.7

Unique Aspects of Cancer Therapy-Associated Bone Loss

Rates of cancer therapy-associated bone loss can be up to ten-fold higher than normal (Table 29.1) [4, 6–11]. In normal men, bone mineral density (BMD) decreases at a rate of 0.5–1.0% per year starting in midlife [4]. Women have higher rates of bone loss around menopause—an average of 2% loss in bone mass per year for 5–10 years—which then declines over time [6]. Patients receiving cancer therapy, however, can experience bone loss at significantly higher rates. For example, bone loss in men with prostate cancer on ADT can occur at a rate of 4–5% per year. Marked changes are detectable at 6 months after initiation of hormonal therapy in men with prostate cancer [8]. Similarly, significant bone loss can occur in women with breast cancer who are treated with aromatase inhibitors (e.g., anastrozole, letrozole, or exemestane) or other endocrine therapies. Results of clinical trials such as the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, the MA-17 trial, the Breast International Group 1-98 (BIG 1-98) trial, and the Intergroup Exemestane Study (IES) have demonstrated that women who received anastrozole lost 4% and 6.1% of bone mass in the lumbar spine after 2 years and 5 years, respectively.

The role of the underlying risk factors in developing bone thinning was highlighted as four of the five women included in the study who had baseline osteopenia, and went on to develop osteoporosis, received anastrozole. On the other hand, no women with normal BMD at study entry developed osteoporosis, regardless of treatment [12]. This suggests that women at highest risk for progressing to osteoporosis on an AI are those with preexisting low BMD. Patients receiving anastrozole had a >1.5-fold higher risk for fracture compared with those not treated with an aromatase inhibitors [13]. Similarly, in men, bone loss commonly occurs in those who are diagnosed with prostate cancer and receive treatment with androgen depletion therapy (ADT). Earlier studies estimated an annual decline of 2–8% of the BMD [14, 15]. In the study carried out by Maillefert et al., it was reported that, after 1 year of ADT, there was a 4.6% decrease in BMD at the lumbar spine and a 3.9% decrease at the femoral neck [10]. Orchiectomy also resulted in substantial changes, with a 15% decrease in trochanter BMD after 1 year reported in one study [16]. After 1 year of ADT, 15 men with adenocarcinoma of the prostate had significantly lower BMD at the total hip and ultradistal radius than age- and sex-matched controls. The mean bone loss was 3.3% at the total hip and 5.3% at the ultradistal radius, an area rich in trabecular bone [17]. Collectively, these results indicate that substantial loss of BMD occurs in patients with breast and prostate cancer treated with a variety of cancer therapies, on the background of certain risk factors, causing significant morbidity and mortality.

Cancer, Hormones, and Bones

Nearly all cancers can have significant negative effects on the skeleton. The increased risk for bone loss and fractures in cancer patients can be attributed to both the direct effects of cancer on the skeleton and to the side effects that come with many cancer-specific therapies. Further, the skeleton is also the most common site of metastatic

disease as cancer cells growing within bone induce osteoblasts and osteoclasts to produce factors that stimulate further cancer growth [18]. Accordingly, the optimal management of skeletal health has become an increasingly important part of the care provided to cancer patients, particularly as it has been reported that improved oncological treatments have enhanced both patient survival and longevity [19]. Several factors have been named as principal elements paving the way for the patients with cancer or receiving cancer therapy to sustain negative outcomes on their bone health. These include the following.

Aging Although cancer is not exclusively a disease of aging, it more commonly occurs in older individuals. Likewise, aging in both men and women is associated with increased rates of osteoporosis and fractures. Central to this bone loss is the decline in sex hormone (primarily estrogen and testosterone) levels that occurs in both sexes with aging. This matter gets more complicated in patients with breast or prostate cancer, for who these sex hormone levels are targeted for further reduction by hormonal therapies, an effect that can potentiate ongoing bone loss already occurring in aged patients [20, 21].

Sex Steroids and Bone

Sex steroids, also known as gonadocorticoids and gonadal steroids, are steroid hormones that interact with vertebrate steroid hormone receptors. The sex steroids include the androgens, estrogens, and progestogens. Their effects are mediated by slow genomic mechanisms through nuclear receptors as well as by fast nongenomic mechanisms through membrane-associated receptors and signaling cascades. The term sex hormone is nearly always synonymous with sex steroid. The polypeptide hormones luteinizing hormone, follicle-stimulating hormone, and gonadotropin-releasing hormone are usually not regarded as sex hormones, although they play major sex-related roles. Both androgens and estrogens have important roles in bone growth and maturation, as well as maintenance of skeletal integrity. However, accumulating evidence suggests a role for other reproductive hormones, such as activins and inhibins, in the preservation of bone health.

Estrogens The net action of estrogens on bone is to decrease bone resorption. Their actions are exerted via estrogen receptors alpha and beta (ERα and ERβ receptors), expressed by osteoblasts and osteoclasts. Estrogens increase osteoblast number and activity, inhibit the maturation of osteoclast precursors [via increased osteoprotegerin (OPG) production], reducing the activation frequency of the BMU and promoting apoptosis of mature osteoclasts [22, 23]. Estrogen deficiency is known to increase the rate of osteocyte apoptosis with a consequent increase in skeletal fragility [24, 25].

In women, estrogens are critical for the maintenance of normal bone mass. At the menopause, loss of ovarian follicular activity causes a significant fall in circulating estrogens, with a consequent disruption of bone remodeling. The most rapid bone loss occurs in the first 3 years postmenopause (2–5%/year), after which skeletal metabolism becomes "acclimatized" to the low-estrogen environment and bone loss slows to around 0.5–1.0% per annum. A greater proportion of bone loss occurs at sites containing trabecular bone (such as the spine) than cortical sites (such as the hip) [26].

In addition, estrogens have been identified as the sex steroids primarily responsible also for the regulation of bone resorption in men. In studies of young male patients unable to produce or respond to estrogens, there was an increased rate of bone turnover and osteopenia [27, 28]. Both estrogens and testosterone are known to be important in the regulation of male bone formation [29].

Androgens Testosterone is the most abundant circulating androgen in men, 95% of which is secreted by the testis. The remaining 5% is formed from the enzymatic conversion of adrenal androgens dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) [30]. In women, the

major circulating androgens are produced by the adrenal glands and ovaries and include DHEAS and DHEA, androstenedione (proandrogens), testosterone, and dihydrotestosterone (DHT). Female testosterone production also occurs via peripheral aromatization of androstenedione. In both men and women, the majority of circulating testosterone is protein bound (to either sex hormone-binding globulin or albumin). Testosterone may act directly on androgen receptors (AR), or indirectly via aromatization to estradiol and consequent activation of estrogen receptors (ER). The indirect actions of testosterone may also occur following conversion to the more potent dihydrotestosterone (DHT) by 5α-reductase in peripheral tissues [31].

In bone, androgens exert direct effects on growth plate chondrocytes and promote longitudinal bone growth [32]. Both testosterone and dihydrotestosterone (DHT) stimulate the proliferation of osteoblast precursors via androgen receptors signaling [33]. Binding of androgens with androgen receptors also upregulates osteoblast androgen receptors expression and promotes their differentiation [34]. Androgens also prevent osteoblast and osteocyte apoptosis and regulate osteoclast activity by inhibiting the interaction of receptor activator of nuclear factor kappa-B ligand (RANK-L) with its receptor (RANK), expressed on osteoclast precursors [35, 36]. Bone formation is promoted by androgen-mediated upregulation of growth factors, such as insulin-like growth factor and transforming growth factor beta (TGFβ) [33]; on the other hand, downregulation of interleukin 6 inhibits osteoclast activity [37] through the reduction in levels of osteoprotegerin (OPG), which is produced by osteoblasts and acts as a soluble decoy receptor to RANK-L [38].

The Interaction Between Cancer, Sex Hormones, and Bones

Breast and prostate cancers are the most common types of cancers where the interaction between cancer, sex hormones, and bones can be overtly studied. Bone loss is a common finding in those people who should be fully aware of their increased risk for osteoporosis and given advice on what they can do to strengthen their bones and lower their risk of fracture. However, the interaction between the cancer, the hormones, and the bones is of interest, particularly it has an impact on the management of both diseases.

Breast and Bone Breast and bone are both estrogen-sensitive organs. A prolonged lifetime exposure to estrogen through early menarche, late menopause, and use of postmenopausal hormone therapy are factors known to reduce the risk of osteoporotic fractures [39, 40]. However, these same factors are associated with an increased risk of developing breast cancer due to the increased estrogen exposure. Endogenous estradiol has not been shown to be directly related to breast density [41]. Nonetheless, breast density (breast density reflects the amount of fibrous and glandular tissue in a woman's breasts compared with the amount of fatty tissue in the breasts) and circulating estrogen levels are independently associated with breast cancer risk. Breast cancer risk was 2.4–4.2% higher in women with very high breast density, particularly in women who use estrogen plus progestin [42]. Women with the highest levels of breast density have been found to have a four- to sixfold increased risk of breast cancer compared with women with less dense breasts [43].

Epidemiological data suggests that higher bone mineral density (BMD) is also associated with a higher risk of breast cancer. Zhang et al. studied BMD in postmenopausal women, and after adjusting for age, found those in the top quartile of BMD had a 3.5 times higher risk ratio of developing breast cancer than women in the lowest quartile of BMD [44]. This association was confirmed in a meta-analysis of 70,878 postmenopausal women from 10 studies, in which 1889 cases of breast cancer followed for mean of 6 years showed that higher BMD was associated with a significantly higher

risk of breast cancer. In this meta-analysis [45], women with the highest hip or spine BMD had a 62% and 82% higher risk, respectively, of developing breast cancer than women in the lowest BMD categories. For each increased standard deviation in BMD at the hip or spine, the risk for developing breast cancer increased by 20% and 26%, respectively [45]. Therefore, higher estrogen levels are associated with higher bone density as well as a higher risk of breast cancer.

Prostate and Bone

Androgens play a critical role in male sexual development and prostate physiology. The two principal androgens in men are testosterone, produced by testicular Leydig cells, and dihydrotestosterone (DHT), produced from testosterone in peripheral tissues by 5-α reductase. In circulation, testosterone is bound primarily to sex hormone-binding globulin (SHBG) while the unbound, or free testosterone, is the most bioavailable and active form. From birth through puberty, the prostate remains small and immature, while in postpubertal males the surge in androgens drives gland development and an increase in prostate volume up to 10 times its prepubertal size [46]. Dihydrotestosterone also plays a well-established role in promoting continued growth of the adult prostate, leading to benign prostatic hypertrophy (BPH) [47].

Men also undergo substantial changes in biologically available sex steroid levels, primarily due to the greater than twofold age-related increase in sex hormone-binding globulin levels over the male lifespan, making bioavailable estrogen and testosterone levels decline an average of 47% and 64%, respectively [48]. Although testosterone is the predominant sex steroid in men, evidence from cross-sectional and longitudinal studies has shown that male BMD is better correlated with circulating levels of bioavailable estradiol (made via aromatization of testosterone to estradiol) than testosterone [21].

Pathophysiology of Cancer Treatment-Induced Bone Loss

Bone is continually remodeled by interactions among bone matrix-producing osteoblasts, bone resorption-associated osteoclasts, and resident bone osteocytes [49]. Estrogen depletion, which occurs in menopause (and also among AI-treated breast cancer), induces preosteoblasts and osteocytes to secrete the receptor activator of nuclear factor-kappa B ligand (RANK-L), resulting in activation of osteoclast precursors and mature osteoclasts [49, 50]. Activated osteoclasts accelerate bone resorption and remodeling, causing increased bone turnover [51].

The principal pathophysiology of cancer treatment-induced bone loss (CTIBL) is linked to one of these seven mechanisms (Fig. 29.1): (1) hypogonadism induced by chemotherapy, (2) hormone therapy, (3) surgical castration, or (4) radiation therapy [52]. Other mechanisms include (5) direct or indirect effects of cancer therapies or the malignancy itself on bone metabolism, (6) inactivity, and (7) inadequate intake of calcium and vitamin D [53–55]. These were reviewed in full details in several articles [19, 56, 57].

Chemotherapy Effect Several chemotherapy agents, including methotrexate, cyclophosphamide, ifosfamide, and doxorubicin, may affect the bone biology either through a direct effect on the bone metabolism or through their effect on gonadal hormones. Results of animal studies have revealed that methotrexate decreases bone formation and increases bone resorption, leading to significant bone loss [58, 59]. While the exact mechanism by which methotrexate increases osteoclast production is unknown, it has been suggested that methotrexate reduces osteoblast production through its inhibition of DNA synthesis [59]. Methotrexate also inhibits matrix mineralization, which in turn decreases bone formation.

On the other hand, cyclophosphamide and its metabolites inhibit bone formation and bone resorption by directly arresting the cell division

Fig. 29.1 Pathophysiology of cancer therapy-induced bone loss: seven principal mechanisms linked to the pathophysiology of cancer treatment-induced bone loss (CTIBL)

of preosteoblasts and osteoclasts, thereby decreasing the number of osteoblasts and osteoclasts on bone surfaces [60].

On another front, ifosfamide's effects on bone differ from those of methotrexate and cyclophosphamide. Ifosfamide is an alkylating agent and one of the nitrogen mustard family of medications, which is used to treat a number of types of cancer. This includes testicular cancer, soft tissue sarcoma, osteosarcoma, bladder cancer, small cell lung cancer, cervical cancer, and ovarian cancer. It works by disrupting the duplication of DNA and the creation of RNA. Renal tubular nephrotoxicity, an adverse effect of high-dose ifosfamide or ifosfamide–cisplatin therapy, causes hypophosphatemia, which eventually results in defective mineralization and demineralization of bone, inhibiting bone formation. However, bone formation may also be inhibited with ifosfamide use in the absence of severe renal dysfunction [61]. Results of in vitro studies have shown that doxorubicin inhibits proliferation and differentiation of osteoblasts and selectively reduces the rate of bone formation by altering the interaction of parathyroid hormone with the osteoblast receptor [62, 63]. Other drugs commonly used in cancer patients, such as glucocorticoids, cyclosporine, and L-thyroxine, have also been associated with bone loss [3].

High-dose chemotherapy regimens, such as regimens used with hematopoietic stem cell transplantation (HSCT), are also toxic to osteoprogenitor cells in a dose-dependent manner. The results of a clinical trial showed that patients with breast cancer or non-Hodgkin's lymphoma (NHL) undergoing high-dose chemotherapy had a 50% reduction in the number of osteoprogenitor cells, independent of gonadal function, whereas similar patients receiving a conventional dose of chemotherapy had neither a decrease in the number of osteoprogenitor cells nor bone loss [62].

Radiation therapy, glucocorticoids, cytokines, and immunosuppressive agents may also promote CTIBL in patients undergoing HSCT [63]. Patients with early-stage gastric carcinoma who

have undergone gastrectomy are also at risk of developing CTIBL. Generally, these patients develop hypocalcemia and low vitamin D levels which has been attributed to (1) their limited intake of dairy products and (2) malabsorption of nutrients as a result of the adverse effects of the surgery (e.g., dumping syndrome, diarrhea), which may result in bone loss and, ultimately, fracture [64]. These patients should receive supplemental calcium and vitamin D and be monitored for the development of osteopenia and osteoporosis.

Radiotherapy Treatment with radiation therapy can also have a direct effect on bone in the treated field, which leads to bone atrophy. It can also indirectly affect bones through vascular changes. Insufficiency fractures are a common complication after radiation therapy and generally occur in bones that are under the most physiological stress, pelvic or rib fractures with pelvic or chest irradiation, respectively. Cranial irradiation has been shown to inhibit growth hormone secretion, resulting in reduced bone mass [3, 65]. Although this effect is most common in children undergoing cranial radiation therapy, adults may also develop growth hormone deficiency, which, in the presence of other bone loss risk factors, increases the risk of CTIBL.

Psychosomatic Changes A variety of physical, metabolic, and psychosocial changes in patients with cancer, such as malnourishment due to nausea, weight loss, and cancer-related fatigue, can also lead to bone loss. Nutritional deterioration can occur at any point in the timeline of cancer diagnosis, treatment, or support [66].

While the etiology of cancer cachexia is multifactorial and complex, it is characterized by the loss of skeletal muscle even in the presence of adequate food intake, which can consequently lead to diminishing muscle strength and bone mass [64, 66]. Cancer-related fatigue also often leads to reduced physical activity, which, in turn, can contribute to mechanical unloading, sarcopenia, and bone loss [66].

Pathophysiology of Bone Loss in Breast Cancer Patients

Bone loss in patients with breast cancer can be attributed to one of two mechanisms: disease-related mechanisms or loss of bone induced by therapies used to treat the cancer itself.

Disease-Related Mechanisms Although patients with breast cancer lose bone primarily because of the negative impact of the medications used to treat the breast cancer, the disease itself is also associated with disruption of healthy bone metabolism [55]. Both increased resorption and accelerated bone turnover have been observed in nonmalignant bone biopsies of breast cancer patients and may be caused by secretion of parathyroid hormone-related protein (PTH-rp), which is often expressed on breast cancer cells [64, 67].

Chemotherapy The negative impact of chemotherapy on gonadal hormone production is the most common cause of CTIBL in premenopausal women with breast cancer. Patients receiving cyclophosphamide-containing regimens [e.g., combination cyclophosphamide, methotrexate, and fluorouracil (CMF); combination fluorouracil, doxorubicin, and cyclophosphamide (FAC); doxorubicin plus cyclophosphamide (AC)] have a high risk of developing hypogonadism because of damages of the ovaries induced by cyclophosphamide (e.g., decreases the number of secondary ovarian follicles, causing total loss of follicles with accompanying ovarian fibrosis), inducing premature menopause [3, 68, 69]. Premature menopause occurs in 63–96% of premenopausal women with breast cancer within 1 year of receiving adjuvant CMF or FAC therapy, with older premenopausal patients and patients receiving higher cumulative doses of cyclophosphamide having the highest risk [69]. Adjuvant taxane-containing regimens (e.g., AC followed by paclitaxel) may also induce menopause; however, it is unknown whether the cyclophosphamide or the combination of a taxane and an alkylating agent causes the bone loss [70]. In addition, low estrogen levels during chemotherapy-induced menopause increase osteoclast for-

mation, resulting in more bone loss than bone formation [3].

Endocrine Therapy

About two-thirds of all breast cancer patients are hormone dependent, either estrogen receptor or progesterone receptor, which are expressed by tumor cells. Therefore, endocrine therapy is an important option in the adjuvant treatment by two mechanisms: (1) to prevent cancer cells to interact with estrogen receptors by use of selective estrogen receptor modulators (SERMs) and (2) to inhibit tissue conversion of androgen into estrogen with aromatase inhibitors. Tamoxifen, one of the SERMs, has been the standard care for the adjuvant treatment of breast cancer; however, aromatase inhibitors have shown better overall responses than tamoxifen by decreased estrogen production, which results in reduced risk of recurrence in postmenopausal women with breast cancer. The third-generation aromatase inhibitors, anastrozole, letrozole, and exemestane, are used recently for first-line hormonal therapy in these women. However, these aromatase inhibitors cause significant enhancement of bone turnover markers and are responsible for accelerated bone loss, resulting in increased fracture incidence [3].

(Hormone) Therapy Hormone therapy differs from AIs in their impact on bone, possibly because of its estrogenic agonistic effects. Tamoxifen, a selective estrogen receptor modulator (SERM), has been shown to both cause and prevent bone loss, depending on the menopausal status of the woman; however, the exact mechanisms of the different effects are unknown [69].

In premenopausal women who have high estrogen levels, tamoxifen may act as a bone antagonist, whereas in postmenopausal women with low estrogen levels, tamoxifen may act as an estrogen agonist [69–71]. Although selective estrogen receptor downregulators, such as fulvestrant, lack estrogen agonist activity, results of preclinical studies have shown that fulvestrant may have agonist and antagonist effects on bone, depending on the presence of circulating estradiol levels [72]. For example, in ovariectomized rats, bone turnover and bone loss increased after fulvestrant therapy, whereas bone turnover and bone loss decreased in rats with intact ovaries receiving fulvestrant. The mechanism by which fulvestrant affects bone differently is unknown. In a small 18-month substudy that included 14 patients treated with fulvestrant as first-line therapy in locally advanced breast cancer, fulvestrant did not increase the bone turnover markers BAP, PINP, and CTX [73]. Unfortunately, hormonal therapies have limited long-term efficacy due to development of resistance [74, 75].

Aromatase Inhibitors (AI) Approximately 70% of breast cancers are hormone receptor-positive (HR+)3; for these, antiestrogen treatment strategies are recommended. Third-generation aromatase inhibitors (AIs) are standard first-line treatment for postmenopausal women with HR+ early or advanced breast cancer [76]. Aromatase inhibitors such as anastrozole, letrozole, and exemestane lack estrogen agonist or antagonist activity. Aromatase inhibitors work by inhibiting the action of the enzyme aromatase, which converts androgens into estrogens by a process called aromatization. As breast tissue is stimulated by estrogens, decreasing their production is a way of suppressing recurrence of the breast tumor tissue. Therefore, AIs deplete circulating estrogen [77], consequently it can negatively impact bone remodeling; this decreases BMD and increases bone loss [78], which is estimated to be twofold greater than menopause-related bone loss [52, 79, 80]. The consequences of decreased BMD and increased bone loss as a result of AI therapy include greater risk for osteoporosis and bone fracture [9, 78, 81, 82] and potentially increased risk for morbidity and mortality [83]. Adjuvant studies confirm that AIs increase fracture risk, with an incidence of 7% after a median of 30 months of treatment with exemestane and an incidence of 9–11% after up to 5 years of treatment with letrozole or anastro-

zole [81, 84, 85]. These drugs may accelerate bone loss by decreasing aromatase activity and inhibiting the conversion of adrenal androgens to estrogen, thereby reducing circulating and tissue levels of estrogen [76, 86].

The results of a study evaluating letrozole's effect on markers of bone turnover in healthy postmenopausal women suggest that aromatase inhibitors cause increased bone resorption when serum estradiol levels are reduced to nearly undetectable levels [87]. Similarly, postmenopausal breast cancer patients receiving anastrozole have shown increases in markers of bone formation and bone resorption [88]. Although a trend toward increased bone loss and an increased rate of fracture have been reported in postmenopausal women with breast cancer receiving exemestane, the effects of exemestane on bone turnover have not been fully evaluated [89].

Ovarian-Ablative Therapies

Ovarian-ablative therapies, such as gonadotropin-releasing hormone (Gn-RH) agents (e.g., goserelin) and oophorectomy, predispose women to the development of accelerated bone loss [90]. The pattern of CTIBL associated with ovarian-ablative therapies is similar to that in menopausal women, with an increased rate and intensity of bone remodeling, a loss of bone formation growth factors, an increased sensitivity to the bone-resorptive effects of parathyroid hormone, and increased bone resorption markers, causing more bone loss than bone formation [91].

Effects of Breast Cancer and Its Therapies on Bone in Men

Although breast cancer largely affects women, approximately 1500 men are diagnosed with breast cancer yearly [92]. The effects of breast cancer and its therapies on bone in men are unknown because of the rarity of this clinical situation. However, men with breast cancer are likely to develop hypogonadism due to breast cancer therapies and are therefore at risk of developing CTIBL [93]. Structured clinical trials that systematically collect information about cancer therapies in men with breast cancer are needed.

Effects of Prostate Cancer Therapies on Bone

Androgen deprivation therapy (ADT), either by surgical castration or the administration of Gn-RHs (e.g., goserelin, leuprolide, triptorelin) with or without an antiandrogen, such as flutamide, bicalutamide, or nilutamide, is commonly used to treat prostate cancer [94]. During ADT, circulating levels of testosterone and estrogen, which is converted from testosterone by aromatization, decrease significantly to less than 95% and 80%, respectively, of normal levels, inducing hypogonadism [95, 96]. The exact mechanism whereby hypogonadism induces CTIBL associated with prostate cancer is unknown [97]. As mentioned earlier in this chapter, for many years, testosterone was believed to be the primary hormone responsible for bone remodeling in men; more recently, researchers have focused on the role of estrogen in male bone remodeling [5]. Androgens increase bone formation directly by binding to androgen receptors on osteoblasts or by increasing the number of cytokines, such as insulin like growth factor-I, and indirectly by maintaining muscle strength; androgens also inhibit bone resorption [98]. Estrogen also regulates bone resorption and may have some role in regulating bone formation [5]. Therefore, in hypogonadal prostate cancer patients, the reduction of circulating testosterone and estrogen levels causes a decrease in osteoblastic bone formation and an increase in osteoclastic bone resorption, leading to accelerated bone loss. In addition, the loss of muscle mass that often accompanies hypogonadism may promote bone loss by decreasing mechanical stretch of and pressure on the bone [97].

Bone Metastases and Skeletal-Related Events (SRE)

Metastatic bone disease is most commonly seen with specific cancer types, notably those arising from the breast, prostate, lung, and kidney, as well as multiple myeloma (MM). The most common sites of bone metastases are throughout the axial skeleton.

Bone metastases affect many patients with advanced disease, and, whether lytic or blastic in appearance, often lead to skeletal complications typically referred to as skeletal-related events (SREs). This term (SRE) usually refers to five major objective complications of tumor bone disease: pathological fracture, the need for radiotherapy to bone, the need for surgery to bone, spinal cord compression, and hypercalcemia, although the latter is often of paraneoplastic origin, especially in the absence of bone metastases. The need for radiotherapy and pathological fractures are the most common skeletal events, reflecting the burden of bone pain and structural damage caused by metastatic involvement. These complications are associated with life-altering morbidity and can reduce overall survival (OS).

Across all tumor types, patients with breast cancer have the highest incidence of skeletal complications. In the absence of bone-targeted treatments, the mean skeletal morbidity rate, that is, the mean number of SREs per year, in breast cancer patients with bone metastases varied between 2.2 and 4.0 [99].

In prostate cancer, histomorphometric studies have shown the characteristic association of osteoblastic response to the presence of metastatic prostate cancer cells, but there is a wide spectrum of bone responses often seen within an individual patient [100]. Bone resorption rates, as determined by measurement of collagen breakdown products, are also high in prostate cancer patients [101], and SREs, notably pain requiring radiotherapy, fractures, and spinal cord compression, are frequent.

In patients with lung cancer and bone metastases, the median survival time is only 6–12 months. However, bone metastases present with an SRE in around one-quarter of patients, while 40% will experience an SRE during follow-up [102]. In renal clear-cell carcinoma, the presence of bone metastasis is the independent variable most significantly associated with poor survival [103].

Bone pain, most often in the back due to vertebral fractures, is a presenting feature in three quarters of patients with multiple myeloma. Extensive lytic lesions are frequent, and, typically, they do not heal despite successful antineoplastic treatment. Diffuse osteoporosis can also be a presenting feature in myeloma [104].

Cancer Treatment-Induced Fractures

The rate of bone loss increases with age in both women and men, and is associated with a rapid increase in fracture rate in both sexes above the age of 70 years [105, 106]. The lifetime risk of a fracture of the hip, spine, or distal forearm from age 50 years onward is almost 40% in white women and 13% in white men [106].

Risk factors for osteoporosis-related fractures have been validated in large prospective as well as population-based studies in postmenopausal women but not specifically defined for either women with a history of breast cancer or men with prostate cancer. These include aromatase inhibitor (AI) treatment/androgen deprivation therapy, BMD T-score of <−2.5, increasing age (>65 years), oral corticosteroid use for more than 6 months, low body mass index (BMI) (<20 kg/m^2), family history of hip fracture, personal history of fragility fracture after age 50, and smoking [107–109].

Screening for Bone Loss in Cancer Patients

Osteoporosis often remains undetected in patients with cancer until bone fracture occurs. Consequently, detection and prevention of bone loss are important clinical goals of therapy. Yet bone density testing is performed in only 3–32% of high-risk patients [110–112].

Identifying which patients with nonmetastatic cancer are at increased risk for developing osteoporotic fractures is crucial for the screening process. The USPSTF review outlined common general risk factors for osteoporotic fractures, including advanced age, current smoking, excessive alcohol consumption, low body weight, parental history of hip fracture, and postmenopausal status in women [113].

Advancing age, defined as age 65 years or older in women and 70 years or older in men, has been reported to be a more critical determinant of fracture than bone mass. A systematic review in men reports advancing age to be a statistically significant risk factor when evaluated as a continuous variable compared in 5- or 10-year increments or when used as a defined variable of age older than 70 years [114]. Increasing alcohol intake to greater than 10 servings per week was also a statistically significant risk factor, as were current smoking and history of chronic glucocorticoid use, although there was variability in how chronic was defined within the included studies [115]. Body weight less than 58 kg (127 lbs) can also increase clinical risk [116]. History of a prior fracture in adulthood is another important risk factor, although some sites, such as the hip, the vertebra, and the humerus, are associated with a higher risk of subsequent fracture than others [117, 118].

Several organizations, therefore, have developed clinical guidelines for screening cancer patients for bone loss, particularly for patients with breast as well as prostate cancer, being the most common forms of cancer, after cutaneous cancer. For breast cancer, a Position Statement, jointly published by seven international and European organizations including the International Osteoporosis Foundation (IOF), Cancer and Bone Society (CABS), International Expert Group for AIBL (IEG), European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), European Calcified Tissue Society (ECTS), International Menopause Society (IMS), and the International Society for Geriatric Oncology (SIOG), stated that all women with breast cancer due for medical treatment should be offered BMD testing with central/axial DXA [119]. Similar recommendations were also published for prostate cancer; the European guidelines for prostate were published jointly by the European Association of Urology (EAU), International Society of Geriatric Oncology (SIOG), and European Society for Radiotherapy and Oncology (ESTRO) recommended that all men starting long-term ADT should undergo dual-energy X-ray absorptiometry (DXA) assessment and the result used in conjunction with the FRAX ® tool to evaluate individual fracture risk.

A key advance in this field has been the development of the FRAX algorithm developed by the former WHO Collaborating Center at Sheffield, UK (http://www.sheffield.ac.uk/FRAX/), an easy to-use online tool for assessing fracture risk in postmenopausal women with or without BMD data. The FRAX algorithm is based on data from large-scale, population-based cohorts from different parts of the world, and uses factors such as age, body mass index (BMI), smoking history, personal and family history of fracture, smoking, glucocorticoid use, and secondary causes of osteoporosis, to assess long-term fracture risk. FRAX is not designed to assess fracture risk in women with breast, prostate, or any other form of cancer. The secondary osteoporosis input affects FRAX calculations when BMD is not entered but not when BMD is included since the risk is assumed to be mediated through BMD [120]. However, FRAX is not designed to assess fracture risk in women with breast cancer or men with prostate cancer, and indeed may substantially underestimate the effect of aromatase inhibitor (AI) therapy or androgen deprivation therapy (ADT)—the "secondary osteoporosis" option in the FRAX tool has a much smaller effect on fracture risk than would be expected for AI or ADT therapy. Moreover, as clinical trials comparing AIs with tamoxifen mature, it is evident that AIs have a large effect on acute fracture risk during active treatment [25, 26], which might be underestimated by FRAX, an algorithm designed to provide long-term (10-year) fracture risk. As it appears that the independent fracture risk in aromatase inhibitor bone loss (AIBL) or androgen

deprivation therapy is equivalent to that seen in RA, it has recently been suggested to use the bypass of rheumatoid arthritis in FRAX as it has been proposed in type 2 diabetes [121].

Each FRAX tool is calibrated for use in a specific country, based on fracture data from that country. An individual's 10-year major osteoporotic fracture risk is stratified into three zones designated low risk (less than 10%), moderate risk (10–20%), and high risk (exceeding 20%). Similarly, a 10-year probability of hip fracture above 3% indicates high risk of fracture hip [122, 123]. Treatment should be considered if the risk of major osteoporotic fracture over 10 years exceeds 20% or hip fracture probability exceeds 3% (among other indications for treatment). Although not validated in the AI or ADT population, these tools assess fracture risk better than BMD alone can, and they can help to inform clinical decision-making in connection with BMD testing and treatment for men receiving ADT as well as women treated for breast cancer [124–127].

As reported by the USPSTF [116], the discriminative ability of FRAX to predict future fracture varied by sex, site of fracture prediction, and whether BMD was used in the risk prediction. Specifically, in women, pooling area under the curves (AUCs) identified in 10–17 studies by the USPSTF yielded estimates that ranged from 0.66 to 0.79. In cohorts of men, pooled estimates from 3 to 44 studies ranged from 0.62 to 0.76. The predictive accuracy of FRAX was found to be greater for hip fractures compared with major osteoporotic fractures, and pooled AUC estimates were higher when BMD was included in the model.

In studies of both men and women combined, pooled estimates for the prediction of major osteoporotic fracture were 0.67 without BMD and 0.69 with BMD. USPSTF also reported on the Garvan Fracture Risk Calculator and found that the pooled AUC estimate for risk assessment with BMD was 0.68 (95% CI, 0.64–0.71) for predicting major osteoporotic fracture in women and 0.73 (95% CI, 0.66–0.79) for predicting hip fracture.

Diagnosis of Cancer Therapy-Induced Bone Loss

Bone Densitometry Early diagnosis and treatment of cancer therapy-induced bone loss are essential to decrease the risk of fracture. Because signs and symptoms of bone loss are not present until a fracture occurs, chemotherapy-induced bone loss is diagnosed by measuring bone mass or the amount of bone tissue [3, 128] Although no technology directly measures bone mass, measurement of BMD—the average concentration of bone mineral in a defined section of bone—has been shown to be the single best predictor of fracture risk because the amount of mineral in the bone directly correlates with bone strength [128, 129].

The techniques used to measure BMD include dual-energy X-ray absorptiometry (DXA), peripheral DXA, peripheral single X-ray absorptiometry, quantitative computed tomography (QCT), radiographic absorptiometry, and quantitative ultrasonography [128]. DXA and QCT are most commonly used to diagnose chemotherapy-induced bone loss [4]. Although DXA is performed using two radiographic beams with different photo energies, providing only a two-dimensional bone area measurement rather than a volumetric density, it provides a highly accurate measurement [129, 130]. DXA can also measure the BMD at different skeletal sites, including the hip and spine and distal forearm with minimal radiation exposure [128].

BMD measurements at any skeletal site may predict fracture risk. However, to diagnose chemotherapy-induced bone loss in women, hip BMD measurements are the best predictor of hip fractures, and hip or spine BMD measurements similarly predict the risk of vertebral fractures [131] In men, however, hip BMD measurements may be better than spinal BMD measurements in diagnosing bone loss because men tend to have more degenerative spinal diseases that prevent accurate spinal BMD measurements [128]. In patients with metastatic bone disease, measuring the BMD of a site unaffected by bone disease is best because metastatic lesions usually are asso-

ciated with higher or lower BMD due to osteoblastic or osteolytic processes that are occurring, respectively [132].

QCT is performed using conventional whole-body computed tomography devices and measures the BMD at any skeletal site, but it is used most frequently to measure spinal BMD [128]. An advantage of QCT is its three-dimensional assessment of BMD, which allows isolated measurements of trabecular bone density. Because trabecular bone is more responsive than cortical bone to many treatments, QCT may be useful in monitoring the effectiveness of bone loss therapies. QCT, however, is associated with high radiation exposure, high costs, and difficulties with quality control [132].

Interpreting the BMD Measurement Comparing the exact BMD measurement of a chemotherapy-induced bone loss patient, reported as grams of calcium hydroxyapatite per square centimeter, with the mean BMD of healthy young patients, who are most likely to have a normal bone mass, avoids differences in calibration among bone densitometry machines [129, 132]. Therefore, bone densitometry results are also reported as T-scores, which represent the difference in the number of standard deviations between an individual's BMD and the mean value for a group of young adults (usually age 25–45 years) of the same sex and, in some cases, the same race [128]. A Z-score, which represents the difference in the number of standard deviations between an individual's BMD and the mean value for a group of adults of the same age and sex, may also be reported.

The World Health Organization has created four diagnostic categories of bone loss at the spine, hip, or wrist based on BMD measurements. Although these categories were designed for postmenopausal Caucasian women, they are also widely used to diagnose bone loss in males, non-Caucasians, and high-risk patients, such as those with CTIBL, until criteria specific for these patient groups have been established [130]. To define osteoporosis in men aged 50 years or older, the WHO recommends using the same classification of BMD (based on the T-score system, with the number of standard deviations that BMD measured by DXA is above- or below average for a young white female reference population) as that used in women. A DXA T-score of the lumbar spine, femoral neck, or total hip less than or equal to −2.5 is consistent with osteoporosis; a T-score between −1.0 and −2.5 is considered low bone mass (osteopenia) [133, 134].

Other Tools for Bone Mineral Density Assessment The USPSTF systematic review [113] identified 11 studies that evaluated the accuracy of QUS, peripheral DXA, digital X-ray absorptiometry, and radiographic absorptiometry in screening for low bone mass or osteoporosis in noncancer populations. The AUC for calcaneal QUS in identifying central DXA-measured osteoporosis ranged from 0.69 to 0.90 in female populations, with a pooled AUC estimate of 0.77 (95% CI, 0.72–0.82). Additional studies in women reported AUCs that ranged from 0.67 to 0.80 for peripheral DXA, 0.84 (95% CI, 0.79–0.89) for digital X-ray absorptiometry, and 0.80 (95% CI, 0.74–0.85) for radiographic absorptiometry. Studies that focused solely on a male population evaluated calcaneal QUS in comparison with a centrally measured DXA BMD T-score cutoff of22.5 or less and reported AUCs that ranged from 0.70 to 0.93, with a pooled AUC estimate of 0.80 (95% CI, 0.67–0.94).

The "ASCO-2019" guidance [135] recommends that patients with nonmetastatic cancer with one or more risk factors for osteoporotic fracture should be offered BMD testing with central/axial DXA. In settings in which DXA is not available or technically feasible, other BMD testing—for example, quantitative ultrasound (QUS) or calcaneal DXA—should be offered.

Monitoring Bone Mineral Density

Men with nonmetastatic prostate cancer receiving continuous or intermittent ADT can have significant bone mineral density (BMD) loss as early as the first 6–12 months after starting ADT

[136, 137]. Men who receive continuous ADT experience bone loss of up to 10% over 2 years [138] and clinically significant annual BMD decrements of −1.4% to −4.6% at the lumbar spine, −0.6% to −3.3% at the total hip, and −0.7% to −3.9% at the femoral neck [135, 139].

Intermittent administration appears to attenuate the negative impact of ADT on bone because the overall odds ratio for having osteoporosis is significantly higher in men on continuous ADT [odds ratio (or): 2.14; $p = 0.032$] than in those on intermittent adt10. Longer duration of continuous ADT was associated with a greater loss in BMD, but the long-term effects of intermittent ADT on BMD are not known.

Similarly, in women with breast cancer receiving AI therapy, earlier studies revealed that in premenopausal women, relative to baseline, endocrine therapy alone resulted in a BMD decline (lumbar spine −11.3%; hip −7.3%) at 36 months. Average losses were greater in women treated with anastrozole compared to women receiving tamoxifen [140, 141]. In postmenopausal women, 5 years of AI (anastrozole) treatment induced significant declines in BMD at both the lumbar spine (−6.1%) and total hip (−7.2%) versus tamoxifen treatment, which slightly increased BMD at the spine (+2.8%) and hip (+0.7%) at 5 years [142].

Ideally, all patients due to start AI or ADT therapy or have history of fracture should have a baseline DXA scan to assess for their bone mineral density, as well as fracture risk assessment using FRAX, before they start their treatment. Subsequent monitoring for bone loss is recommended based on baseline T-score and the presence of confounding risk. Patients with a score ≥ −1 should be monitored and rescreened every 2 years. Those with a T-score of −1 to −2.5 should have BMD testing repeated after 6–12 months. Patients with nonmetastatic cancer with osteoporosis (T-scores of −2.5 or less in the femoral neck, total hip, or lumbar spine) or who are at increased risk of osteoporotic fractures based on clinical assessment or risk assessment tools (10-year probability of ≥20% for major osteoporotic fractures or ≥3% for hip fractures), bone-modifying agents, such as oral bisphosphonates, intravenous bisphosphonates, or subcutaneous denosumab, at the osteoporosis-indicated dosage should be offered to reduce the fracture risk [131].

Other Diagnostic Evaluations: The clinical history of a patient at risk for CTIBL is also an important factor in determining fracture risk. Therefore, a thorough review of the patient's history and risk factors, including previous and current cancer therapies, is an important aspect in the diagnosis of CTIBL. In addition, a thorough physical examination should be conducted to rule out the presence of asymptomatic vertebral fractures. For example, kyphosis, height loss, and bone pain may indicate the presence of a vertebral fracture. If any of these symptoms exist, vertebral radiography can confirm the presence of a fracture [139].

Laboratory Tests Lab tests should also be conducted to exclude secondary causes of bone loss. Key constituents of bone, including serum calcium, phosphate, and alkaline phosphatase, are usually present in normal levels in patients with bone loss; however, alkaline phosphatase levels may be transiently elevated after a fracture. Blood urea nitrogen and serum creatinine levels and liver function should be measured to exclude renal and hepatic disease, and a complete blood count should be performed to exclude hematologic disorders. In addition, hyperthyroidism, hyperparathyroidism, and vitamin D deficiency should be excluded by measuring serum TSH, parathyroid hormone, and 25-dihydroxyvitamin D levels, respectively [143].

Bone Markers Another method of bone loss assessment is the measurement of biochemical markers, including enzymes, nonenzymatic peptides, and mineral components of the skeletal matrix, which specifically indicate either bone formation or bone resorption [144]. Biochemical markers of bone turnover provide insight into ongoing rates of skeletal metabolism and tumor–bone interactions in patients with malignant bone disease. This interplay between tumor and bone dysregulates these otherwise balanced and spa-

tially coupled activities, resulting in increased rates of osteolysis and osteogenesis and release of high levels of distinct biochemical markers that are amenable to noninvasive measurement in blood or urine [19]. Therefore, biochemical markers of bone metabolism, such as the cross-linked collagen peptides that are breakdown products from osteolysis (e.g., the amino [N]- and carboxy [C]-terminal cross-linked telopeptides of type I collagen, or NTX and CTX) and the terminal peptides that are cleaved from procollagen before its integration into new bone matrix (e.g., procollagen type I N-terminal and C-terminal peptides, or PINP and PICP) can provide meaningful insight into the ongoing effects of tumor growth on bone turnover. Serum levels of CTX and urinary concentration of NTX reflect ongoing rates of osteolysis, whereas bone-specific alkaline phosphatase (bone ALP) and PINP levels in serum reflect ongoing rates of osteogenesis [22]. In addition, some markers of bone metabolism may be associated with both osteolysis and osteogenesis (e.g., osteocalcin).

Biochemical markers of bone metabolism reflect ongoing rates of bone resorption and formation in the body as a whole. Therefore, bone marker assessments do not provide information specific to individual lesion sites. Moreover, changes in bone marker levels are not disease specific, but are associated with alterations in skeletal metabolism independent of the underlying cause [2]. Emerging evidence suggests that bone markers may help identify patients at high risk for bone metastasis or bone lesion progression, thereby allowing improved follow-up [140, 141]. Results from ongoing clinical trials evaluating such potential applications of bone markers are awaited to identify the true value of bone markers in clinical practice [95].

Clinical Sequelae of Cancer Therapy-Induced Bone Loss

Bone loss occurs more rapidly and tends to be more severe in patients with chemotherapy-induced bone loss compared with patients with normal age-related bone loss. Chemotherapy-induced bone loss that is associated with ADT or AI exponentially increases the risk of fracture. The loss of 10–15% of BMD doubles the fracture risk [145], and men receiving ADT for prostate cancer are five times more likely to develop a fracture than healthy age-matched controls [146]. Similar results were reported among women with breast cancer treated with AI [147–150].

A retrospective study carried out by Shahinian and colleagues [151] evaluated the fracture risk of 50,613 prostate cancer patients listed in the Surveillance Epidemiology and End Results (SEER) program between 1992 and 1997. Among men who survived at least 5 years after prostate cancer diagnosis, those receiving ADT exhibited a significantly higher risk of fracture, as compared to untreated men (19.4 vs. 12.6%, $p < 0.001$). Moreover, patients undergoing orchiectomy or receiving at least nine doses of LHRH agonists had the lowest fracture-free survival, although the analysis did not exclude bone metastasis-related fractures [146].

Another similar analysis involved 11,661 patients with nonmetastatic prostate cancer and confirmed the significantly higher fracture rate in men undergoing ADT (7.88 vs. 6.51%/year of controls, $p < 0.001$), and the highest hazard ratio (HR) in those receiving LHRH agonists for at least 12 months (1.16, 95% CI 1.08–1.26; $p < 0.001$). Interestingly, when considering fractures at specific sites, both vertebral and hip/femur ones were more frequent in patients undergoing ADT, as compared to controls ($p < 0.001$ and $p = 0.002$, respectively) [148].

Not only are such events associated with subsequent fractures and loss of independence, but they also represent an independent adverse predictor of survival. Indeed, the relative risk of death is sevenfold greater in men with prostate cancer receiving ADT and who have a previous fracture compared to those with no fracture history [149].

In concordance, in women with breast cancer, the depletion of the circulating estrogen is caused by AI and can negatively impact bone remodeling; this decreases BMD and increases bone loss, which is estimated to be twofold greater than

menopause-related bone loss [150–152]. The consequences of decreased BMD and increased bone loss as a result of AI therapy include greater risk for osteoporosis and bone fracture [147–149] and potentially increased risk for morbidity and mortality [150]. Adjuvant studies confirm that AIs increase fracture risk, with an incidence of 7% after a median of 30 months of treatment with exemestane and an incidence of 9–11% after up to 5 years of treatment with letrozole or anastrozole [153–157].

One potential clinical sequela of chemotherapy-induced bone loss in patients with breast or prostate cancer is the development and progression of bone metastases. Historically, bone metastases in these patients were believed to result from the release of bone-cell-activating factors from malignant cells, altering the bone microenvironment [157–160]. Furthermore, the release of bone-derived growth factors and cytokines from resorbing bone cells has been shown to attract malignant cells to the bone surface, facilitating their growth and development. Thus, it has been hypothesized that the inhibition of bone resorption, by the prevention or early treatment of chemotherapy-induced bone loss, may prevent the development and progression of bone metastases [155, 161–163].

Management

In patients with nonmetastatic cancer, both the disease itself, through an association with increased local and systemic inflammation, and its treatment can pose challenges to skeletal integrity. Chronic inflammation can promote increased bone loss through altered systemic bone remodeling, increased bone resorption, and impaired bone formation. This is a result of the effect of inflammatory mediators on the differentiation and activity of osteoclasts and osteoblasts [164]. Osteoclastogenesis and osteoclasts' activity can be influenced by proinflammatory cytokines, such as tumor necrosis factor, interleukin-1, interleukin-6, macrophage colony-stimulating factor, and RANK ligand (RANK-L) [165].

The goal of CTIBL management is to optimize bone mass, thus preventing osteoporosis. For patients with existing bone loss, the goal of CTIBL management is to prevent further bone loss, fractures, subsequent clinical sequelae (e.g., pain), and decreased functional capabilities. The treatment of CTIBL includes diet and lifestyle changes as well as pharmacological therapy.

Diet and Lifestyle Changes

Patients at risk of or those who have CTIBL can make lifestyle changes that help to maintain or improve bone mass, including consuming sufficient calcium and vitamin D, exercising regularly, and modifying behaviors that increase the risk of bone loss. Clinical trials evaluating these interventions in patients with cancer have not yet been conducted; thus, the recommendation for these interventions is primarily based on clinical trials evaluating these interventions in others at risk of bone loss, such as postmenopausal women and elderly men.

Calcium and Vitamin D Intake Because calcium deposition is an important step in bone formation, maintaining adequate serum calcium levels by optimizing calcium intake is important for patients with or at risk of bone loss. Administration of vitamin D maximizes intestinal calcium absorption; therefore, daily supplementation of both calcium and vitamin D is recommended for all adult women and men with or at risk of osteoporosis.

Because calcium and vitamin D are beneficial in reducing bone loss in patients without cancer, these agents are essential components of CTIBL prevention and treatment but are not a substitute for pharmacological therapy in cancer patients with CTIBL. The most effective daily dose of calcium and vitamin D in patients with or at risk of CTIBL is unknown. However, the recommended daily dose for other patients at risk of bone loss is likely to be effective in patients with CTIBL. The recommended daily calcium intake for adults at risk of bone loss is 1200–1500 mg. A

daily vitamin D intake of at least 800–1000 IU/day is appropriate for most adults; however, patients at risk of vitamin D deficiency, such as elderly, chronically ill, housebound, or institutionalized patients, should receive supplements to reach those levels that are recommended [128, 166].

Exercise Regular physical activity is beneficial in reducing fractures in patients at risk of bone loss. Results of a prospective cohort study of women 65 years or older showed that increasing levels of physical activity correlated with a reduced relative risk of hip fracture, with the most physically active women having a 42% lower risk of hip fracture than the least active women [166].

Increases in BMD have also been observed with consistent exercise programs. Weight-bearing exercise, such as walking, weight training, or high-impact exercise, induces a 1–2% increase in BMD at some, but not all, skeletal sites [167]. Results of a recent randomized trial comparing the BMD of elderly patients who followed a 6-month high- or low-intensity resistance exercise program with those who did not exercise demonstrated that a high-intensity resistance exercise program significantly increased femoral neck BMD by 1.96% [168]. Furthermore, bone formation markers increased significantly, suggesting that a long-term, high-intensity resistance program may further improve BMD. A routine exercise program also may provide other benefits, such as improved muscle strength, coordination, balance, and mobility, which may decrease the risk of fracture, and improves overall quality of life and reduces body fat and fatigue [113]. Based on the positive effects of exercise on osteoporosis-associated complications, a routine exercise program consisting of both weight-bearing and muscle-strengthening exercises for up to four sessions each week is also recommended to minimize or prevent CTIBL in cancer patients. Patients need to engage in a combination of exercise types, including balance training, flexibility or stretching exercises, endurance exercise, and resistance and/or progressive strengthening exercises, to reduce the risk of fractures caused by falls. Whenever possible, exercise should be tailored according to the needs and abilities of the individual patient. Patients with an impairment that hinders their gait or balance should be offered medical rehabilitation. Therefore, the type of exercise program should be tailored to the individual patient's condition (e.g., weight machines versus resistance exercises, walking versus jogging) and should be customized for each patient [128].

Lifestyle Modification Modification of lifestyle behaviors, such as smoking and excessive alcohol and caffeine consumption, that may increase the risk of bone loss and fractures is another important aspect of managing patients with or at risk of developing CTIBL. Patients should be encouraged to stop smoking and to limit alcohol and caffeine consumption to two or fewer servings per day. A meta-analysis showed that bone loss is greater in current smokers than in former smokers [169], whereas an animal study found that smoking cessation reverses bone loss, suggesting that smoking cessation not only prevents further bone loss but can reverse existing bone loss [170]. Furthermore, patients should be educated about fall-prevention strategies, such as using non-skid rugs, having adequate lighting, and holding on to handrails when using stairs [113].

Specific Lifestyle Measures for CTIBL in Prostate Cancer

Lifestyle Measures: Both smoking and excessive alcohol intake are associated with reduced BMD and should be avoided [171]. Other consequences of ADT are sarcopenia and fatigue, both of which increase the likelihood of frailty, falls, and fractures [172]. Regular exercise is helpful to minimize this risk, and supervised aerobic and resistance exercise programs, performed at least twice a week for 12 weeks, are currently recommended for all men undergoing ADT [173–175].

Calcium and Vitamin D Supplementation: Men with PC are frequently deficient in both cal-

cium and vitamin D [176]. Since vitamin D deficiency in men receiving ADT is independently associated with spinal fractures [177], supplementation with calcium and vitamin D should be considered in all men receiving ADT. However, the recommended doses (500–1000 mg calcium and 200–500 IU vitamin D per day) may be insufficient to prevent bone loss [178].

Specific Lifestyle Measures for CTIBL in Breast Cancer

Lifestyle Measures: Limitation of alcohol consumption and smoking cessation are recommended. Moderate weight-bearing exercise should be practiced regularly to take advantage of the beneficial effects of exercise on BMD [179].

Calcium and Vitamin D Supplementation: If dietary intake is inadequate, calcium supplementation is recommended (1000 mg/day) together with vitamin D supplementation (800–1000 IU/day). Concomitant steroid uptake interferes with vitamin D absorption and requires higher dosage [180]. Elderly patients, and those with reduced sunlight exposure and/or physical activity, should be assessed for vitamin D serum levels and deficient levels treated with high-dose vitamin D followed by ongoing supplementation [179].

Bone-Targeted Agents (BTAs)

The "2019" ASCO Clinical Practice Guideline recommend that for patients with nonmetastatic cancer with osteoporosis (T-scores of −2.5 or less in the femoral neck, total hip, or lumbar spine) or those who are at increased risk of osteoporotic fractures based on clinical assessment or risk assessment tools (10-year probability of >20% for major osteoporotic fractures or >3% for hip fractures based on the US-adapted FRAX tool), BMAs such as oral bisphosphonates, intravenous (IV) bisphosphonates, or subcutaneous denosumab at the osteoporosis-indicated dosage may be offered to reduce the risk of fracture. Hormonal therapies for osteoporosis management (e.g., estrogens) were generally avoided in patients with hormonal-responsive cancers. For patients without hormonally responsive cancers, estrogens may be offered along with other BMAs when clinically appropriate [135].

Bisphosphonates The bisphosphonates are analogues of pyrophosphate, with carbon replacing the central oxygen, whereas the side chains from the central carbon provide the different bisphosphonate medications. Bisphosphonates have high affinity for mineralized bone matrix, where they bind selectively to hydroxyapatite and are released during resorption. Ingestion of bisphosphonate by osteoclasts results in their inhibition, either through induction of apoptosis (non-nitrogen-containing bisphosphonate such as clodronate) or through inhibition of the mevalonate pathway required for osteoclastogenesis (nitrogen-containing BP such as zoledronate, ibandronate, and pamidronate), thereby acting as potent inhibitors of bone resorption. Bisphosphonates concentrate in the skeleton, primarily at active remodeling sites. They are embedded in bone, released in the acidic environment of the resorption lacunae under active osteoclasts, and are taken up by them. They will then interrupt the "vicious cycle" of tumor-mediated osteolysis by inhibiting the activity of bone-resorbing osteoclasts and inducing their apoptosis [28]. In preclinical models, the nitrogen-containing bisphosphonates have also been shown to influence macrophages, gamma delta T cells, and osteoblasts. In addition to their effects on host cells, bisphosphonates may also have antitumor and/or antiangiogenic effects, but this is a controversial area. Investigations are ongoing to better define the clinically relevant antitumor effects of bisphosphonates in patients with cancer [181].

There are two classes of bisphosphonates, non-nitrogen-containing and nitrogen-containing, with somewhat different effects on osteoclasts. Etidronate, clodronate, and tiludronate are non-nitrogen-containing bisphosphonates, and the nitrogen-containing bisphosphonates (more potent osteoclast inhibi-

tors and the most often used nowadays) include pamidronate, alendronate, ibandronate, risedronate, and zoledronic acid (Fig. 29.2). Many bisphosphonates are administered orally; however, the most comprehensively studied is zoledronate, which is given intravenously. It requires dosage adjustment in patients with a creatinine clearance (CrCl) <60 ml/min and is contraindicated in severe renal impairment (CrCl <30 ml/min).

Although radiotherapy is the treatment of choice for localized bone pain, many patients have widespread pain that is difficult to localize, while others experience recurrence of bone pain after radiotherapy. The bisphosphonates provide an additional treatment approach for the relief of bone pain that is useful across the range of tumor types [182].

Denosumab is another BTA approved for the treatment of CTIBL. It is a fully humanized monoclonal IgG2 antibody that targets RANK-L and prevents its interaction with RANK on osteoclast precursors, in a way that is similar to the natural endogenous inhibitor osteoprotegerin [183]. Consequent inhibition of osteoclast differentiation and activation causes a rapid reduction in bone resorption. As a circulating antibody, denosumab is expected to reach all sites within bone, whereas the strong affinity of bisphosphonates for hydroxyapatite and sites of active bone turnover may limit their even distribution throughout the skeleton.

In early clinical development, a single s.c. dose of denosumab was shown to cause rapid suppression of bone turnover in multiple myeloma and breast cancer patients [184] and encouraged the clinical development of this targeted treatment. Denosumab also provided substantially greater percentage reductions in tartrate resistant acid phosphatase, a surrogate marker of osteoclast number, compared with i.v. bisphosphonate therapy. This indicated that functioning osteoclasts are still present in patients showing an inadequate biochemical response to bisphosphonate therapy, and that switching to denosumab may help suppress their activity. This finding suggests that denosumab may prove to be especially effective in patients who respond poorly to bisphosphonate therapy [185].

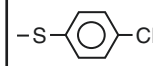
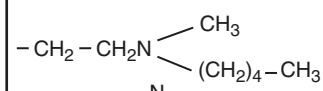
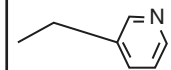
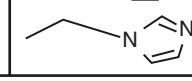
Agent	R_1 side chain	R_2 side chain
Etidronate	–OH	$-CH_3$
Clodronate	–Cl	–Cl
Tiludronate	–H	
Pamidronate	–OH	$-CH_2-CH_2-NH_2$
Neridronate	–OH	$-(CH_2)_4-NH_2$
Olpadronate	–OH	$-(CH_2)_2N(CH_3)_2$
Alendronate	–OH	$-(CH_2)_3-NH_2$
Ibandronate	–OH	
Risedronate	–OH	
Zoledronate	–OH	

Fig. 29.2 Side chains of different bisphosphonate medications

Prevention of Skeletal Morbidity in Metastatic Bone Disease

Over the past two decades, multiple, randomized, controlled trials have clearly demonstrated that both bisphosphonates and denosumab are effective in reducing skeletal morbidity from metastatic cancer, hence they become established as a valuable additional approach to the range of current treatments [186].

Assessment of treatment effects has often used the first-event analyses, such as the proportion of patients with at least one SRE or time to the first event. These are objective but conservative end points that do not take into account all subsequent events. From a clinical perspective, an aggregate score of symptomatic SREs is more relevant. Multiple-event analyses have been increasingly used as they are able to model all events and the time between events, allowing the calculation of a hazard ratio (HR) that indicates the relative risk of events between two different treatments [187].

Breast Cancer

Randomized placebo-controlled trials of pamidronate infusions for up to 2 years in addition to chemo- or hormonal therapy in breast cancer patients with at least one lytic bone metastasis demonstrated that bisphosphonates can reduce skeletal morbidity rate by more than one-third, increase the median time to the occurrence of the first SRE by almost 50%, and reduce the proportion of patients having any SRE [188, 189].

Subsequently, more convenient and effective amino-bisphosphonates have emerged including zoledronic acid and both i.v. and oral ibandronate [190, 191]. A randomized, double-blind, multicenter trial compared the efficacy of zoledronic acid and pamidronate in 1648 patients with breast cancer or MM. The proportion of patients with at least one SRE (the primary efficacy end point) was similar in all treatment groups and the preestablished criterion for noninferiority of zoledronic acid to pamidronate was met [192]. A multiple-event analysis in the breast cancer subgroup, however, showed that zoledronic acid (4 mg) reduced the risk of developing a skeletal complication by an additional 20% compared with that achieved by pamidronate ($P < 0.05$) [193]. The short infusion time also offers a more convenient therapy. Oral ibandronate has been also compared with i.v. zoledronic acid in a large randomized trial in 1404 patients. Oral ibandronate was deemed inferior to zoledronic acid in reducing the overall risk of skeletal events [rate ratio for SREs 1.148, 95% confidence interval (CI) 0.967–1.362], although similar to zoledronic acid in delaying time to the first event [194].

Denosumab has been evaluated in three identical, double-blind, phase III registration studies that included a total of 5723 bisphosphonate-naive patients with bone metastases [195–197]. The patients were randomly assigned to receive four weekly s.c. injections of denosumab (120 mg) or i.v. zoledronic acid (4 mg), with supplements of calcium and vitamin D. The primary end point was the time to first SRE. In the 2046 patients with bone metastases secondary to breast cancer, denosumab was statistically superior to zoledronic acid in delaying the first SRE (HR 0.82, 95% CI 0.71–0.95; $P = 0.01$). The median time to a first SRE was 26.4 months for zoledronic acid-treated patients, whereas the median time to first SRE was not reached during the study in those treated with denosumab [195].

Denosumab was also superior to zoledronic acid in preventing subsequent SREs and reduced the overall risk by 23% (HR 0.77, 95% CI 0.66–0.89; $P = 0.001$) [195]. In patients who had no/mild pain at baseline, a 4-month delay in progression to moderate/severe pain was observed with denosumab compared with zoledronic acid, while fewer patients who received denosumab reported a clinically meaningful worsening of pain severity [196]. An additional 10% of patients had a clinically meaningful improvement in health-related QoL with denosumab relative to zoledronic acid, regardless of baseline pain levels [197].

Therefore, it has been recommended to start zoledronic acid or denosumab in all patients with metastatic breast cancer and bone metastases, whether they are symptomatic or not [198].

Prostate Cancer

Zoledronic acid is the only bisphosphonate to demonstrate a significant reduction in skeletal complications from bone metastases in patients with advanced prostate cancer. In a placebo-controlled study of 643 patients with CRPC, zoledronic acid was significantly more effective than placebo across all primary and secondary end points including fewer SRE(s) (33% versus 44% with placebo; $P = 0.021$), and a 4-month prolongation in time to first skeletal complication ($P = 0.011$) [199]. Using the Andersen–Gill multiple-event analysis, zoledronic acid reduced the overall risk of skeletal complications by 36%, and reduced bone pain at all time points. In a placebo-controlled double-blind study comparing denosumab to zoledronic acid for the prevention of skeletal morbidity in men with bone metastases from CRPC, superiority in terms of time to first SRE and cumulative mean number of SREs with denosumab was achieved. The time to first SRE was extended from 17.1 to 20.7 months (HR 0.82, 95% CI 0.71–0.95; $P = 0.008$ for superiority) [200]. Second and subsequent SREs were also delayed, resulting in an 18% reduction in cumulative SREs.

It is recommended to start zoledronic acid or denosumab in all patients with CRPC and bone metastases, whether they are symptomatic or not [198].

Prevention of Bone Loss in Prostate Cancer

ADT leads to accelerated bone loss and an increase in fracture rate, as evidenced by large retrospective epidemiological studies [201]. Earlier studies revealed that in men with prostate cancer treatment with ADT leads to an accelerated and disrupted bone turnover process and BMD loss in the range of 5–10% in the first year of ADT [162, 202, 203]. One study showed that, in 390 patients with prostate cancer, age 54–89 years, the prevalence of osteoporosis was 35% in hormone-naive patients, 43% after 2 years of ADT, and 81% after 10 years of ADT [32, 63, 196].

Alendronate, risedronate, pamidronate, and zoledronic acid have all been shown to prevent loss in BMD in patients with locally advanced prostate cancer [204]. Of these treatments, 6–12-monthly zoledronic acid and 6-monthly denosumab are considered the most convenient and reliable treatments [205, 206]; however, only denosumab has a specific license for treatment-induced bone loss associated with ADT. In a placebo-controlled trial of denosumab in 1468 men receiving ADT for nonmetastatic prostate cancer, 36 months of denosumab treatment was associated with a 62% relative reduction in new vertebral fractures (1.5% with denosumab versus 3.9% with placebo) (2017).

BMD increased from baseline at all sites in the denosumab group but declined in the placebo group, leading to BMD differences of 6.7% at the lumbar spine and 4.8% at the total hip after 36 months [207, 208].

Prevention of Bone Loss in Breast Cancer

With recent guidelines [62] recommending an increased duration of AI treatment in higher-risk patients for up to 10 years, fracture risk is believed to increase by 2–3% per annum [209]. Therefore, upon starting AI, it has been recommended [210] that a BMD measurement is carried out, and, if the T-score was greater than −2, then lifestyle measures were to be implemented. BMD is then to be repeated after 1–2 years as accelerated bone loss is an indication for starting antiresorptive treatments. If the BMD T-score is less than −2 or if the patient had major risk factors, such as prior fracture, then antiresorptive treatments should be administered.

The strongest evidence of benefit from antiresorptive drugs is for treatment with denosumab at the osteoporosis dose of 60 mg every 6 months. This has been demonstrated to reduce the risk of fracture; however, when denosumab is discontinued, there may be an increase in the risk of verte-

bral fractures. The European Calcified Tissue Society suggests the use of a bisphosphonate to reduce this risk upon stopping denosumab [211].

There is good evidence of benefit based on gain in BMD from treatment with zoledronic acid. In osteoporosis, the licensed dose is 5 mg administered once per year by IV infusion. For osteopenia, zoledronic acid is dosed 5 mg every 2 years. However, in the AI trials, it was usually administered as 4 mg twice per year by IV infusion. The treatment is highly effective in preventing bone loss and decreasing bone turnover, as well as building bone mass, but there is limited data on fracture risk reduction. Zoledronic acid can result in an acute-phase response within the first week of administration, in which case an antipyretic, such as acetaminophen or ibuprofen, may be useful. There is fairly good evidence of benefit from treatment with several oral bisphosphonates, including alendronate (70 mg once per week), risedronate (35 mg once per week), and ibandronate (150 mg once per month), and the clinical trials cited used these osteoporosis doses. The treatment prevents bone loss and decreases bone turnover, but again, there are no data on fracture risk reduction. The challenge with these treatments is to maintain good adherence as they have GI adverse effects [135].

Hadji et al. [210] noted also the value of bisphosphonates to prevent breast cancer recurrence and to increase breast cancer survival, and so there may well be benefits of these antiresorptive treatments beyond bone.

Oophorectomy, GnRH Agonist (ASCO)

In healthy individuals, peak bone mass occurs at age 30 years [212]. After age 30 years, the two sources of bone loss are age related, which happens throughout the remainder of life, and hormonally related. In women and men, the estrogen deprivation of menopause and the more gradual decreasing of androgens, respectively, also contribute to bone loss. Almeida et al. [213] describe a review of the mechanisms by which estrogens and androgens are protective against bone loss.

Cancer treatments cause bone loss via hypogonadism [214]. Bone loss is caused by orchiectomy [215], oophorectomy [216, 217], and GnRH agonists [88, 205, 218], which cause reversible medical castration. These treatments form the basis of endocrine therapies in men with prostate cancer and premenopausal women with breast cancer.

Cessation of Ovarian Function (CIOF)

Cessation of ovarian function in premenopausal women causes rapid bone loss [9, 219]. This bone loss occurs as early as 6 months after the initiation of adjuvant chemotherapy and further increases at 12 months [9]. Effects of chemotherapy on ovarian function depend on the age at treatment, the specific class of drugs, and the cumulative doses. Risk of CIOF increases with age, likely because of a diminished ovarian reserve related to the reduced number and quality of follicles [220]. Alkylating agents, such as cyclophosphamide, are associated with the highest risk of CIOF, followed by platinum agents, anthracyclines, and taxanes. Higher cumulative doses of cyclophosphamide are associated with a higher rate of CIOF [72]. In women who retain menstrual function after chemotherapy, natural menopause can occur at an earlier age than in those who did not receive chemotherapy [221].

It is essential to distinguish between transient amenorrhea, which often occurs in younger premenopausal women who receive adjuvant chemotherapy, and permanent ovarian failure. Women who experience transient amenorrhea with a loss of bone mass at 6 months tend to recover their bone density by 12 months [9]. In addition, it has implications for the choice of endocrine therapy and fertility.

There are randomized trials of zoledronic acid in women receiving GnRH agonists with either tamoxifen or the AI anastrozole [222, 223] and CIOF [224, 225]. These trials have BMD as the primary end point as opposed to trials in healthy populations that have prevention of fractures as a primary end point. BMD is a surrogate end point,

however, and fracture risk is not only determined by bone loss, but also by bone mass before initiating treatment.

Patients with Chronic (> 6 Months) Glucocorticoid Use

Treatment with glucocorticoids over a long-term period can lead to drug-induced osteoporosis, which has been associated with rapid and significant bone loss [226]. As such, the resulting increased vertebral fracture risk occurs at higher BMD thresholds in glucocorticoid-induced osteoporosis.145 The American College of Rheumatology recently released a guideline on the assessment, prevention, and treatment of glucocorticoid-induced osteoporosis in patients taking prednisone at doses 2.5 mg per day for three or more months [227]. Based on a systematic review of the literature, recommendations are made for treating only with calcium and vitamin D in adults who are at low fracture risk, treating with calcium and vitamin D plus an additional osteoporosis medication (oral bisphosphonate preferred, when appropriate) in adults at moderate-to-high fracture risk, and continuing oral bisphosphonate treatment or switching to another antifracture medication in adults who complete a planned oral bisphosphonate regimen but continue to receive glucocorticoid treatment. The ASCO guidance supports the ACR recommendations for the management of patients on long-term glucocorticoids [135].

Management of Bone Metastases

Palliative Radiotherapy

Local external beam irradiation is highly effective for bone pain. Overall, response rates of around 85% are reported, with complete relief of pain achieved in one-half of patients. Pain relief usually occurs rapidly, with more than 50% of responders showing benefit within 1–2 weeks. If improvement in pain has not occurred by 6 weeks or more after treatment, it is unlikely to be achieved [228]. Several trials have shown no difference in outcome between fractionated radiotherapy treatment and use of a single fraction. The accumulated evidence now strongly favors single fraction radiotherapy as the treatment of choice for most patients with painful bone metastases [229].

Targeted radiotherapy with therapeutic radioisotopes has theoretical advantages over external beam radiotherapy in that the radiation dose may be delivered more specifically to the tumor and normal tissues partially spared unnecessary irradiation. Follicular carcinoma of the thyroid commonly metastasizes to bone, and the treatment of bone metastases with 131-iodine is well established. In prostate and breast cancers with blastic metastases, useful palliation of bone pain has been demonstrated with ^{89}strontium and ^{153}samarium [230]. Most recently, the bone seeking, α-particle-emitting radiopharmaceutical ^{223}radium chloride has been developed. The high-energy α-particles provide a high dose of radiotherapy to cells within 1 μm of the bone surface with minimal systemic effects. In castrate-resistant prostate cancer (CRPC) patients, a randomized phase III trial evaluating the addition of radium chloride to best supportive care in advanced castrate-resistant prostate cancer (CRPC) showed a 3.6-month significant improvement in overall survival in addition to beneficial effects on quality of life and the incidence of skeletal morbidity [231].

Multidisciplinary Management Approach of Bone Metastases

In general, the treatment of bone metastases is aimed at palliating symptoms, with cure only rarely a realistic aim (e.g., in lymphoma). Treatments vary depending on the underlying disease. External beam radiotherapy, endocrine treatments, chemotherapy, targeted therapies, and radioisotopes are all important. In addition, orthopedic intervention may be necessary for the structural complications of bone destruction or nerve compression. Complementing these treatments is the role of bone-targeted agents.

Optimal management requires a multidisciplinary team that includes not only medical and radiation oncologists, orthopedic surgeons, (interventional) radiologists, and nuclear medicine physicians, but also palliative medicine specialists and a symptom control team with some expertise in bone complications from cancer. Treatment decisions depend on whether the bone disease is localized or widespread, the presence or absence of extraskeletal metastases, and the nature of the underlying malignancy. Radiotherapy is relevant throughout the clinical course of the disease. Resistance to systemic treatments can be expected to develop, necessitating periodic changes of therapy in an effort to regain control of the disease [148].

Clinical Implications

The choice of the bone-targeting agent to be administered remains open. The recent guidelines from the American Society of Clinical Oncology (ASCO) [135] state that oral bisphosphonates, IV bisphosphonates, and subcutaneous denosumab are each an efficacious option. The choice of which BMA to offer should be based on several important considerations, including patient preference, potential adverse effects, quality-of-life considerations, adherence, safety for that population, cost, and availability. However, while the greater efficacy of zoledronic acid compared with pamidronate in breast cancer could only be shown by post hoc multiple-event analyses [193], this is not the case for the comparisons between zoledronic acid and denosumab, in which the greater efficacy of the latter was demonstrated in various classical prespecified end points.

There is a lack of consensus regarding the optimal duration of treatment. It is now recommended to start bisphosphonates or denosumab as soon as bone metastases are definitively diagnosed in order to delay the first SRE and reduce subsequent complications from metastatic bone disease. ASCO guidelines recommend that, once initiated, i.v. bisphosphonates should be continued until there is a substantial decline in the patient's general performance status [232]; however, criteria are lacking to determine whether and for how long an individual patient benefits from bone-targeted therapy. Stopping zoledronic acid therapy after several years, at least temporarily, or reducing the frequency of the infusions (e.g., an infusion every 3 months) are often considered in patients whose bone disease is not "aggressive" and is well controlled by the antineoplastic treatment. However, ongoing treatment is recommended for patients with progression of underlying bone metastases, a recent SRE, and/or elevated bone resorption markers.

There are no prospective data on the validity of intermittent treatments, and data on reduction in the frequency of zoledronic acid infusions are limited. The ZOOM trial randomly assigned 425 patients, after completion of 12–15 months of monthly treatment with zoledronic acid, in a 1:1 ratio to either continue treatment every 4 weeks or extend to 12-week treatment intervals for at least 1 year [73]. The skeletal morbidity rate was 0.26 (95% CI 0.15–0.37) in the 12-week group versus 0.22 (95% CI 0.14–0.29) in the 4-week group, suggesting that the 12-week schedule was similar in efficacy to the 4-week schedule, at least during the first year after monthly treatment. However, noninferiority could not be established within this relatively small study. Furthermore, higher bone turnover levels were seen with the 12-weekly schedule [233]. In the BISMARK trial, a bone marker-directed schedule of zoledronic acid was compared with standard 3- to 4-weekly treatment in 289 patients. Multivariate analysis for all SREs showed an HR for marker-directed versus standard treatment of 1.41 (90% CI 0.98–2.02; P = 0.12) and noninferiority could not be established. NTX levels were significantly higher at all time points with the marker-directed schedule [234].

The pharmacokinetics of denosumab argues against intermittent treatments. Unlike bisphosphonates, denosumab is not stored in bone and interrupting its administration is probably not without risks, at least if the bone disease is not well controlled by the antineoplastic treatment. Based on current knowledge of its pharmacodynamics and systemic distribution, denosumab for metastatic bone disease appears to require continuous monthly therapy [235].

Age Considerations: Older Adults

Although antiresorptive therapies are especially important for elderly patients with cancer, they are typically underutilized in this population [236]. Older age is associated with increased risk for invasive malignancies, such as breast and prostate cancer, with a higher risk of bone metastasis. Underuse of antiresorptive therapies may be more detrimental in elderly patients compared with younger patients because of multiple fracture risk factors, including physiological decreases in BMD and increases in vertebral fracture rate with increasing age [237].

Specific considerations should be made for elderly patients who may have renal impairment from hypertension or diabetes and are likely to be taking more concomitant medications due to comorbid conditions. Careful monitoring of such comorbidities is essential to ensure the safety and comfort of elderly patients, especially during chemotherapy [238]. In addition to preventing SREs in the oncology setting, antiresorptive therapies are indicated for fracture risk reduction in elderly patients with osteoporosis [239]. Although oral bisphosphonates such as risedronate and alendronate have demonstrated efficacy in the postmenopausal osteoporosis setting, their dosing schedule and strict dosing regimen can lead to poor patient compliance [240]. Alternatively, i.v. bisphosphonates can be considered; a single annual infusion of zoledronic acid has proven effective for the treatment of postmenopausal osteoporosis [241]. Thus far, no dose adjustments based on age have been suggested for denosumab, and this would be necessary only if safety issues (e.g., severe hypocalcemia) developed.

Safety Considerations

Both denosumab and bisphosphonates are generally well-tolerated treatments. However, zoledronic acid is associated with more episodes of acute-phase response and renal dysfunction than denosumab, while hypocalcemia is more frequent and more likely to be symptomatic with denosumab [242]. It is important that physicians strongly advise patients to take calcium and vitamin D supplements and regularly monitor serum calcium levels, especially in denosumab-treated patients.

The most important adverse event associated with prolonged administration of potent inhibitors of bone resorption is ONJ. The definition, diagnosis, and follow-up of ONJ have been reviewed in a separate chapter in this book (for further readings: this topic has been reviewed and a report was published by the American Society for Bone and Mineral Research task force and various experts [243, 244]). ONJ is more common when i.v. bisphosphonates or denosumab is administered more frequently and/or at higher doses, for example, on a monthly basis for control of metastases, and is much less frequent with less intensive use of bisphosphonates or denosumab for preservation of bone mass, for example, oral bisphosphonates or use of 6-monthly basis parenteral treatment [244].

In the prespecified, integrated analysis of the three phase III denosumab trials, the incidence of ONJ did not differ significantly between the denosumab and zoledronic acid-treated groups [245]. Of 5372 patients, 89 (1.6%) were determined to have ONJ; 37 of these (1.3%) had received zoledronic acid and 52 (1.8%) had received denosumab ($P = 0.13$). However, the risk of ONJ increases with time and reaches 5% when denosumab is continued beyond 3 years. The clinical characteristics of ONJ cases were similar between treatment groups. ONJ management was mostly conservative, and healing occurred in more than one-third of patients. Evidence is insufficient to conclude that discontinuing zoledronic acid or denosumab therapy will facilitate the resolution of ONJ. Most of the patients with confirmed ONJ had a history of tooth extraction (62%), poor oral hygiene, and/or use of a dental appliance [245]. Before zoledronic acid or denosumab therapy is initiated, patients should undergo an oral examination and appropriate preventive dentistry, and be advised on maintaining good oral hygiene. Patients should avoid invasive dental procedures (extractions and implants) during therapy if possible.

The side effects of bisphosphonates in older adults as well as myeloma patients are similar, although particular attention should be paid to the potential renal toxicity of bisphosphonates and renal monitoring. The product label advocates stepwise dose reductions when baseline creatinine clearance is 30–60 ml/min, and zoledronic acid is not recommended in patients with severe renal deterioration or those taking nephrotoxic medications. The frequency of ONJ in MM patients may be higher than in those with solid tumors [148].

Algorithm for Identifying and Managing Cancer Treatment-Induced Bone Loss

Several guidelines recommend that women with breast cancer receiving an aromatase inhibitor (AI) or ovarian suppression [246, 247] and men with prostate cancer undergoing ADT [248] should have their bone health monitored for fracture risk (Fig. 29.3). BMD measurement should not be the sole criterion for determining fracture risk but an overall fracture risk assessment used that combines risk factors provides the most accurate evaluation [88]. The World Health Organization Fracture Risk Assessment tool (FRAX) algorithm is valid for postmenopausal women and calculates the 10-year fracture risk with or without BMD measurement and includes several fracture-related risk factors, although anticancer treatments are not included as a specific risk factor [249].

To identify and manage secondary causes of osteoporosis, a comprehensive laboratory assessment is required and should include serum levels of calcium, phosphate, 25-hydroxyvitamin D, parathyroid hormone, hemoglobin, C-reactive protein, alkaline phosphatase, thyroid-stimulating

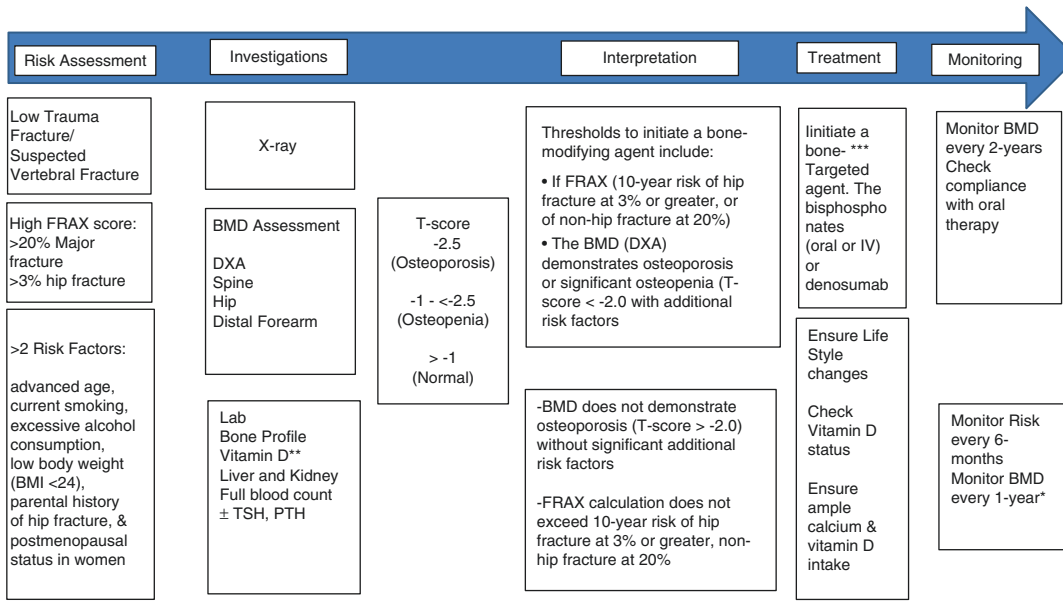


Fig. 29.3 Algorithm for maintaining bone health in individuals with patients with nonmetastatic cancers. Clinicians should be aware that patients with nonmetastatic cancer may have baseline risks for osteoporosis as well as the added risks of treatment-related bone loss due to hypogonadism from endocrine therapy (i.e., oophorectomy, GnRH agonists, chemotherapy-induced ovarian failure, aromatase inhibitors, antiandrogens), chemotherapy, or other cancer therapy-associated medications (e.g., glucocorticoids/chemotherapy). *If patients experience an annual decrease in BMD of ≥10% (or ≥4–5% in patients who were osteopenic at baseline) using the same DXA machine, they should be considered for bone-targeted therapy. Use lowest T-score from spine and hip. **Secondary causes of bone loss such as vitamin D deficiency should be evaluated and managed. ***Although osteonecrosis of the jaw is a very rare event with bone-targeted therapy, regular dental care and attention to oral health are advisable

hormone, creatinine clearance, and protein electrophoresis (serum and/or urine). The position statement by Hadji et al. [210] recommended a BMD measurement upon starting AI and, if the T-score was greater than −2, then lifestyle measures were to be implemented. BMD is then to be repeated after 1–2 years as accelerated bone loss is an indication for starting antiresorptive treatments. If the BMD T-score is less than −2 or if the patient had major risk factors, such as prior fracture, then antiresorptive treatments should be administered.

In premenopausal women, treatments may induce premature menopause or be specifically designed to suppress ovarian function and reduce circulating estrogen levels. In addition to bone loss associated with low estrogen levels, cytotoxic chemotherapy may also have a direct negative effect on bone metabolism. As a result, cancer treatment-induced bone loss poses a significant threat to bone health in premenopausal women with breast cancer. Current fracture risk assessment tools are based on data from healthy postmenopausal women and do not adequately address the risks associated with treatments in younger premenopausal women. Guidance from expert groups for premenopausal women with breast cancer has been published and recommends that all premenopausal women be informed about the potential risk of bone loss before beginning anticancer therapy with use of antiresorptives if the BMD T-score is <−2 [247, 250].

All patients receiving treatments that are known to adversely affect bone health should be advised to consume a calcium-enriched diet, exercise moderately (resistance and weight-bearing exercise) [251], and take 1000–2000 IU vitamin D every day [252].

The data from randomized clinical trials in >5000 patients show that bisphosphonates (both i.v. and oral) and denosumab administered at doses and schedules that approximate to those used for the treatment of postmenopausal osteoporosis can prevent bone loss in women with breast cancer [253]. Although these trials were not designed for a fracture-prevention end point, data from the osteoporosis setting have demonstrated a correlation between BMD improvements and fracture prevention. Therefore, data from the larger studies may be considered as evidence for preserving skeletal health during therapy.

In conclusion, early identification and treatment of CTIBL are essential to prevent fractures. Patients should be screened for risk factors and assessed for bone mineral density as well as fracture risk. All patients should be advised to optimize calcium and vitamin D intake, participate in a regular exercise program, and modify lifestyle behaviors known to cause bone loss. Patients with CTIBL should be treated with an oral/intravenous bisphosphonate, or denosumab. Treatment should be tailored to the patient's disease status as well as associated comorbidities.

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Bone Health in Chronic Kidney Disease

30

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Introduction

Osteoporosis is the most prevalent condition leading to low-trauma fractures in humans worldwide. Many metabolic disturbances, including renal bone disorders, lead to osteoporosis and the pathologic fractures associated with osteoporosis and non-osteoporotic fragility fractures. Osteoporosis can be part of the impaired bone quality (altered architecture, remodeling, mass, and volume) seen in chronic kidney disease-mineral bone disease (CKD-MBD) patients; however, despite this overlap, osteoporosis and CKD-MBD progress via distinct pathways, each resulting in impaired bone strength and higher risk of low-trauma fracture.

The prevalence of osteoporosis varies according to chronic kidney disease (CKD) stage. Early CKD patients, from stages 1 to 3, do not exhibit altered bone strength or pathological fractures according to any prospective or observational data, even with the presence of mildly elevated PTH level and intermittent hyperphosphatemia. Thus, any fracture in these early CKD stages is mostly associated with osteoporosis, rather than CKD-MBD. Derangements in phosphorus, PTH, or bone turnover markers or bone histomorphometry associated with CKD-MBD can be seen as early at stage 3 CKD. Most patients with stage 4 and 5 CKD exhibit alternations in bone quality due to metabolic bone disorders and/or decreases in BMD [1, 2]; at the time of initiation of dialysis, up to 50% of patients have had a fracture [3, 4]. Furthermore, CKD patients are more commonly associated with poor nutrition, inactivity, myopathy, and peripheral neuropathy, which altogether play a role in muscle weakness and falls [5]. A study conducted by Huang et al. revealed that advanced age, low body weight, low serum albumin level, and high ALP and iPTH levels were

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associated with low bone mass in hemodialysis patients [6].

CKD is associated with higher morbidity and mortality fractures. The third National Health and Nutrition Examination Survey of 6270 men and women showed a twofold increased risk of hip fracture in those with an estimated glomerular filtration rate (eGFR) < 60 mL/min, as compared to those with an eGFR ≥60 mL/min [7]. The Study of Osteoporotic Fractures surveyed 9704 women of 65 years and older and revealed a 1.5-fold increased hip fracture risk among those with an eGFR between 45 and 50 mL/min and a twofold increase among women with an eGFR <45 mL/min, when compared to women with an eGFR ≥60 mL/min [8]. Another cross-sectional study conducted on 5481 elderly men and women also revealed that those with an eGFR <65 mL/min had an approximate 1.5-fold increased risk of hip, spine, and wrist fractures, compared to those with eGFR >65 mL/min [9]. The incidence of fractures increases with advanced CKD stage and is highest in stage 5 CKD patients on dialysis. A large retrospective study based on data from the United States Renal Data System (USRDS) showed an increased relative risk of hip fracture in both men and women with stage 5 CKD on dialysis, compared to the general population [10]. After suffering a hip fracture, these stage 5 CKD patients on dialysis also had an increased 1-year mortality rate of 64%, as compared to the 15–20% 1-year mortality rate in the general population; this patient group also tended to experience hip fracture at a younger age compared with the general population (16 and 13 years earlier among men and women, respectively) [11]. Knowing which patients are at a higher risk for fractures and falls among CKD patients may enable the establishment of protocols to decrease the economic costs, morbidity, and mortality associated with fractures in this patient group. In CKD patients with severe pathological fractures, assessment of bone markers and, in some cases, bone biopsy may be needed to diagnose CKD-MBD with osteoporosis, which may influence the prescribed pharmacological therapies.

Mechanisms Underlying the Development of Osteoporosis

Dysregulation of RANK/RANKL/OPG System (Fig. 30.1)

Bone tissue is composed of osteocytes, osteoblasts, and osteoclasts, which interact with each other. The quality of bone and mass of bone tissue are determined by bone remodeling [13]. Bone remodeling is characterized by coordination between anabolic and catabolic phases. Regulators such as parathyroid hormone (PTH) and calcitriol and hormones such as growth hormone, glucocorticoids, thyroid hormones, estrogen, insulin-like growth factors, prostaglandins, tumor growth factor-βa, bone morphogenetic proteins (BMPs), and cytokines affect the balance between the anabolic and catabolic phases of bone remodeling [14]. Molecular-level bone remodeling is regulated by the receptor activator of the NF-κB (RANK)/RANKL/osteoprotegerin (OPG) system. RANK present on the surface of osteoclasts induces osteoclast activation and proliferation upon binding to RANKL that is produced by osteoblasts [15, 16] and promotes bone resorption. OPG, which is secreted by osteoblasts, functions as a decoy receptor for RANKL, prevents RANKL from binding to RANK [15], and prevents excessive bone resorption. At the initial phase of bone resorption, osteoclast activation inhibits osteoblast formation by inducing a Sema4D/plexin/B1 signal, which transiently

1. Dysregulation of RANK/RANKL/OPG system
- Excessive osteoclast activity (OCs≠; more bonr resorption)
- Eg.: High PTH, Estrogen Deprivation, RA, SLE

2. Excessive Wnt signaling inhibitors
- Insufficient osteoblast function (OBs ; less bone formation)
- Eg.: CKD, Menopause, Vasxular calcification

3. Inflammatory cytokines related osteolysis
- Excessive Osteoclast activity (OCs≠; more bone resorption)
- Eg.: Intestinal microbiota, Vit-D deficiency

Fig. 30.1 Mechanism related to major causes of osteoporosis [12]

inhibits bone formation during bone resorption [17]. At the end of bone resorption, after the removal of apoptotic osteoclasts by macrophages, osteoblast precursor cells are recruited from the bone marrow to the bone matrix where they undergo differentiation into osteoblasts and osteocytes [18]. Thus, the RANKL/OPG system tightly couples bone resorption and formation to maintain skeletal integrity. The increased in RANK/RANKL and decreased in OPG levels will accentuate the osteoclast related bone resorption.

Excessive Wnt/β-Catenin Signaling Inhibitors

The Wnt signaling pathway in bone cells affects the osteoblast differentiation and bone formation [1]. Rare diseases that affect bone formation, such as van Buchem disease or osteoporosis-pseudoglioma syndrome, highlight the importance of the Wnt pathway in bone formation [1]. The Wnt signaling pathway has three major branches, namely, the canonical Wnt pathway [10], noncanonical Wnt–planar cell polarity pathway, and Wnt–calcium pathway. In the canonical Wnt pathway, binding of Wnt ligands to a dual receptor complex comprising frizzled (FZD) and LRP5 or LRP6 activates cytoplasmic β-catenin and decreases gene transcription [2]. Activation of the Wnt/β-catenin pathway represses the differentiation of mesenchymal stem cells into adipocytes and chondrocytes and promotes their differentiation into osteoblasts and osteocytes [3, 4]. Activation of the Wnt/β-catenin pathway in bone cells induces osteoblastogenesis and inhibits osteoclastogenesis. Wnt antagonists such as sclerostin and Dickkopf-related protein 1 (DKK1) offset osteoblastogenesis and inhibit bone formation [5, 6]. Other hormonal change such as increase in serum PTH enhanced the bone formation by inhibiting Wnt inhibitors [7] or by phosphorylating β-catenin [8]. Immobile stat decrese bone formation by increasing sclerostin, a Wnt signaling antagonist on osteoblasts produced by osteocytes [9]. Increased renal production and circulating levels of DKK1 in CKD have been associated with decreased osteoblastogenesis and increased osteoclastogenesis [10]. In addition, immunohistochemical staining of sclerostin indicating expression of the protein by osteocytes, vascular atherosclerotic lesions and calciphylaxis skin in CKD [11]. Thus, in CKD patients, excessive of Wnt/β-catenin signaling inhibitors (Dickkopf-related protein 1, DKK1 and Sclerostin, SOST) will attenuate the osteoblast viability and increase osteoclast activity resulted in an obvious bone loss.

Inflammatory Cytokine-Related Osteolysis

Inflammatory cytokines affect bone turnover. A study on patients with inflammatory arthritis indicated that excessive cytokine production induced osteoclast activation and bone resorption [19]. Cytokines released by type 1 T helper cells, such as tumor necrosis factor (TNF), interleukin-1 (IL-1), IL-17, and IL-23, activate osteoclastogenesis [20, 21]. IL-6 and soluble IL-6 receptor are suggested to act synergestically on osteoblasts to activate the differentiation of osteoclast precursor cells into osteoclasts [22]. TNF-α activates osteoclastogenesis beyond the RANKL/OPG signal [23]. These findings indicate that a cytokine or cytokine storm activates osteoclastogenesis, which may contribute to bone loss in the various clinical inflammatory scenarios.

Specific disorders that disturb bone homeostasis, such as overactivation of osteoclastogenesis or inhibition of osteoblastogenesis, decrease bone mass and promote osteoporosis.

Disturbed Bone Remodeling: High or Low Bone Turnover-Related Osteoporosis

Normal bone turnover is defined as an appropriate bone surface/volume, and the rate of bone remodeling is affected by the balance between bone formation and resorption [24, 25]. Higher bone turnover indicates higher bone resorption because of overactivation of osteoclastogenesis [26]. Increased osteoid formation and endplate

fibrosis are histopathological hallmarks of high bone turnover disorder. In patients with high bone turnover disorder, several metabolic diseases such as secondary hyperparathyroidism, systemic lupus erythematous, or other autoimmune disease; pregnancy; and postmenopausal disorder increase the activity of osteoclasts and accelerate bone resorption. By contrast, inhibited bone formation or accelerated osteoblast apoptosis decreases osteoclastogenesis and bone turnover. Nonanastamosing trabeculae and low osteoid layer are histopathological hallmarks of low bone turnover disorder [25]. In patients with low bone turnover disorder such as adynamic bone disorder, osteomalacia [27, 28], liver cirrhosis [29], and glucocorticoid-induced osteoporosis (GIO), osteoblast-induced bone formation is attenuated. Both high and low bone turnover disorders induce osteoporosis.

High Bone Turnover Disorder

High bone turnover disorder is induced by bone resorption due to osteoclast activation that exceeds osteoblast formation. Factors that stimulate osteoclast activity or alleviate calcification inhibitors induce bone resorption and decrease bone mass. Several diseases—such as secondary hyperparathyroidism, postmenopausal disorder, and systemic inflammation—accelerate bone turnover.

Secondary Hyperparathyroidism

Secondary hyperparathyroidism is common in patients with CKD, which is caused by phosphate retention induced by decreased renal excretion [30]. Progressive GFR lowering and nephron loss, a decrease in renal phosphate excretion, fibroblast growth factor 23 (FGF23) activation, and vitamin D deficiency increase parathyroid gland activation [31]. High PTH levels affect *RANKL* and *OPG* mRNA expression in osteoblasts and sequentially activate osteoclast-related bone resorption by activating the RANKL pathway [32]. PTH also regulates the hematopoietic niche by acting on osteoblasts by interacting with the Wnt pathway [33]. During the early stage of CKD, bone turnover is suppressed because of an increase in the expression of sclerostin and PTH receptor-1 in bone. Excessive osteoblastic activity compensates for bone resorption, resulting in osteosclerosis and excessive fibrosis in the bone marrow cavity. Excessive osteoid accumulation at the endplate and fibrosis are histopathological hallmarks of high bone turnover bone disorder [34]. The persistent elevated serum PTH dysregulated bone remodeling by activated osteoclastic resorption [35], which induced bone loss and extraosseous calcium deposition.

Chronic Inflammation

Chronic inflammation, such as that observed in patients with systemic lupus erythematous and rheumatoid arthritis, activates osteoclastic resorption. Chronic inflammation is characterized by disturbance of cytokine levels; intestinal absorption of calcium, phosphate, and nutrients; fatigue; and vitamin D deficiency, which increase bone resorption and degree of osteoporosis [36]. Chronic inflammation increases resting energy expenditure (400–500 kJ/day) [37]. The increase of energy expenditure induced anorexia-relate hypovitaminosis, and the decrease in intestinal calcium uptake made the bone as the only source of plasma calcium [38]. Besides, glutathione depletion by chronic inflammation increased the oxidative stress in the intestine, which altered the transcellular and paracellular calcium absorption [39]. The increase of TNF, RANKL, and IFN-γ activates the calcium mobilization by downregulating the osteoblastic osteocalcin and activating the RANKL signaling [40–42]. In addition to cytokine secretion, inflammasome accumulation is associated with osteoclast activation. Persistence of inflammation increases intracellular calcium concentration to induce inflammasome assembly and activates the osteoclast [43–45]. In order to control the inflammation, high-dose glucocorticoid would be applied. However, excess glucocorticoids enhance bone resorption by reducing OPG expression, increasing RANKL expression and reactive oxygen species, and prolonging the life span of osteoclasts [46]. High-dose glucocorticoid increased the skeletal muscle wasting, which related to sarcopenia and immobility. Both sarcopenia and immobility inhibit the osteoblast survival and activate the osteoclast [47]. Therefore, involve-

ment of inflammation in osteoclast activation should be the main focus for treating osteoporosis.

Low Bone Turnover Disorders

Low bone turnover disorders include adynamic bone disease, osteomalacia, GIO, and liver cirrhosis. Low bone turnover disorder is characterized by decreased osteoid and osteoblast volume and increased mineralization lag time. Such pathologic hallmark is caused by the absence of osteoblast activity and osteoblast apoptosis [48, 49]. Medications such as bisphosphonates, excessive inhibition of PTH in patients with advanced CKD, and prolonged use of glucocorticoid worsen osteoblast apoptosis and suppress the osteoclast-mediated bone remodeling [50, 51].

Adynamic Bone Disease and Osteomalacia in CKD

Age, insulin resistance or diabetes mellitus, uremic toxin accumulation, and treatment-related factors (oral calcium-containing phosphate binder or excessive vitamin D analog usage) induce adynamic bone disease in patients with CKD [52]. In the early stage of CKD, accumulation of uremic toxins such as indoxyl sulfate suppresses the formation of mineralized bone nodules from osteoblasts [53] and simultaneously inhibits osteoclast-related bone resorption. Decelerated bone remodeling lessens the calcium uptake from osteoblast and increase the extraosseous calcium deposition in soft tissues. In order to prevent further extraosseous calcification, osteocyte secrets sclerostin [11]. However, increased sclerostin secretion decreases osteoblast activity by inhibiting the Wnt signaling pathway during osteoblast bone formation [54]. Sclerostin accumulation exacerbates PTH resistance. Persistence of PTH resistance increases the pentosidine-to-matrix ratio and decreases the crystallinity-deteriorated viscoelastic property of extracted long bones and bone strength [55]. In patients with advanced CKD receiving excessive active vitamin D, oversuppression of PTH decreases osteoblast activity. Excessive use of aluminum-containing phosphate binders also decreases osteoblast activity because of the intestinal absorption of aluminum [56]. In summary, adynamic bone disease in CKD is multifactorial, and the bone formation is suppressed profoundly.

Glucocorticoid-Induced Osteoporosis (GIO) (Fig. 30.2)

High bone turnover occurs in the initial phase of GIO because of the steroid direct effect. However,

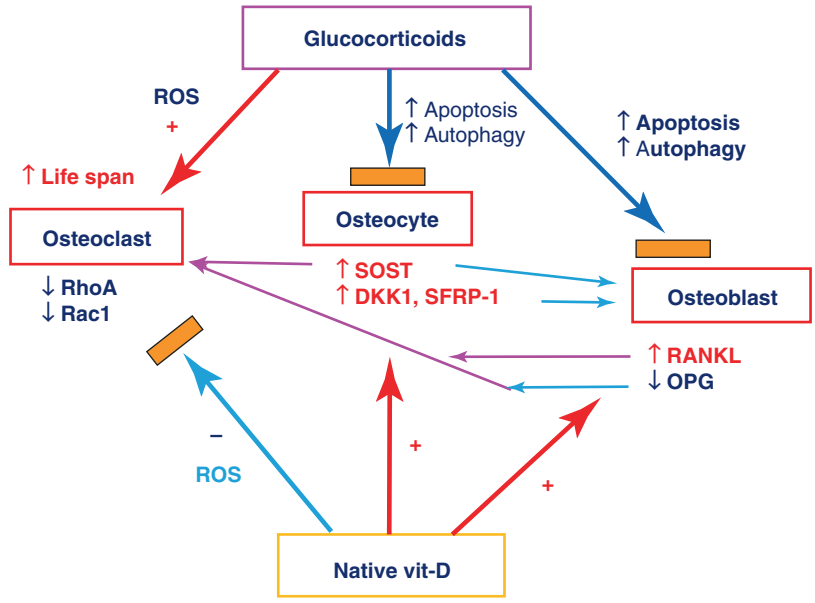

Fig. 30.2 The mechanism of low turnover bone disorder: Glucocorticoid-induced osteoporosis as example [12]

they also suppress the bone-degrading capacity of osteoclasts by disturbing the organization of the cytoskeleton and suppresses the osteoclast-mediated bone formation [46, 57]. Prolonged use of glucocorticoids decreases bone resorption [58], which is mainly characterized by low bone turnover disorder [59]. Glucocorticoids inhibit bone formation through several mechanisms: (1) by inhibiting mesenchymal stem cell differentiation into osteoblasts through PPARγ2 [60]; (2) by inhibiting Wnt/β-catenin signaling by enhancing Dickkopf expression and by maintaining GSK 3-β expression [61]; (3) by inhibiting type I collagen synthesis from osteoblasts [62]; (4) by arresting M-CSF activation of RhoA and Rac1 of osteoclast cytoskeleton[57]; and (5) by inducing osteoblast apoptosis by activating caspase 3 [63]. Increase in the duration of glucocorticoid exposure decreases bone turnover rate by inducing osteoblast apoptosis [64] resulting in decrease bone formation. Moreover, intermittent PTH secretion improves bone remodeling and bone formation in patients with GIO-related low bone turnover disorder [65].

Bone Quality Loss

Bone is composed of inorganic minerals (mainly calcium and phosphate hydroxyl apatite crystals) and type I collagen [66]. Deterioration of the structural arrangement and orientation of bone minerals because of a metabolic disorder decreases bone quality, which increases bone fragility without inducing a severe loss of bone quantity [67]. Animals with high and low bone turnover disorders have lower material-level bone toughness compared with normal animals. This indicates that skeletal pentosidine-to-matrix ratio is increased in advanced CKD and that this increase is independent of the bone turnover rate and inversely associated with a decrease in kidney function. Although hydration changes occur in patients with both high and low bone turnover disorder, data suggest that nonenzymatic collagen cross-links may be a key factor in compromising the mechanical properties of patients with CKD. [68]. Results of a dynamic study on the mechanical properties of the femur assessed using a dynamic mechanical analyzer [69] showed that both low and high bone turnover disorders are associated with poor bone quality.

In summary, the characteristics of low bone turnover disorder are inhibited osteoblast formation, and restoration of osteoblast viability in addition to treatment for the underlying disorder is crucial.

Bone Mineral Density in Patient with CKD

Relationship Between BMD and Renal Osteodystrophy

Renal osteodystrophy (ROD) includes a variety of bone lesions that differ in both mechanisms of development and therapeutic approaches. The TMV (turnover, mineralization, and volume) system is a recently developed, simple, and clinically comprehensive system to classify CKD-MBD [19]. The TMV system provides information on the range of pathologic abnormalities that can occur in CKD patients. Bone turnover and bone volume can be classified as high, normal, or low. Bone mineralization is classified as normal or abnormal. The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines distinguish the following six types of bone disorders on the basis of TMV system: hyperparathyroid bone disease (high turnover, normal mineralization, and any bone volume), mixed bone disease (high turnover with mineralization defect and normal bone volume), osteomalacia (low-turnover bone with abnormal mineralization and low-to-medium bone volume), adynamic bone disease (low-turnover bone with normal mineralization and low or normal bone volume), amyloid bone disease, and aluminum bone disease [20–22].

The types of bone histology depend on the degree and duration of renal impairment, patient age and comorbidities, mode and years of dialysis, associated medications for hyperparathyroidism, serum calcium and phosphate levels, etc. In addition to ROD, these patients are also more

likely than the general population to have osteoporosis, which is also influenced by age, gender, menopausal status, drugs, nutrition, and exercise [23]. Thus, it is difficult to separate these disease entities clinically.

The most common high turnover abnormality in ROD is hyperparathyroid bone disorder (HPBD; osteitis fibrosa cystica: OFC) with excessive osteoclastic bone resorption and bone marrow fibrosis [24]. HPBD may present with several types of radiographic findings. Due to increased osteoclastic activity, bone resorption may occur in many skeletal sites, including subperiosteal, intracortical, endosteal, trabecular, subchondral, and subligamentous, etc. [25]. Subperiosteal bone resorption most commonly occurs in the phalanges, humerus, and distal epiphyseal region of clavicles [26]. Subchondral resorption in sacroiliac joints may lead to "pseudo-widening" of the joint. Losses of lamina dura of the teeth are also common in SHPT patients [25]. Excessive osteoblastic activity may follow as compensation for the bone resorption, with resultant osteosclerosis [25], which is commonly seen in most sites of axial skeleton, including the pelvis, ribs, spine, and skull. Excessive osteoid accumulation below the endplates of vertebral bodies occurs, and with normal density in the middle parts, these vertebral bodies appear under radiological films as "rugger jersey spine sign" [27]. Excessive terminal phalange resorption may result in a deformity known as acroosteolysis [25]. Brown tumors, known to be caused by rapid osteoclastic activity and peritrabecular fibrosis, may affect pelvis, ribs, and clavicles and sometimes may result in pathological fractures. Brown tumors of vertebral column may also present with spinal cord compression [28, 29]. Metastatic calcification, a result of increased calcium/phosphate solubility product in extracellular fluid [30], is responsible for the vascular calcification in SHPT patients. Metastatic calcifications mostly affect the hips and shoulders, although other joints may also be affected [31, 32].

Low-turnover bone diseases include osteomalacia, aluminum-induced bone disease, and adynamic bone disease (ABD). Osteomalacia alone is an uncommon presentation in HD patients [33]. This mineralization defect is related to reduced 1,25-dihydroxyvitamin D (1,25D) and chronic metabolic acidosis [34]. Aluminum ingestion causes a mineralization defect, markedly reduces both osteoclast resorption and osteoblast surface, and is associated with the low-bone turnover disease osteomalacia. Chronic low-dose aluminum exposure with high intake of vitamin D in dialysis patients reduces parathyroid hormone synthesis and secretion, even in the presence of hyperphosphatemia; these patients may present with adynamic bone disease rather than osteomalacia [35]. The prevalence of aluminum-related bone disorders has been reduced over recent decades due to emergence of nonaluminum-containing dialysate solutions and phosphate binders [36].

CKD Progression and BMD Changes

Low BMD in CKD Not Yet Receiving Dialysis

With progressive decline in renal function, CKD patients suffer from hyperparathyroidism secondary to a decrease in serum calcium, a reduction in 1,25D (calcitriol) synthesis, and/or impaired phosphate excretion. The cloning of klotho and fibroblast growth factor 23 (FGF-23) has enabled the progressive unraveling of their roles in calcium/phosphate metabolism over the past decade. Progressive P accumulation leads to increases in serum PTH and FGF-23, both of which play important roles in consequences like renal osteodystrophy, hyperparathyroidism, calcemic uremic arteriopathy, and uremic cardiomyopathy.

Normal serum phosphorus and calcium levels are maintained by the integrative actions of PTH and 1,25 D. The phosphatonin FGF-23 directly controls renal phosphorus excretion and, along with the aforementioned hormones, plays a role in regulating systemic mineral metabolism. FGF-23, a 25-amino acid protein, prevents renal phosphate reclamation by decreasing the type 2a sodium-dependent phosphate cotransporters (NaPi-2a) expression in PCT. FGF-23 also suppresses the

expression of 1α-hydroxylase, the enzyme that converts 25D to calcitriol, resulting in decreased renal production of activated vitamin D [37–39]. FGF 23 and FGF receptor interaction is facilitated by the coreceptor Klotho [40]. Serum FGF-23 levels are found to be increased as early as CKD stage 3, which helps to keep serum P within the normal laboratory range. FGF-23 may also be responsible for early reduction in calcitriol levels during early CKD [41–43]. These findings indicate that clinical strategies to decrease FGF-23 may be therapeutically useful for normalizing calcitriol levels in these patients. Hasegawa et al. [44] found significantly increased FGF23 levels in CKD rats as compared with the normal rats, as early as 10 days after kidney destruction, preceding the rises of phosphate and creatinine. The factors that lead to this early FGF23 elevation are unknown.

Further loss of renal tissue leads to reduced Klotho expression, resulting in FGF resistance and correspondingly increased serum FGF level. This frequently occurs in stage 4 and 5 CKD, when hyperphosphatemia persists despite marked elevations of FGF-23 and PTH [45]. Hyperphosphatemia eventually becomes clinically significant due to many factors, including diminished nephron mass [46], FGF-23 resistance, and reduced calcitriol synthesis. The accumulated P combined with Ca results in calcium phosphate crystal deposition in soft tissue. Hypocalcemia, hyperphosphatemia, and low calcitriol levels all stimulate PTH formation and secretion, known as secondary hyperparathyroidism [47]. Excessive skeletal remodeling occurs in secondary hyperparathyroidism during progressive CKD, resulting in excessive bone resorption, defective bone formation, and abnormal mineralization. Finally, defective bone mineralization with heterotopic mineralization or metastatic calcification occurs in blood vessels and heart tissue, also known as calcific uremic arteriolopathy (CUA) [48, 49].

Patients with CKD have reduced BMD due to multifactorial causes, including acid-base disturbances, and impaired vitamin D and PTH homeostasis. Chronic metabolic acidosis in CKD patients may increase bone resorption due to bone buffering and slow dissolution of bone mineral [50]. Bone biopsies of mild to moderate CKD patients reveal PTH excess and increased bone turnover [51]. Bone turnover markers have been found to correlate with PTH levels and GFR [52], and low calcitriol level is found to be an independent risk factor for hip fractures [8]. Although many studies reported a decrease BMD in CKD patients, the exact relationship between BMD and CKD was still unclear due to study limitations [53]. In the Third National Health and Nutrition Examination Survey (NHAHES-III) Study, subjects with worse renal function had significantly lower femoral BMD; however, this association was explained by confounding factors, like age, sex, ethnicity, etc. Renal function itself was not found to be independently associated with BMD after taking sex, age, and body weight into account [54].

Influence of Comorbidities

CKD is a complex comorbid condition with a multiplicity of clinical manifestations. It is closely linked with cardiovascular disease and associated with a very high mortality rate. In the United States, CKD consumes about one-third of Medicare expenditures. Comorbid conditions of CKD include hypertension, diabetes, dyslipidemia, cardiovascular disease, anemia, and bone and mineral disorders. Changes in mineral metabolism with alterations of hormonal regulation have recently been found in CKD, associated with various forms of bone diseases; this has become known as the kidney-bone axis. During the past decade, investigators have focused more on the bone-vascular axis and the relationship between mineral metabolism disorders and soft tissue and cardiovascular calcifications.

The complex pathophysiologic mechanisms of arterial calcification include disturbances of mineral metabolism and mineral-regulating proteins. Longitudinal population-based studies reveal an association between progressive vascular calcifications (VC) and bone demineralization. In dialysis patients, coronary artery calcification score was found to be inversely correlated with vertebral bone mass. In other words, increasing arterial stiffness coexists with pro-

gressive bone loss, which is responsible for most of the cardiovascular events in CKD patients. Vascular calcification is an active process involving various proteins that are similar to those involved in bone and mineral metabolism [55, 56]; this process represents a part of CKD-mineral and bone disorder [19].

Risk factors for premature VC in end-stage renal disease (ESRD) patients differ from the traditional atherogenic risk factors. Hyperparathyroidism and alterations in Ca-P mineral metabolism, especially hyperphosphatemia, modulate both renal osteodystrophy and vascular calcification [57, 58]. An association has been observed between extraosseous calcifications and hyperparathyroidism [59, 60] and reversal of extraosseous calcifications with reduction of bone turnover after parathyroidectomy [61–63]. In contrast, one study described an association between low bone turnover and vascular calcifications [64]. Therapeutic measures for SHPT—like PTX and excessive calcium or aluminum load, which lead to lower bone turnover and adynamic bone disease—may also influence the development of arterial calcification [64]. A recent study carried out by Asci et al. [65] on 207 CKD stage 5 regular HD patients revealed an association between bone turnover, bone volume, and coronary calcifications. After adjusting for traditional risk factors (e.g., age, gender, DM, smoking, serum lipid, history of CVD, and hs-CRP), they found that low bone turnover was negatively correlated with coronary artery calcification (CAC), high bone turnover was positively correlated with CAC, and no association was found between normal turnover and CAC [65]. Age is a known risk factor for cardiovascular calcification in both general populations [67] and HD patients, and an interaction between cancellous bone volume and age was also found to be associated with CAC [66]. Thus, in addition to the demonstrated nonmodifiable risk factors (age, sex, diabetes mellitus, and HD duration), bone turnover and bone volume should also be considered as nontraditional risk factors that may influence CAC.

Diabetic ESRD patients tend to present with adynamic bone disease with or without aluminum deposition [68, 69], whereas present with hyperparathyroid bone disease in less than 10% of cases [70]. Bone resorption markers like serum tartrate-resistant acid phosphatase (TRAP) and urinary hydroxyproline are increased, especially when associated nephropathy develops. Insulin plays a role in bone anabolism through the insulin-like growth factor 1 (IGF-1) pathway. Patients with type 1 diabetes mellitus (DM) with true insulin deficiency may exhibit more bone loss than type 2 DM patients, in whom serum insulin levels are increased due to tissue resistance. Although bone mass can remain high in type 2 DM patients, bone quality is impaired due to accumulation of advanced glycation end products (AGE) in collagen. Increased bone fragility may also result from low bone turnover, reduced unmineralized bone matrix, and increased collagen glycosylation [71, 72]. Thus, bone density in these patients may not predict increased bone fragility [73]. Furthermore, diabetic ESRD patients often have other risk factors for fractures, including longer diabetes duration, diabetic retinopathy, neuropathy, and insulin treatment [74–77]. The regular oral hypoglycemic medications may also play a role in bone loss in these patients.

Metabolic syndrome (MS) is also associated with low bone mineral density (BMD) in patients with chronic kidney disease. Studies have shown that in both MS group and non-MS groups, BMD was negatively correlated with age, hemodialysis period, and PTH [78, 79].

Influence of Treatments (Medications) on CKD-Related Osteodystrophy

Drug-induced osteoporosis is an important consideration in CKD patients. Unfractionated heparin (UFH) is the most common anticoagulant used in hemodialysis units, due to its relative ease of use, safety, and low cost; however, it is associated with many known side effects, such as heparin-induced thrombocytopenia, hypertriglyceridemia, and hyperkalemia. It is unclear whether intermittent heparin use is related to low bone mineral density, since most dialysis patients have other associated risk factors for osteoporosis, like diabetes mellitus, secondary hyperparathyroidism, old age, and physical inactivity.

Therefore, UFH is only replaced with other anticoagulants (e.g., direct thrombin inhibitors, citrate dialysate, and heparin-free dialysis) when other complications develop, such as heparin-induced thrombocytopenia. A study conducted by Grzegorzewska et al. [80] revealed that dialysis patients who receive regular LMWH, antiplatelet agents, or both, show lower bone mineral density in the femoral neck, but results of larger clinical trials are pending.

In diabetic CKD patients, skeletal effects of pharmacological treatments of type 2 diabetes also play a role in determining BMD. Biguanides like metformin increase the differentiation of bone marrow mesenchymal stem cells (MSC) into osteoblasts through the transactivation of Runt-related transcription factor 2 (RUNX2), resulting in increased bone formation. Glitazones, by simultaneously activating peroxisome proliferator-activating receptor γ (PPARγ) and inhibiting RUNX2, shift MSCs toward the adipocyte lineage, resulting in a reduced osteoblastic lineage [81].

Glucocorticoids are the drugs that most often cause osteoporotic fractures in both general and ESRD populations. Other medications have also been proven to be associated with bone loss, including calcineurin inhibitors, antiretroviral drugs, selective inhibitors of serotonin reuptake, anticonvulsants, loop diuretics, oral anticoagulants, and proton pump inhibitors. Cyclical hormone replacement therapy (HRT) may maintain BMD in postmenopausal women with secondary amenorrhea after dialysis [82]. Therapeutic measures like continuous hormone-replacement therapy (HRT), bisphosphonates, and selective estrogen receptor modulators (SERMS) may improve BMD in normal renal function status, but their roles in ESRD patients are still unclear.

Influence of Age and Gender

As the average age of CKD and ESRD patients increases, age-associated osteoporosis is also increased in these patients, at a higher rate than in general population. Age is an independent factor associated with bone loss in CKD and ESRD patients. Protein malnutrition, inflammation, and glucose abnormalities are more frequent in older ESRD populations and are responsible for more BMD loss in this group compared with in younger patients. Postmenopausal osteoporosis is also a complication related to renal mineral and bone disorder. In a study including 112 postmenopausal hemodialysis patients, serum estradiol levels were found to be higher in hemodialysis patients than in those without CKD, and endogenous estrogen was found to play a role in preventing bone loss in postmenopausal hemodialysis women [83]. Many studies have found a high prevalence of calcidiol deficiency and insufficiency in predialysis patients, regardless of geographic location. A significant inverse correlation between calcidiol and parathyroid levels has also been noted in both general and predialysis populations, but the underlying mechanism underlying calcidiol deficiency is unknown [84].

Decreased physical activity may be associated with loss of bone strength in dialysis populations, and a rehabilitation program may play an important role in preventing this problem. Not only high impact activities have been proven osteogenic [85], but low-impact activities, like moderate intensity walking may also increase lumbar BMD [86]. Since CKD and ESRD patients are prone to fatigue and generally have a lower exercise capacity, low-impact activities are more favored in this population. A recent study revealed that active ESRD patients with adynamic bone disease have greater mineralized bone volume than less active patients [87]. Human studies including hemodialysis patients show a correlation between muscle strength and BMD [88]. The mechanical load applied by the muscle on bone is directly responsible for bone formation and remodeling [89]; therefore, simple, low-impact, weight-bearing exercises, such as walking and resistance exercise (strength training), are encouraged as daily physical activities in CKD patients to improve BMD.

Dialysis Modalities on BMD

BMD in Hemodialysis Patients

Even before dialysis, CKD patients with lower GFR (with or without higher iPTH values)

present with lower BMD [90]. Prospective studies have revealed both gain and loss of BMD after the initiation of dialysis [91, 92], with increased dialysis associated with increased fracture risk. In HD patients, factors influencing low BMD include age, gender, lower body weight, and higher level of parathyroid hormone [93]. Compared with a general population, a dialysis patient population showed a 4.4-fold greater relative risk for hip fracture and a 2.4-fold higher mortality rate [11]. Risk factors like female gender, lower BMI, and white race influence hip joint fractures in the general population; however, in dialysis patients, lower serum iPTH values may indicate a greater risk of hip fractures [11]. Dialytic male patients seem to have higher risk of vertebral fractures, which is predicted by both BMD (a doubling prevalence for each 1-SD reduction in lumbar spine BMD) and by iPTH values [94]. Lower serum iPTH values are also associated with higher vertebral fracture prevalence; the serum iPTH values that predict the lowest fracture prevalence seem to be approximately one to three times the upper normal range [94].

Overall, osteoporosis is prevalent in hemodialysis patients. A cross-sectional study of hemodialysis patients using bone biopsy and histomorphometric analysis showed that hemodialytic osteoporosis patients have a low bone formation rate with normal bone eroded surface (BFR/BS), even with normal bone resorption. The results of this study are also alarming due to the fact that osteoporosis, a common disorder of aging, was determined to be prevalent in younger dialysis patients [95]. Cytokines that play roles in bone remodeling, like OPG, soluble receptor-activator of NF-κB ligand (sRANKL), and TNF-α, are also involved in the mechanisms of osteoporosis, in addition to many other traditional risk factors [95].

BMD in Peritoneal Dialysis Patients

The nature of bone disease differs in peritoneal dialysis (PD) patients and HD patients, since different factors influence calcium, phosphate, and PTH metabolism between the two modules. PD patients have better phosphorus clearance, higher removal of transferrin-bound aluminum, higher intake of phosphorus due to the recommended high protein diet, and higher bicarbonate loss than HD patients; they are also used to experiencing a constant glucose load and constant calcium load with regular or high calcium solutions [96]. PD patients are also more frequently associated with adynamic bone lesions (61% in PD patients vs. 36% in HD patients) [97, 98]. In PD patients, low BMD indicates poor outcome, since predictors of low BMD (age, poor nutrition status, metabolic acidosis, high phosphorus, anemia, etc.) are associated with worse prognosis in PD patients [99]. Low body weight seems to be the most important risk factor for osteoporosis in chronic PD patients [100]. Insufficient dialysis dose and older age also play an important role in osteoporosis of those patients. A recent cross-sectional study conducted by Jeong et al. evaluated the risk factors associated with BMD in chronic PD patients. Traditional markers of bone turnover (e.g., iPTH, 25D, osteocalcin, bone alkaline phosphatase, and serum C-telopeptide) were not associated with BMD in PD patients, whereas nutritional markers (e.g., prealbumin, nPNA, and BMI) predicted BMD in chronic PD patients [101].

Secondary Hyperparathyroidism and Renal Osteodystrophy

The Pathophysiology of Secondary Hyperparathyroidism (SHPT)

As the glomerular filtration rate decreases in CKD progression, phosphate begins to accumulate due to the decrease in the functional nephron number. In addition, 1,25D produced in the remaining kidney is decreased, and renal 1α-hydroxylase activity is further inhibited by FGF-23 and other uremic factors that lead to 1,25D deficiency. Both phosphate burden and 1,25D deficiency cause hypocalcemia and stimulate PTH secretion from PTG, called SHPT. The PTH synthesis, transcription, and parathyroid

cell proliferation are mainly regulated through serum calcium and 1,25D level. Both hypocalcemia and 1,25D deficiency among CKD patients result in PTH secretion and PTG hyperplasia [22] and consequently result in unbalanced bone remodeling, soft tissue/vascular calcification, and increases the risk of cardiovascular event and all-cause mortality [23–26]. Recently, evidence has emerged supporting the role of FGF-23 as the primary event in the pathogenesis of SHPT. Administration of the FGF-23 antibody can markedly increase 1α-hydroxylase expression in kidney, which means that it can restore 1,25D levels significantly [27, 28]. These findings suggested that the increase of FGF-23 may be the principal mechanism behind reduced 1,25D levels in early CKD.

As hypocalcemia, 1,25D and 25-hydroxyvitmain D (25D) deficiency worsen in CKD progression, a general increase in the total number of parathyroid cells with a normal lobular structure occurs called diffuse hyperplasia. After progressing into the end stage of renal disease or even dialysis-dependent status, SHPT becomes more severe and PTG becomes grossly enlarged and exhibits some nodular formation (nodular hyperplasia) (Fig. 30.3). In advanced SHPT, the multi-nodule may develop into a single large nodule [29]. Once nodular hyperplasia in SHPT is established, these glands might be refractory to medical treatment, and surgical parathyroidectomy is indicated [30]. Hyperphosphatemia is a main risk factor aggravating the severity of PTG hyperplasia, and dialysis vintage and serum PTH level are also in a relation with nodular hyperplasia [31].

Pathophysiologically, hyperplasia precedes the decrease in CaSR expression. The decrease in vitamin D receptor (VDR) is parallel to the increases in hyperplastic growth and contributes to decrease the induction of the CaSR by VDRA [32, 33]. Downregulation of CaSR may be attributed by parathyroid cell hyperplasia, but not uremia per se [33]. Inadequate CaSR and VDR density in PTG cause the poor response of extracellular calcium to suppress PTH and failure of calcitriol (1,25 D) in treating SHPT. In general, parathyroid hyperplasia presents in CKD stage 5 patients with PTH > 400 ng/mL [34]. A PTG weight over 500 mg predicted nodular hyperplasia, and this is equivalent to an estimated value of 330 mm^3 [35]. In addition, a PTG volume > 300 mm^3 or maximum diameter > 8 mm predicted nodular hyperplasia [36, 37]. Furthermore, a PTG volume > 500 mm^3 or maximum diameter > 10 mm might be refractory to the calcitriol treatment to SHPT.

Impact of SHPT on BMD

Increases in bone marrow fibrosis and both osteoblastic and osteoclastic activity occur in progressive SHPT. With increased bone resorption and defective mineralization, the resultant cortical bone thinning may lead to bone pain and/or pathological fractures. These types of high turnover bone lesions, including osteitis fibrosa and mixed uremic osteodystrophy, are common in patients with serum intact PTH levels over 400 pg/mL. The resultant increased bone remodeling may lead to reduced bone mineral density. The radius bone considered to be the site that correlates best with serum PTH levels in long-term dialyzed patients. In a prospective study of vitamin D deficiency and SHPT, high serum PTH was a significant predictor of mortality [102].

Vitamin D Deficiency in Bone Loss

The Alteration of Vitamin D Metabolism in CKD

Decrease Vitamin D Synthesis and Increase Vitamin-D Catabolism in CKD

In CKD, PTH synthesis is increased in response to both 1,25D deficiency and hypocalcemia, and then PTH stimulates renal CYP27B1 expression to rescue the 1,25D level. 1,25D consequently induces VDR-mediated intestinal calcium absorption to keep calcium homeostasis. PTH also downregulates renal CYP24A1 mRNA transcription, a 24-hydroxylase enzyme responsible for vitamin D degradation, and leads to

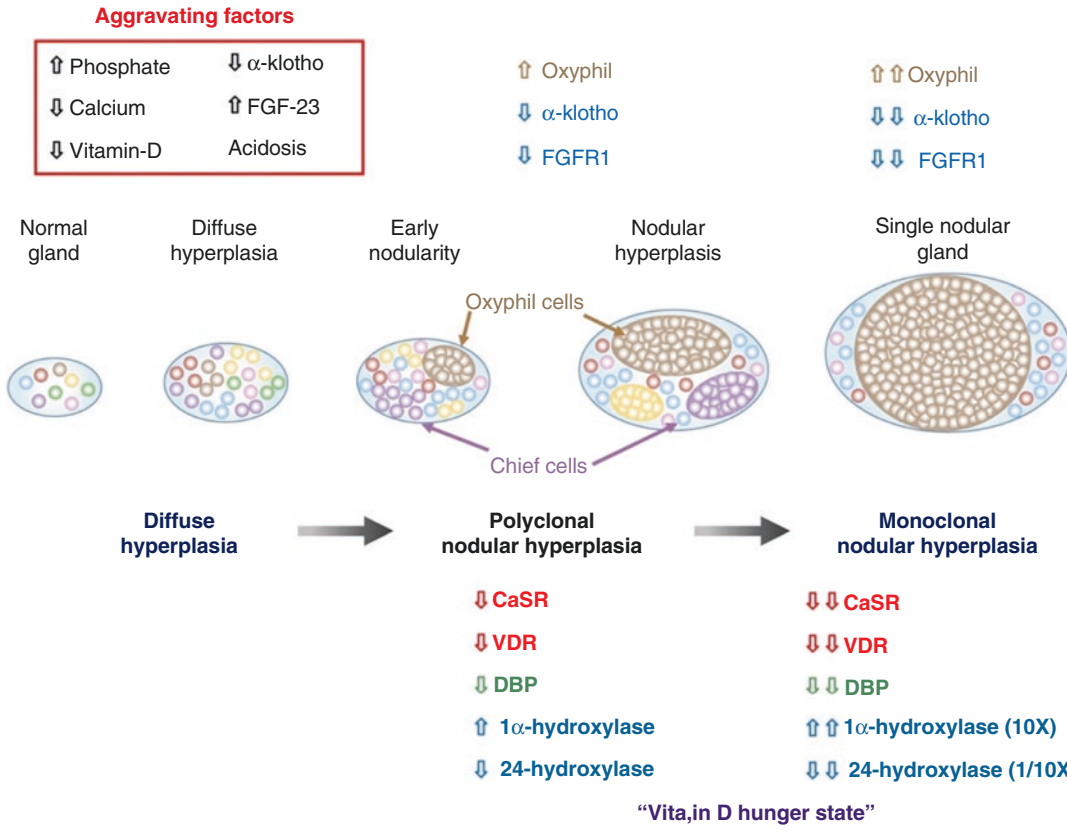

Fig. 30.3 The development of parathyroid gland hyperplasia in secondary hyperparathyroidism (SHPT). In advanced SHPT, monoclonal cell growth vigorously that occupy the most of the gland and form a single large nodule. Both α-klotho and FGFR1 expression on parathyroid cells are decreased during the progress of hyperplasia and are negatively correlated with the volume of the hyperplastic parathyroid tissue. The reduced VDR and CaSR expression is prone to nodular hyperplasia and is considered to be in a relation to calcitriol or calcimimetics resistant. Increased 1α-hydroxylase and decreased 24-hydroxylase expression in secondary hyperplasia PTG cells would highlight the requirement of more 25D in SHPT. In parathyroid cell, the translocation of vitamin D from cytosol into mitochondria for 1,25D synthesis with the help of cytosolic DBP, and reducing the cytosolic DBP content within oxyphilic cell predominant parathyroid nodules might decrease the amount of local intracellular 1,25D production. This hydroxylase enzyme and cytosolic DBP change highlight the requirement of more 25D in SHPT, called vitamin D hunger. Increasing the serum level of 25D increases the intraparathyroid free and bound 25D levels, which might overcome the decreased DBP levels, and improve the vitamin D hypo-responsiveness state in PTG among SHPT patients.(Abbreviation: SHPT secondary hyperparathyroidism, FGFR1 fibroblast growth factor receptor 1, VDR vitamin D receptor, CaSR calcium sensing receptor, 1,25D 1,25-dihydroxy vitamin D, PTH parathyroid hormone, PTG parathyroid gland, VDD vitamin D deficiency, DBP vitamin D binding protein, 25D 25-hydroxy vitamin D) [70]

attenuating 25D and 1,25D degradation via the cAMP/PKA signaling pathway [61, 62].

As PTH controls blood calcium to keep serum calcium homeostasis, FGF-23 regulates the serum phosphate level and is involved in vitamin D metabolism. Hyperphosphatemia can induce osteocytes and osteoblasts to express FGF-23 and subsequently reduces phosphate reabsorption by inhibiting NaPi-IIa activity directly and indirectly by inhibiting renal CYP27B1 expression to lower blood 1,25D level, then reduces intestinal phosphate absorption [63]. Additionally, FGF-23 induces renal CYP24A1 expression to degrade 25D and 1,25D levels [62].

The function of PTH and FGF-23 in regulating CYP27B1 works in a reciprocal manner and

competes with each other on CYP27B1 transcription. The direct administration of recombinant FGF-23 or its overexpression in mice induces a dose-dependent decrease in renal CYP27B1 mRNA expression, an increase in renal CYP24A1 mRNA expression, and a consequent decrease in serum 1,25D concentrations [28]. Instead, the administration of FGF-23 antibodies can increase renal CYP27B1 mRNA and decrease renal CYP24A1 mRNA to restore serum 1,25D concentration to normal. These changes are followed by increased serum calcium level, leading to decreased serum PTH [27]. Hence, FGF-23, rather than PTH, is a primary factor accounting for inappropriately low serum 1,25D concentration in CKD since the early stage of CKD. In brief, an increase of FGF-23 in CKD follows 1,25D deficiency and hypocalcemia, thereby increasing the PTH level and results in SHPT in CKD. The FGF-23 action may aggravate VDD if concurrently used with calcitriol or VDRA analogs during SHPT treatment as both FGF-23 and VDRA analogs both downregulate CYP27B1 and upregulate CYP24A1 expression to degrade 25D and 1,25D.

There is also another metabolic factor commonly presented in CKD that disturbs CYP27B1 expression such as diabetes [64], acidosis [65], and hyperuricemia [66, 67]. Therefore, high FGF-23 and CKD-related metabolic factors are associated with CYP27B1 transcription inhibition in CKD.

Lower 25D bioavailability in CKD is also another cause of VDD. As limited sun exposure and dietary vitamin D intake, less 25-hydroxyvitmain D filtered by declining GFR, diminished megalin expression, and albuminuria increase filtered 25-hydroxyvitmain D lost in urine are all aggravating factors that lead to 25D shortage and cannot provide an inadequate substrate for 1α-hydroxylase and worsens VDD in CKD [46, 68].

Nutritional Vitamin D Hunger in the Parathyroid Gland

In normal physiological conditions, FGF-23 can directly suppress PTH production by directly inhibiting PTH transcription and secretion and indirectly by increasing parathyroid 1α-hydroxylase activity [69]. FGF-23 can also increase CaSR and VDR expression and decrease PTG volume. However, low PTG α-Klotho and FGFR1 expression lets FGF-23 lose its inhibitory effect on parathyroid cells and fails to increase CaSR and VDR [70]. Moreover, the administration of FGF-23 in CKD animals cannot reduce the PTH level, which indicates FGF-23 resistance in PTG caused by the low expression of α-Klotho and FGFR1 [71]. In summary, in patients with CKD, FGF-23 levels increase progressively to compensate phosphate retention, but the high FGF-23 levels fail to suppress PTH secretion due to decreased Klotho-FGFR1 complex expression in hyperplastic PTG, called FGF-23 resistance. Furthermore, recent literature in dialysis patients of SHPT has shown that the expression of α-Klotho and FGFR1 is decreased in PTG of dialysis patients and were negatively correlated with the volume of the hyperplastic parathyroid tissue [71].

Compared with the normal gland, the mRNA expression and protein level for 1α-hydroxylase (CYP27B1) in secondary hyperplastic parathyroid cells is higher [73]. Increased 1α-hydroxylase (approximately tenfold) and decreased 24-hydroxylase (approximately 1/ten-fold) concentrations are found in 78% of secondary hyperplasia PTG cells and highlight the requirement of more 25D in SHPT [74]. The expression of 1α-hydroxylase is much higher in oxyphil cells than chief cells, which is the dominant cell group in SHPT. Calcimimetic treatment had a further 42% increase in parathyroid 1α-hydroxylase mRNA and 2.2-fold decrease in 24-hydroxylase mRNA that resulted in an ~53% decrease in PTH mRNA [75]. Besides, the decrease of megalin expression in the parathyroid gland may decrease 25D uptake and mediate the demand for more circulating 25D to correct PTH synthesis. Hence, the requirement for a substrate for vitamin D synthesis dramatically increases in SHPT and becomes hungrier if receiving treatment of calcimimetics in severe SHPT, called "vitamin D hunger status" as SHPT progresses in CKD. Therefore, more evidence in the data have overwhelmingly indicated the adjuvant role of

NVD in SHPT prevention and PTH lowering effect in combination with calcitriol or calcimimetics treatment.

Vitamin D Deficiency: Effect on Bone Quantity and Quality Loss

Vitamin D deficiency is a prevalent problem worldwide, including critically ill patients. Because vitamin D exerts multiple pleiotropic effects such as immunity, inflammation, cell proliferation, differentiation, apoptosis, and angiogenesis, there is growing evidence of a close relationship between vitamin D insufficiency and various systemic disorders [72]. Because vitamin D affects the interaction between osteoblasts, osteoclasts, and osteocytes, vitamin D deficiency is associated with insufficient bone mass or inadequate bone remodeling, which leads to fragile bones and increases the risk of fracture.

Vitamin D Deficiency and Bone Quantity Loss

Insufficient vitamin D is associated with low intestinal calcium absorption and sequential activation of PTH [73]. The histopathological characteristics of vitamin D deficiency with respect to loss of bone quantity include excessive nonmineralized bone matrix, a decrease in bone volume and premature bone formation. [74]. In low bone turnover disorder such as osteomalacia, the viability of mature osteoblasts decreased due to vitamin D deficiency [75]. Vitamin D deficiency is predictive of low BMD in both high and low bone turnover disease.

In high bone turnover disorder, lower serum vitamin D is related to severe inflammatory status and activated osteoclastogenesis. Low serum vitamin D concentration is associated with increased bone turnover and decreased bone volume in elderly people and postmenopausal women [76, 77]. In patients with ESRD, bone formation and trabecular mineralization are positively associated with serum vitamin D concentration independently of PTH or use of active vitamin D [90]. In patients with systemic lupus erythematous, low vitamin D concentration is associated with high disease activity and is a predictor of osteoporosis [78].

In the low bone turnover disorder, vitamin D deficiency reflects poor bone formation and osteoporosis. In patients with diabetes mellitus, the proportion with osteoporosis and osteopenia increases with a decrease in bone formation [79, 80]. In patients receiving long-term home parental nutrition, vitamin D insufficiency (<30 ng/mL) is predictive of femoral neck fracture [81].

Based on the data by the Institute of Medicine, a serum concentration of 25(OH) D higher than 20 ng/mL was sufficient for adequate bone health. However, the data from the National Health and Nutrition Examination Survey III revealed that such concentration was not sufficient for older people in bone health and falling prevention [82]. The serum concentration of 25(OH)D lower than 75 ng/mL was predictive to higher all-cause mortality, and such concentration should be optimal for falling prevention [83]. In summary, metabolic disease induces vitamin D deficiency, and such deficiency is associated with increased bone resorption, insufficient calcium–phosphate absorption, decreased osteoblast activity, and sequential loss in bone quantity.

Vitamin D Deficiency and Bone Quality Loss

Because bone is composed of calcium–phosphate hydroxyl apatite crystals and type 1 collagen, tissue mineral density and collagen cross-linking are associated with bone stiffness and strength. A disoriented arrangement of the crystals and collagen due to systemic illness affects bone formation, mineral deposition, and bone quality. Vitamin D affects gene expression in the ECM of bone, and insufficient vitamin D is associated with dysregulated arrangement of collagen and crystal. Progressive ankylosis protein, which is expressed in nonmineralizing tissue, is sensitive to VDRs and antagonizes mineralization in bone tissue. In VDR-knockout mice, activation of this protein maintains serum calcium concentration by enhancing bone resorption [84]. Higher mineral content with mature collagen and mineral constituents, which are observed in mature osteoblasts, results in more osteoids in vitamin D defi-

cient mice. Such crystallized osteoids hamper remodeling of the remaining bone tissue, causing the tissue to lose its resistance to fracture [85]. Patients with vitamin D deficiency may show disturbed microstructure and maturation of bone cells and weak bone strength, even if bone mass is maintained [86]. Although the direct effect of vitamin D on the interaction between osteoblasts, osteoclasts, and ECM needs further investigation, vitamin D deficiency is known to be associated with poor bone quality.

Role of Vitamin D Supplementation in High and Low Bone Turnover Disorders

Treatment of High Bone Turnover Disorder

Effect of Vitamin D Supplementation on Bone Quantity Loss (Fig. 30.4)

For the currently available medications for treating osteoporosis, the therapeutic window is dependent on the uncoupling between bone resorption and formation. During treatment with antiresorptive agents, inhibition of bone resorption precedes a later decrease in bone formation. For PTH treatment, the therapeutic window corresponds to the lag time required for increased bone formation to be coupled with increased bone resorption [87]. Because the balance of bone remodeling and formation requires the coupling of osteoblasts and osteoclasts, narrowing of the therapeutic window may be beneficial for maintaining bone quality and quantity simultaneously. In the high turnover bone disorders, the anti-resorption agent decreases bone resorption as the reflect by change of bone resorption markers, and it also couple with decrease the osteoblast viability, which was reflected by changing the serum bone formation markers. The therapeutic window would be the blue area in the Fig. 30.4a. In the high turnover bone disorders, adding nutritional vit-D on the anti-resorption agent will lessen the decreased bone resorption as the reflect by change of bone resorption markers, which means more old/fragile bone will be removed as blank areas "Φ" showed (Fig. 30.4b). Meanwhile, it also couple with slightly increase osteoblast viability, which would produce more good quality bone (blue area "Φ") as reflected by changing the serum bone formation markers. The therapeutic window would shift to right upperward when compared with Fig. 30.4a. Thus, during antiresorptive drug treatment for high bone turnover disorder, nutritional vit-D should be added.

Results of clinical trials have demonstrated that nutritional vitamin D supplementation maintains bone density and conjunctive use of vitamin D with antiresorptive agents increases treatment efficacy, and the effect on BMD was not inferior in comparison with active vitamin D supplement. In Chinese postmenopausal women, combination treatment with bisphosphonate and cholecalcif-

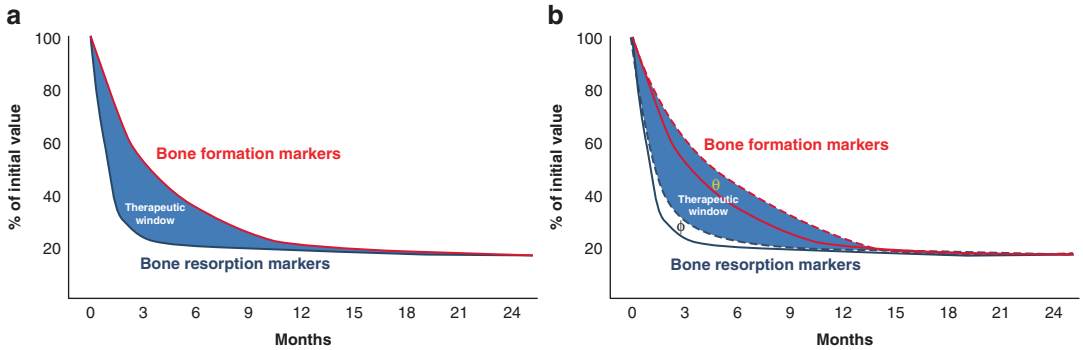

Fig. 30.4 Therapeutic window of anti-resorption drug for high bone turnover with osteoporosis (**a**) and the effect of adding nutritional vit-D (**b**) on the therapeutic window of anti-resorption drug [12]

erol increased lumbar BMD compared with that in women receiving a combination of bisphosphonate and calcitriol. Moreover, combination treatment with bisphosphonate and cholecalciferol results in a higher decrease in the levels of bone turnover marker than combination treatment with bisphosphonate and calcitriol [88]. Besides, the BMD-augmenting effect by cholecalciferol was dose-dependent. In patients with pediatric nephrotic syndrome, cholecalciferol supplementation improves BMD with dose-dependent effect [89].

In summary, when treating the high bone-turnover disorder, supplement of nutritional vitamin D with anti-resoptive agent is beneficial in maintaining BMD, and of its modulation on osteoblast and avoidance of oversuppression of osteoclast decreases the therapeutic window. In contrast to active vitamin D, the action of nutritional vitamin D on bone formation is dose-dependent.

Effect of Vitamin D Supplementation on Bone Loss: Bone Quality

Vitamin D supplementation plays an adjunctive or therapeutic role in treating quality bone loss. Khajuria et al. [90] found that alfacalcidol supplementation with bisphosphonates maintains bone mass and bone strength in ovariectomized rats with osteoporosis. Vitamin D3 and vitamin K supplementation attenuates detrimental damage induced by advanced glycosylate end products on osteoblasts by upregulating collagen expression [91]. However, the supplement of supraphysiologic active vitamin D abated the RANKL signaling and expression between osteoblast/osteoclast, and excessive intestinal calcium and phosphate absorption might influence the bone quality. Instead, cholecalciferol supplementation with a target level of up to 75 nmol/L, on the other hand, improves PTH level and muscle strength in a dose-dependent manner [92]. Nutritional vitamin D supplementation is helpful in maintaining bone microarchitecture in a dose-dependent manner. Tabatabaei et al. found that the architecture of long bones in guinea pig offspring improved more with higher maternal cholecalciferol supplementation [93]. Therefore, vitamin D supplementation should play a role in maintaining bone strength and architectural stability during osteoporosis treatment.

Extraskeletal Effect of Vitamin D in Treating Osteoporosis: Alleviating Inflammation and Oxidative End Products

Take estrogen-deficiency related osteoporosis as example in treating high bone turnover disorder (Fig. 30.5). Estrogen deficiency is associated

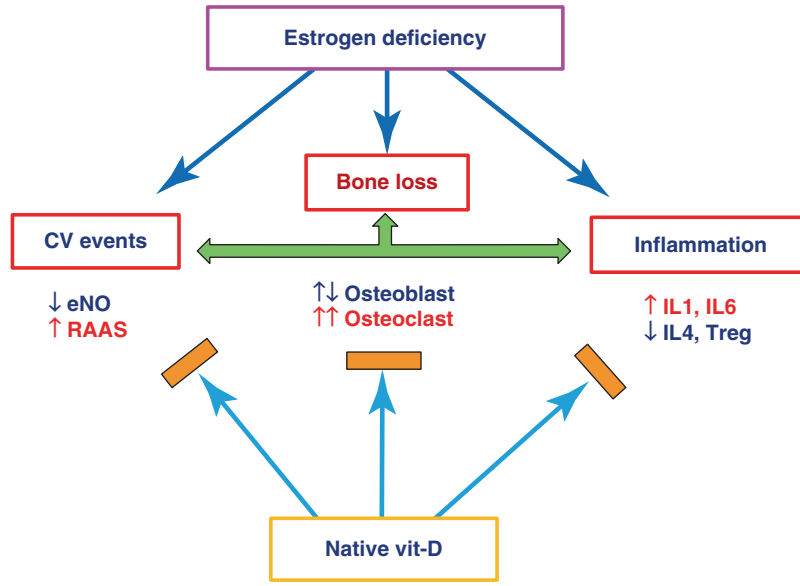

Fig. 30.5 Beneficial effects of vit-D on high bone turnover disorder treatment: menopause-related osteoporosis as example [12]

with bone loss, inflammatory status, and higher cardiovascular event due to dysregulation of the renin-angiotensin-aldosterone system (RAAS). Several lines of evidence suggest estrogen deficiency due to menopause may contribute to over activity of the RAAS. Animal models of estrogen deficiency also showed upregulated tissue expression of ACE and AT1R and decreased tissue expression of AT2R. The endothelial-derived nitric oxide (NO), synthesized by endothelial NO synthase (eNOS) from amino acid L-arginine and molecular oxygen, plays a pivotal role in maintaining vascular homeostasis and vasodilation. Animal study also showed ovariectomy downregulated cardiac eNOS gene expression. There are many cross talk between inflammation-bone loss-CV events in estrogen deficiency status. Vitamin D functions as an inflammatory modulator by affecting T cells. Low serum 25(OH)D3 level is associated with high systemic levels of inflammatory cytokines such as IL-6 or IL-1, which function as osteoclast stimulators [94]. 1α,25(OH)2D affects adaptive immunity by increasing the activity of type 2 T helper cells and decreasing the number of inflammatory type 1 T helper cells [95]. It also counteracts the overactivation of the RAAS and might decrease the incidence of cardiovascular events. Inflammatory cytokines directly increase osteoclast activity and bone resorption. Nutritional vitamin D alleviates renin-angiotensin-aldosterone activity, which may decrease endogenous NOS level and relieve oxidative stress [96]. On the other hand, the gut microbiota and increased gut permeability play in triggering inflammatory pathways that are critical for inducing bone loss in sex steroid-deficient mice. The probiotics that decrease gut permeability have potential as a therapeutic strategy for postmenopausal osteoporosis. Villa et al. reported that vitamin D supplementation improved femur and lumbar trabecular number in the offspring of pregnant rats by altering intestinal permeability and systemic lipopolysaccharide concentrations [97]. Therefore, vitamin D helps in treating osteoporosis by functioning as an anti-inflammatory modulator, which may improve excessive bone resorption.

Vitamin D for Treating Low Bone Turnover Disorder: Combination with Anabolic Agents

Low-energy bone fracture is common in patients with low bone turnover disorder such as GIO or prolonged bisphosphonate use [98, 99]. Nutritional vit-D treatment for GIO will not only decrease inflammation and oxidative stress on the osteoclast but also rescue the viability of osteocyte and osteoblast, which will recover the remodeling activity of the lower bone turnover states. In osteoporosis patients with low bone turnover, osteoanabolic agent therapy will increase bone formation and sequentially enhance bone resorption (Fig. 30.6a). The therapeutic window in this figure would be the blue color area. In osteoporosis patients with low bone turnover, adding nutritional vit-D on osteoanabolic

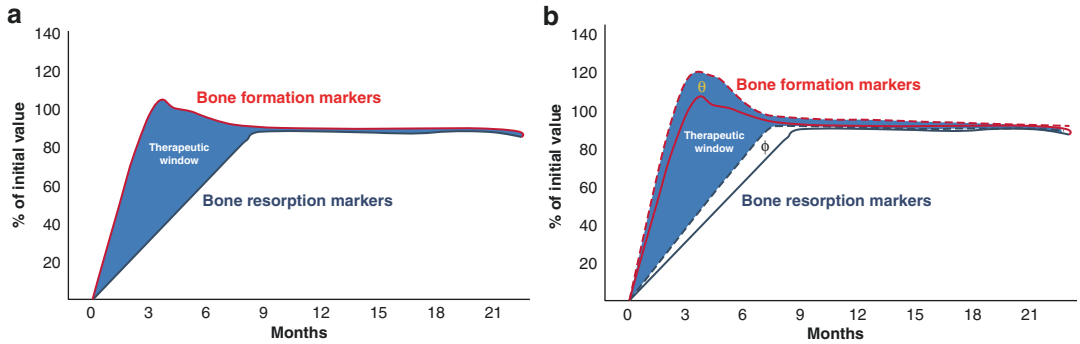

Fig. 30.6 Therapeutic window of anti-resorption drug for low bone turnover with osteoporosis (**a**) and the effect of adding nutritional vit-D (**b**) on the therapeutic window of anti-resorption drug [12]

agent therapy will further increase bone formation with osteoblast that may produce more good quality bone (Fig. 30.6b). It also will be sequentially further enhanced bone resorption, which will remove more old/fragile bone. The therapeutic window would shift to left upperward when compared with Fig. 30.6a. Thus, during antiresorptive drug treatment for low turnover bone disorders, nutritional vit-D should be added.

The rate of osteoblast survival is low, and sequential coupling of bone remodeling is abated in patients with low bone turnover disorder. Therefore, osteocyte/osteoblast apoptosis is common when using anti-resorptive agent alone [100]. From the EuroGIOP trial, bone-forming agents improved BMD and bone quality better than with treatment with bisphosphonate [101]. In HD patient with adynamic bone disease who received PTH analog treatment, 6 months of PTH analog improved, the bone formation rate was increased, and bone histopathology showed normal bone turnover [102]. Although recent meta-analysis reported a neutral effect on the vitamin D supplement for preventing fracture in a community-indwelling elderly, vitamin D deficiency was less common in such patients because the source of vitamin D was more diverse in community [103]. Therefore, physicians should be cautious while using pharmacological doses of active vitamin D for treating osteoporosis; moreover, nutritional vitamin D may be considered for treating low bone turnover disorder when treating with PTH analog in order to maintain the osteoblast viability.

Treatment of Osteoporosis: According to Bone Turnover (Fig. 30.7)

Preventing the bone loss in quality and quantity can be achieved by normalizing the bone remodeling process. Bone mass can be maintained using agents that decrease bone resorption, activate bone formation, or prevent osteoblast apoptosis. However, bone quality should be maintained using treatments based on the bone turnover rate. In patients with high turnover bone disorders such as PMO, RA, AS, COPD, or other chronic inflammatory disorders with the characteristic of

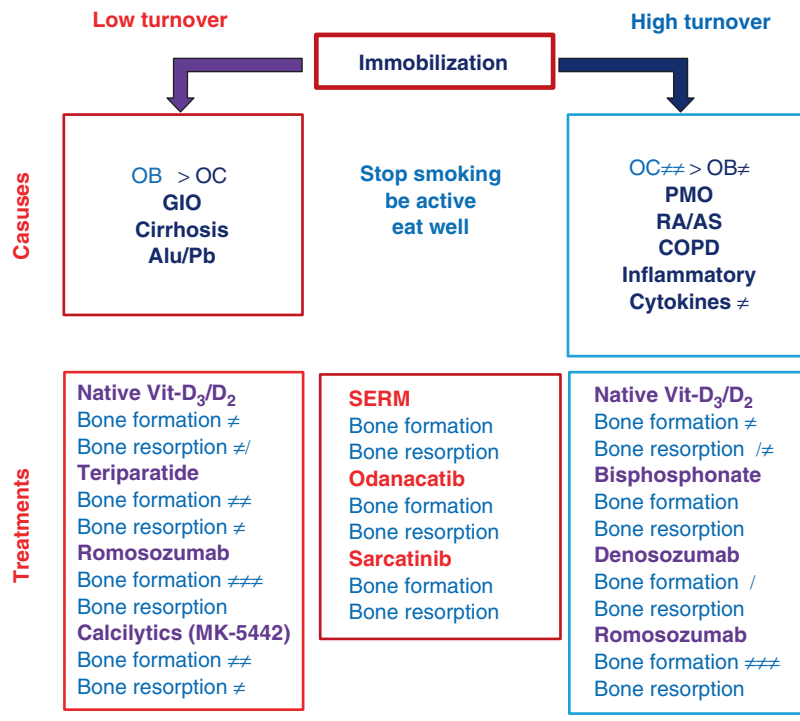

Fig. 30.7 Rational therapeutic consideration in osteoporosis: based on bone turnover rate [104]

higher osteoclast function than osteoblast, antiresorption medication such as bisphosphonate or denosumab could be considered. Other medication such as SERM, Odanacatib could be considered in special situations. In patients with immobilization, both increased osteoclast activity and decreased osteoblast viability were present. Choice of anti-resorption or osteoanabolic agent treatment should base on patient's bone remodeling status.

High Bone Turnover Disorder: Enhance Osteoclastogenesis Couple With More Increased in Osteoblast Viability

Antiresorptive Agents

Antiresorptive agents should be used for treating patients with osteoporosis having low bone mass. Widely used antiresorptive agents include bisphosphonates, calcimimetics, and denosumab.

Bisphosphonates

Bisphosphonates are the derivatives of inorganic pyrophosphates. Because of their high affinity to hydroapatite crystals in bone, bisphosphonates enter cells lining the surface of bone and prevent further cleavage by alkaline phosphatase. Moreover, bisphosphonates induce osteoclast apoptosis after they are taken up and metabolized into metabolites that interrupt the ATP generation [105]. It induces the osteoclast apoptosis rather than osteoclast progenitor cells, and bone formation may be abated by interfering the osteoblast viability and Wnt signaling [106, 107]. Well-established evidence is available on the use of bisphosphonates for treating osteoporosis in postmenopausal women and in patients with secondary hyperparathryoidism who show accelerated bone resorption due to osteoclast activation. Borah et al. reported that bisphosphonate treatment decreased fracture rate in patients with increased levels of serum bone turnover marker compared with that in patients with decreased levels of serum bone turnover marker [108]. In patients undergoing dialysis, bisphosphonate treatment decreases serum ionic calcium concentration; moreover, concurrent use of bisphosphonates with active vitamin D suppresses the aggravation of hyperparathyroidism [109]. If bisphosphonate is applied in low bone turnover disease, it indirectly inhibits bone formation by interfering with osteoblast viability, resulting in the occurrence of osteomalacia or fracture in atypical sites [106]. For example, patients with early stage CKD (stage II–IV) with more severe low bone turnover disorder, bisphosphonate treatment may inhibit bone turnover and adynamic bone disease [110]. Therefore, bisphosphonate treatment should be selected for patients with osteoporosis who have high bone turnover disorder and should be administered along with medications that maintain osteoblast viability.

Anti-RANKL Antibody

Denosumab. Denosumab is a monoclonal antibody that targets osteoclast-differentiation-inducing cytokine RANKL. It directly inhibits osteoclast activation and bone formation [87]. Moreover, use of denosumab induces the apoptosis of osteoclasts and osteoclast progenitor cells, which are the source of Wnt/β-catenin inhibitor [111]. Its application in the general population decreases the incidence of new vertebral, nonvertebral, and hip fractures. The efficacy of denosumab for decreasing the incidence of fractures is not inferior to that of bisphosphonates; moreover, denosumab maintains more BMD than bisphosphonates [112]. In patients with CKD, denosumab reduces fracture rate and increases BMD at all sites with respect to the different stages of eGFR [113]. Therefore, the use of denosumab can induce a mild positive balance in bone formation compared with the use of bisphosphonates [112].

Calcimimetics

Extracellular calcium concentration regulates PTH secretion through calcium-sensing receptor (CaSR), which is a G protein-coupled receptor. CaSR-induced activation of intracellular protein kinase C and mobilization of intracellular calcium from nonmitochondrial storage inhibit PTH secretion [114]. In patients with secondary hyperparathyroisim, calcimimetics may play a role in decelerating bone turnover and maintaining

BMD. CaSR affects osteoblasts by affecting RANKL/OPG signaling. In old animals, CaSR activation augments osteoblast-related bone formation by regulating the coupling between osteoblasts and osteoclasts, whereas in young animals, CaSR directly inhibits osteoclasts [115]. In patients with HD who have secondary hyperparathyroidism and increased baseline serum alkaline phosphatase levels, cinacalcet treatment increases BMD [116]. In patients undergoing dialysis and with secondary hyperparathyroidism, cinacalcet treatment for 6–12 months decreased serum PTH concentration and inhibited bone turnover rate [117]. The results of an EVOLVE study revealed decreased fracture rate in elderly patients receiving cinacalcet, with the relative hazard of fracture being 0.72 (95% CI, 0.58–0.90) [118]. Therefore, it would be applied in high bone turnover disorder.

Low Bone Turnover Disorder: Rescute the Osteoblast Viability: Anabolic Agents: PTH Analogs, Monoclonal Antibodies Against Wnt Pathway Inhibitors

Parathyroid Hormone

PTH activates the cyclic AMP-dependent protein kinase A and calcium-dependent protein kinase C signaling pathways to regulate osteoblast function. Moreover, it modulates the effect of IGF-1 and sclerostin [119]. Therefore, it should be applied as an anabolic therapy in patients with low bone turnover disorders. Subcutaneous teriparatide (recombinant 1–34 N-terminal sequence of human PTH) has been approved as an anabolic therapy. It decreases osteoblast apoptosis and activates dormant bone-lining cells to form active osteoblasts. Histomorphometric analysis showed increased trabecular bone volume, connectivity, bone microarchitecture, and bone trabecula number in elderly with osteoporosis [120]. In osteoporotic patients with normal PTH [77], subcutaneous teriparatide injection reduces the risk of vertebral or nonvertebral fractures. The efficacy of subcutaneous teriparatide injection for treating low bone turnover disorders such as adynamic bone disease or osteomalacia in patients with CKD has not yet been identified. However, in patients undergoing dialysis and with low bone turnover disorder, teriparatide supplementation increases the levels of bone turnover marker [121–123]. Even in the elderly with high bone turnover disease, there is an anabolic window after using PTH of 24 months [124] that allows the augmentation of bone formation rather than bone resorption. In patients with low bone turnover disorder such as GIO, teriparatide injection increases bone formation and corrects BMD [99].

Monoclonal Antibodies Against Wnt Pathway Inhibitors

Odanacatib and romosozumab are potential anti-osteoporotic agents against Wnt signaling pathway inhibitors [125, 126]. As mentioned previously, Wnt/β-catenin signaling is crucial for osteogenesis. Inhibitors such as sclerostin and DKK1 decrease osteoclastogenesis and bone turnover [127]. Monoclonal antibody against sclerostin augments Wnt-signaling-related osteoblast formation and inhibits bone resorption. Romosozumab treatment has been proved to maintain bone mass along with the increasing serum PINP level [128]. The application of romosozumab decreases the risk of fracture at the same time [129, 130]. During the treatment, therapeutic window of treatment with neutralizing anti-SOST antibodies is expected to be considerably large because an increase in bone formation is associated with a slight decrease in bone resorption [87]. In the animal model with sclerostin gene mutation, the bone strength increased along with the bone volume, and there is still no notable disadvantage on bone quality[131].

Effect of Nutritional Vitamin D on Osteoporosis

As mentioned in the previous sections, vitamin D receptors exist on the osteoblast, osteoclast, osteocytes, and ECM in osseous tissue. Vitamin D defi-

ciency is predictive to low bone quality and quantity, and the pharmacologic concentration of active vitamin D would pose damage to osteoblast. Since nutritional vitamin D provides a microenvironment of physiologic concentration of 25(OH)D for bone tissue, we discussed the role of nutritional vitamin D in treating high and low bone turnover disorders. Serum concentration of 25(OH)D reflects the status of vitamin D. It has been noticed that body fat and body mass index influence the serum concentration of 25(OH)D because of the fat distribution and fat tissue around intestine[132]. When treating vitamin D deficiency, it has been noticed that there is no a linear correlation between the supplemented dosage of cholecalciferol and the response in the serum vitamin D [133]. Previous retrospective analysis of nondialysis-requiring CKD patients was conducted to assess the relative effectiveness of D2 versus D3 replacement on circulating 25(OH)D levels. The results showed cholecalciferol may be superior to ergocalciferol in treating nutritional vitamin D deficiency in nondialysis CKD [134]. The meta-analysis also indicates that vitamin D3 is more efficacious at raising serum 25(OH)D concentrations than is vitamin D2, and thus vitamin D3 could potentially become the preferred choice for supplementation [135]. It has been found that daily supplement of cholecalciferol with dosage of 1000 IU/day could cause the largest increment in the patients with more severe vitamin D deficiency(<10 ng/ml). The increment of 25(OH)2D would decrease if the starting value of 25(OH)D is higher. Single dosage supplement of cholecalciferol (such as 70,000 IU ~ 300,000 IU) had been applied in several clinical trials [136–138]. Such supplement provided a sustained increase in serum 25(OH)D for less than 2 months, and the incidence of adverse effect such as hypercalcemia were not common. Therefore, when treating the severe hypovitaminosis, monitoring the variation of serum 25(OH)D is important and supplement with higher dosage or intensive interval should be considered in more severe vitamin D deficient status [139].To date, the evidence of drug interaction and supplement of vitamin D, especially cholecalciferol is limited. As the previous sections mentioned, there was a huge margin in 25(OH)D concentration for vitamin D deficiency and the optimal concentration. Therefore, a daily dosage 1000 IU for children <1 year on enriched formula,1500 IU for breastfed children older than 6 months, 3000 IU for children >1 year of age, and around 8000 IU for young adults might be recommended for maintaining the bone health [83].

Conclusions

Bone tissue is composed of osteocytes, osteoblasts, and osteoclasts and tightly controlled by RANK/OPG system. The increased in RANK/RANKL ratio and decreased in OPG levels will accentuate the osteoclast-related bone resorption. Excessive of Wnt/β-catenin signaling inhibitors, including DKK1 and SOST also attenuate the osteoblast viability and increase osteoclast activity resulted in an obvious bone quantity reduction. Abnormality of bone turnover disorders deteriorates bone structural arrangement and decreases bone quality, which cause bone fragility and bone loss. High PTH level stimulated by phosphate burden and vitamin D deficiency affects RANKL and OPG activity in osteoblasts and sequentially activates osteoclast-related bone resorption. Vitamin D deficiency is associated with increased bone resorption, insufficient calcium–phosphate absorption, decreased osteoblast activity, and sequential loss in bone quantity. In high turnover bone disorders, adding nutritional vit-D on the anti-resorption agent will lessen the decreased bone resorption and increase the therapeutic window. Similarly, in osteoporosis patients with low bone turnover, adding nutritional vit-D on osteoanabolic agent therapy will further increase bone formation and produce more good quality bone. Therefore, adequate vitamin D concentration might be recommended for maintaining the bone health in CKD.

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31 Glucocorticoids and Musculoskeletal Health

Yasser El Miedany

Introduction

Much has been learned since 1932 when Harvey Cushing described the set of symptoms that denoted hypersecretion of ACTH most often due to a pituitary adenoma. A set of symptoms prominently featured include truncal obesity, a rounded face, increased fat around the neck, and peripheral muscle wasting, weakened bones, leading to vertebral compression fractures, striae on the abdomen and buttocks, hirsutism, fatigue, muscle weakness, fatigue, fluid retention, hypertension, and hyperglycemia [1]. The original publication by Cushing [2], as it turns out, was the first description of the effects of endogenous glucocorticoids on bone and muscle, a description that became identified with the effects of exogenous glucocorticoids, or steroid medication, for a variety of chronic inflammatory and neoplastic diseases.

Over the past decades, glucocorticoids booked its place as one of the most commonly prescribed classes of drugs for several medical conditions and in states of hypocortisolism [3]. Although the adverse skeletal effects of glucocorticoids have been recognized for decades, attention to this side effect has gained increased attention because of the widespread long-term clinical use of glucocorticoids in a variety of disorders including autoimmune, pulmonary, and gastrointestinal diseases, malignancies, and in patients receiving organ transplants. The problem has become so widely appreciated that guidelines for the prevention and treatment for glucocorticoid-induced osteoporosis (GIO) have been established in many countries based upon recommendations by expert scientific organizations [4].

The bone loss secondary to initiation of glucocorticoids is early and rapid, and the bone mineral loss correlates well with cumulative dose and duration. Fracture risk is increased even with a daily dose of prednisolone that is <5 mg/day [5]. Parenteral, oral, and even long-term inhaled glucocorticoids are associated with a significant bone loss. The rate of bone loss is noted to be more than 10% in the first year of therapy and thereafter tends to stabilize at 2–3% every year [6]. It predominantly involves trabecular bone, thus increasing the risk of vertebral fractures. Later, cortical bone is also involved (e.g., femoral neck) [7]. About 20% of those treated with glucocorticoids will have a fragility fracture within the first year of treatment [8]. Postmenopausal women and elderly men are at a higher risk for developing glucocorticoid-induced bone loss and fractures [9]. Similarly, the catabolic effects of glucocorticoids on skeletal muscles have been well known for many years. Administration of high doses of glucocorticoids to animals causes not only decreased muscle mass but also muscle

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dysfunction characterized by reduced force and weakness [10].

Even though the negative effect of glucocorticoid therapy on both bone and muscle health has been recognized and well documented, more than half of those on treatment do not receive bone mineral density (BMD) assessment or the recommended preventative therapy for osteoporosis [11]. A number of guidelines have already been published highlighting the importance of considering preventive measures for patients receiving glucocorticoid treatment on a long-term basis, or until the steroid therapy course is stopped. This chapter will review the epidemiology and pathophysiology of glucocorticoid-induced osteoporosis. This will be followed by discussing the effect of glucocorticoids on the musculoskeletal health, namely bones and muscles, clinical correlations of glucocorticoid-induced osteoporosis, risk stratification, screening and assessment and glucocorticoid-associated changes in bone mineral density and bone architecture. The chapter will then discuss the monitoring of BMD and fracture risk assessment as well as management of the glucocorticoid-induced osteoporosis. The chapter will conclude with an algorithm for assessment and management of glucocorticoid-induced osteoporosis.

Epidemiology

Epidemiologic studies provide valuable information about the use of glucocorticoids and its negative impact on musculoskeletal system. The prevalence of use of oral glucocorticoids in the community population ranges between 0.5% and 0.9%, rising to 2.7% in adults and older adults aged ≥50 years [12–14]. The prevalence has been reported to be similar in men and women. In the Global Longitudinal Study of Osteoporosis in Women (GLOW), conducted in 10 countries, 4.6% of 60,393 postmenopausal women were receiving glucocorticoids at baseline visit [15, 16]. The most frequent indications for oral glucocorticoids are inflammatory rheumatic disorders (rheumatoid arthritis, systemic lupus erythematosus, polymyalgia rheumatica, and temporal arteritis), lung disorders (asthma and chronic obstructive lung diseases), and organ transplantation.

Of the multiple side effects that can occur with glucocorticoid therapy, glucocorticoid-induced osteoporosis (GIO) has been identified the most prevalent form of bone affection. Examining the prevalence of GIO revealed that at least 50% of people receiving long-term glucocorticoid therapy are estimated to develop osteoporosis [17]. Furthermore, osteoporotic fractures are one of the most devastating glucocorticoid musculoskeletal complication, affecting 30–50% of patients [18–21]. Furthermore, secondary causes of osteoporosis, such as that induced by glucocorticoids, are particularly common in pre- or perimenopausal women. In a clinical study of pre- and postmenopausal women attending a specialty osteoporosis clinic (n = 384 patients), a secondary cause for osteoporosis was established in 8.6% of cases, and 21% of these were attributed to glucocorticoids, all of which were in premenopausal women [22]. Khosla and colleagues reported GIO in over 50% of patients aged 20–44 years with an established diagnosis of secondary osteoporosis [23].

In concordance, the risk of fractures is increased by twofold in patients treated with glucocorticoids, and the risk of vertebral fractures is even higher. In a study comparing 244, 235 oral glucocorticoids users and 244, 235 controls, the risk of hip fracture is 1.6, and that of vertebral fracture is 2.6; these numbers have been reproduced in many studies [24–26]. The global prevalence of fractures in patients receiving long-term glucocorticoids has been reported to be 30–50%. In 551 patients receiving long-term glucocorticoids, the prevalence of vertebral fractures was 37%, with 14% of patients having two or more asymptomatic vertebral fractures; 48% of patients aged ≥70 years and 30% of those aged <60 years had at least one vertebral fracture [27]. The prevalence increases with age, a key point for preventive strategies.

The highly cited study [8] from the United Kingdom General Practice Research Database demonstrated that a dose of about 5 mg of pred-

nisone equivalent led to a measurable increase in fracture risk after only 3 months of glucocorticoid treatment. More recently [28], a report suggested that even 1 month of systemic glucocorticoid therapy was associated with increased fracture risk. If this is confirmed by other studies, it strengthens the need for clinicians to consider fracture risk at the time of prescribing prednisone and similar drugs. Indeed, it has been shown that on the first day of prednisone therapy, bone formation markers will be suppressed [29]. Even injections into joints can affect bone turnover markers for 2 weeks or more [30].

Pathophysiology

Mechanism of Action of Glucocorticoids

Glucocorticoids are a class of corticosteroids, which are a class of steroid hormones. Glucocorticoids are corticosteroids that bind to the cytosolic glucocorticoid receptor, which is present in almost every vertebrate animal cell [31]. The name "glucocorticoid" is a portmanteau (*gluco*se + *cort*ex + ster*oid*) and is composed of its role in regulation of glucose metabolism, synthesis in the adrenal cortex, and its steroidal structure. A less common synonym is glucocorticosteroid. Glucocorticoids are distinguished from mineralocorticoids and sex steroids by their specific receptors, target cells, and effects. In technical terms, "corticosteroid" refers to both glucocorticoids and mineralocorticoids (as both are mimics of hormones produced by the adrenal cortex). Glucocorticoids are chiefly produced in the zona fasciculata of the adrenal cortex, whereas mineralocorticoids are synthesized in the zona glomerulosa. Glucocorticoids are part of the feedback mechanism in the immune system, which reduces certain aspects of immune function, such as inflammation. They are therefore used in medicine to treat diseases caused by an overactive immune system, such as allergies, asthma, autoimmune diseases, and sepsis.

Upon activation of the glucocorticoid receptor, the complex translocates to the nucleus, where it binds glucocorticoid response elements of an array of genes (Fig. 31.1). This in turn modulates transcription of target genes, resulting in expression of enzymes crucial for normal cellular functions such as gluconeogenesis and anti-inflammation. As such, hydrocortisone is one of the most important hormones in the human body. Noncanonical pathways play less important roles, but these nongenomic effects have also been shown to contribute to various mechanisms of downregulating inflammatory markers [32].

At physiologic concentrations, endogenous glucocorticoids may have a role in promoting osteogenesis [33], while excess glucocorticoids increase osteoclastogenesis and suppress osteblastogenesis in cell culture, murine, and human models [7, 34]. Local metabolism of glucocorticoids in bone cells is controlled by a pair of complementary enzymes, 11β-hydroxysteroid dehydrogenase types 1 and 2 (11β-HSD1, 11β-HSD2), which respectively activate or deactivate glucocorticoid action by metabolizing the interconversion of biologically active or inert forms (Fig. 31.2) [35, 36]. Additional pathways of glucocorticoid action are thought to be multiple, including inducing proapoptotic molecules in osteoblasts and osteocytes and through antagonizing the osteoblastogenic Wnt pathway [34, 37, 38]. There continues to be active work into uncovering pathways of glucocorticoid mechanism at the cellular level [39], including suggestions of enhancing osteoblast activity through heat shock protein 90 [40].

Glucocorticoid therapy affects all three bone cell lines—osteoblasts, osteoclasts, and osteocytes (Fig. 31.3). The predominant action is by suppression of osteoblastic activity, resulting in inhibition of bone formation. Direct effects of glucocorticoids on bone formation are mediated largely through upregulation of peroxisome proliferator-activated receptor gamma receptor 2 (PPARγ2) [41] and effects on the Wnt/β-catenin signaling pathway [42, 43]. The former mechanism favors the differentiation of pluripotent precursor cells to adipocytes in preference to osteoblasts, resulting in decreased numbers of

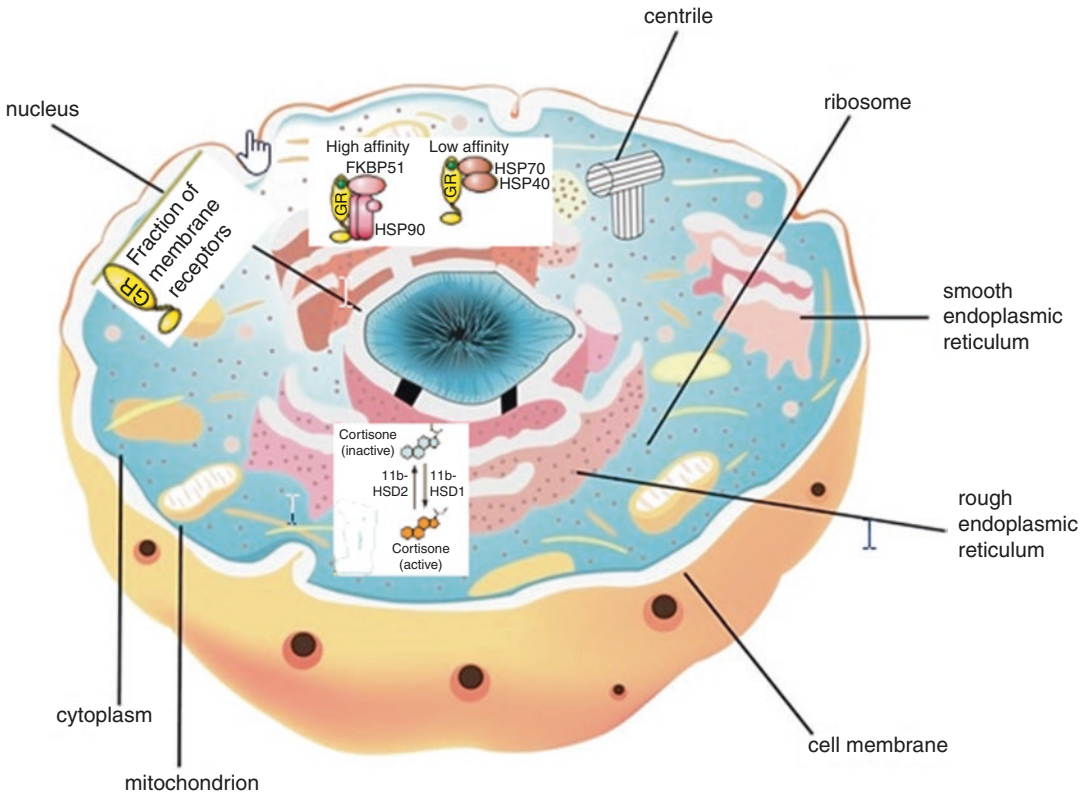

Fig. 31.1 Molecular effects of glucocorticoids excess on bones: GC's effects occur by four mechanisms: the classic genomic (the most important), which involves the cytosolic GC receptors (cGCR) and is divided into two processes, transrepression, and transactivation; nongenomic secondary, which is also initiated with cGCR; nongenomic executed by membrane receptors (mCGR); and nonspecific nongenomic, resulting from interactions with cell membranes (including the organelles). Glucocorticoids enter cells and become activated by 11β-HSD1 or occasionally deactivated by 11β-HSD2. The activated glucocorticoids bind to a cytoplasmic protein complex containing heat shock proteins and the glucocorticoids receptor. Complexes with Hsp70 and Hsp40 render the glucocorticoids receptor as a low-affinity receptor; however, complexes with Hsp90 give rise to a high ligand affinity of the glucocorticoids receptor. Upon ligand binding, the chaperone FKBP51 is exchanged for FKBP52, thereby allowing shuttling of the complex into the nucleus and into contact with the chromatin

osteoblasts. On another front, the expression of dickkopf-related protein and sclerostin and the inhibitors of WNT signaling pathway are upregulated. Increased expression of sclerostin, which binds to the co-receptors for frizzled, Lrp4 and Lrp5, results in inhibition of Wnt signaling pathway leading to reduced differentiation of osteoblast precursors to mature osteoblasts and increased osteoblast and osteocyte apoptosis. The importance of sclerostin in mediating the effects of glucocorticoids on bone formation is emphasized by the demonstration, in mice with sclerostin deficiency, that bone integrity is maintained in the presence of glucocorticoid excess [44]. Furthermore, in a mouse model of glucocorticoid-induced osteoporosis, treatment with an antibody to sclerostin prevented the reduction in bone mass and strength [45].

Role of Underlying Inflammation

In the general population, even mild elevations of C-reactive protein within the normal range increase nontraumatic fracture risk [46]. While some studies revealed that variations within the low levels of inflammatory markers and cytokines predict bone loss, other studies reported

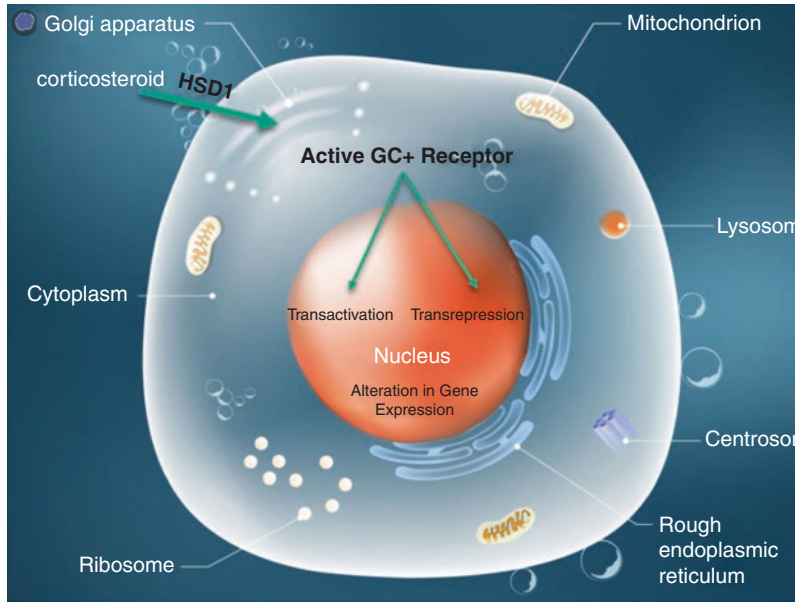

Fig. 31.2 As glucocorticoids enter cells it become activated by 11β-HSD1, thus inactive forms of corticosteroids (cortisone and prednisone) are converted into active forms (cortisol and prednisolone). 11β-HSD1 is also expressed in osteoblasts, which increase with age, which in turn favors the greater concentration of glucocorticoids in these cells. Increased expression of 11β-HSD1 enzyme is considered a risk factor for GC-induced osteoporosis. In its active form, the glucocorticoid binds with a receiver (GRα or GRβ), a member of the nuclear receptor super family, and migrates from the cytoplasm to the nucleus, where it can bind to glucocorticoid response elements (GREs), and to other transcription factors. The other side of the HSD system equation is composed of GC-inactivating enzyme and 11β-HSD2. The sensitivity of different types of glucocorticoids to this enzyme varies, and dexamethasone, by having a fluorine atom at the 9α position of the B ring, with site of HSD2 blocked, is the steroid which is most resistant to such inactivation, and therefore is what causes osteoporosis the most

that elevated inflammatory markers are prognostic for fractures [47, 48].

Independently, it was reported that rheumatoid arthritis (RA) doubles the risk of hip and vertebral fractures, regardless of the use of glucocorticoids, and disease activity is consistently associated with low BMD [49]. In a prospective study of patients with early RA conducted at a time when biotherapies were not available, high bone loss was observed, mainly in patients with persistent inflammation during follow-up (supported by persistent high CRP) [50]. In ankylosing spondylitis, an inflammatory disease in which glucocorticoids are not used, there is bone loss and an increased risk of vertebral fractures, driven by inflammation [51, 52].

There is a strong biological rationale for these clinical observations. Osteoclastogenesis is under the control of RANK-ligand, which is produced not only by osteocytes in normal bone remodeling but also by lymphocytes and fibroblasts in other situations, such as estrogen deficiency and inflammation [53]. Osteoclastogenesis can be enhanced by a number of cytokines, the main pathway being driven by T-helper 17 cells subpopulation (i.e., interleukin IL-6 and IL-23) [54–58]. Tumor necrosis factor α (TNF-α) transgenic mice are models of osteoporosis with dramatic decrease in bone mass and deterioration of bone microarchitecture. Moreover, an over expression of sclerostin has been observed in these models, with a consequence of inflammation-related decrease in bone formation [59]. Finally, autoimmunity has a role in bone remodeling, as antibodies against citrullinated proteins (ACPAs) can increase osteoclast numbers and activity through citrullinated vimentin located at the surface of precursors and cells (through a TNF-α local effect) [60].

All these clinical observations and biological studies show that inflammation has a deleterious effect on bone remodeling, inducing an increase in resorption and a decrease in formation, before any effect of glucocorticoids themselves.

Effect on the Bone

Direct Effect on the Bone

The predominant effect of glucocorticoids on bone is the impairment in bone formation, with an additional early but transient increase in bone resorption. The initial increase in remodeling rate is accompanied by reduced bone formation at the level of the individual bone multicellular unit (BMU), and this combination of increased bone turnover and a negative remodeling balance results in rapid bone loss [61–65]. Subsequently, the decrease in bone formation, both at tissue and BMU levels, predominates leading to a low turnover state. The evidence that this is a direct effect, independent of the inflammation effect, comes from studies conducted in healthy volunteers where prednisone 5 mg daily is enough to rapidly and significantly decrease serum P1NP and osteocalcin, which are specific markers of bone formation; the changes are reversed after discontinuation of the prednisone [66].

Glucocorticoids also have direct effects on bone resorption, increasing the production of macrophage colony stimulating factor (M-CSF) and RANKL and decreasing production of osteoprotegerin (OPG) by osteoblastic cells and osteocytes, resulting in an increase both in the number and activity of osteoclasts [67, 68]. As a consequence, a prolonged lifespan of osteoclasts is observed (contrasting with the decrease in the lifespan of osteoblasts). This effect diminishes with time, possibly as a result of the reduction in number of osteoblasts and osteocytes. Therefore, it can be said that much of the glucocorticoid-related bone loss is caused by the reduced bone formation, which persists throughout glucocorticoid administration. Finally, there is some evidence from animal models that glucocorticoids affect osteocyte morphology and mineralization [69].

Indirect Effects on Bone

Other mechanism that may contribute to glucocorticoid-induced bone loss is that occur through indirect effects on bone. The first mechanism is that attributed to the effects of glucocorticoids on calcium metabolism. Glucocorticoids cause decrease of gastrointestinal absorption of calcium and induction of renal calcium loss. A secondary hyperparathyroidism state has been suggested as a determinant of bone effects. However, there is no evidence for elevated endogenous levels of parathyroid hormone in these patients, and histological features are not those related to an increased parathyroid hormone secretion [70]. Glucocorticoids also reduce production of sex steroid hormones inducing a state of hypogonadism. In addition, the bone loss has been linked to reduced physical activity and reduced production of growth hormone, insulin-like growth factor 1 (IGF1), and IGF1-binding protein (IGF-BP) [71]. Furthermore, as mentioned earlier, the underlying diseases for which glucocorticoid therapy is administered are often associated with increased inflammation, which contributes to bone loss through increased production of pro-inflammatory, pro-resorptive cytokines. While glucocorticoids suppress inflammation and hence should mitigate the adverse effects of inflammation, disease relapse despite therapy is associated with episodes of increased bone resorption.

Effect on the Muscles

The clinical side effects of steroid medications on bone and muscle have been the subject of numerous reviews and textbook descriptions. Glucocorticoids are known to regulate protein metabolism in skeletal muscle, producing a catabolic effect, which is opposite to that of insulin. In many catabolic diseases, such as sepsis, starvation, and cancer cachexia, endogenous gluco-

corticoids are elevated contributing to the loss of muscle mass and function.

Similar to bone, skeletal muscle homeostasis is disrupted by glucocorticoids. Glucocorticoids not only decrease muscle anabolism by inhibiting amino acid transport into muscle [72] but also increase muscle catabolism by altering three major pathways: the myostatin signaling pathway, the IGF-1–PI3K–Akt pathway, and the NF-κB pathway [73]. The result is a shift in net skeletal muscle protein balance toward proteolysis. There is also evidence that glucocorticoids inhibit muscle regeneration by interfering with myogenic differentiation [74] and/or immune responses that detect injury and trigger repair [73]. Furthermore, Schakman et al. demonstrated that glucocorticoids, but not IGF-I or TNF-α–NF-κB, play a key role in inducing proteolysis in acute inflammatory states via the autophagy and the ubiquitin–proteasome pathways [75]. Patients at risk include elderly patients, those with poor nutritional intake and those not participating in exercise that could counterbalance the negative metabolic effects of glucocorticoids [76].

In addition, glucocorticoids are associated with glucocorticoid-induced myopathy and critical illness myopathy (CIM). Glucocorticoid-induced myopathy is typically associated with the use of glucocorticoids in high doses, and, in particular, fluorinated glucocorticoid preparations. Patients develop insidious pain-free proximal muscle weakness that primarily affects the lower extremities several weeks or years into glucocorticoid therapy. Throughout its course, serum muscle enzyme levels generally remain in the normal range or mildly elevated [15, 77]. On histopathology, glucocorticoid-induced myopathy is characterized by preferential loss and atrophy of type II muscle fibers [78]. Muscle weakness usually begins to ameliorate within 3–4 weeks after glucocorticoid cessation but may last for up to 6 weeks.

On the other hand, critical illness myopathy (CIM) has been linked to treatment with high doses of glucocorticoids and neuromuscular blocking agents. Other risk factors such as renal failure, hyperglycemia, and increased severity of the underlying disease are also important [79]. It has been estimated that at least a third of the intensive care unit patients treated for status asthmaticus develop critical illness myopathy (CIM) [80]. Patients typically present with acute-onset, diffuse, flaccid muscle weakness that generally affects all limb muscles, neck flexors, and often the diaphragm and facial muscles [79]. Serum creatinine kinase levels generally increase 10- to 100-fold higher than normal, peaking at day 3–4 and normalizing after 10 days [81]. The diagnosis is made on the basis of distinctive electrophysiological activity and muscle/nerve biopsies analyses. Electrodiagnostic testing reveals low amplitude, short duration and polyphasic motor unit potentials, low amplitude compound action potentials, and fibrillation and sharp wave potentials [82]. On histopathology, critical illness myopathy (CIM) is characterized by varying degrees of muscle fiber necrosis and regeneration, no lymphocytic inflammation, preferential atrophy of type II fibers, and loss of thick myosin filaments [83].

Clinical Correlations of Glucocorticoid-Induced Osteoporosis

Owing to a much lower mechanical bone strength than would appear to be the case from observing BMD and a significant increase in fracture risk associated with the use of glucocorticoids, patients taking steroids should be assessed with care, and consideration should be given to several factors that make glucocorticoid-induced osteoporosis (GIO) a unique form of bone loss (Fig. 31.4). These factors can be summarized as follows:

GIO vs postmenopausal osteoporosis: The primary difference between GIO and postmenopausal osteoporosis is the suppression of osteoblastic activity, leading to decreased bone formation. In GIO, following an early phase consists of rapid loss of bone mineral density due mostly to excessive bone resorption and impaired bone formation usually manifests and is more progressive with long-term therapy. Trabecular

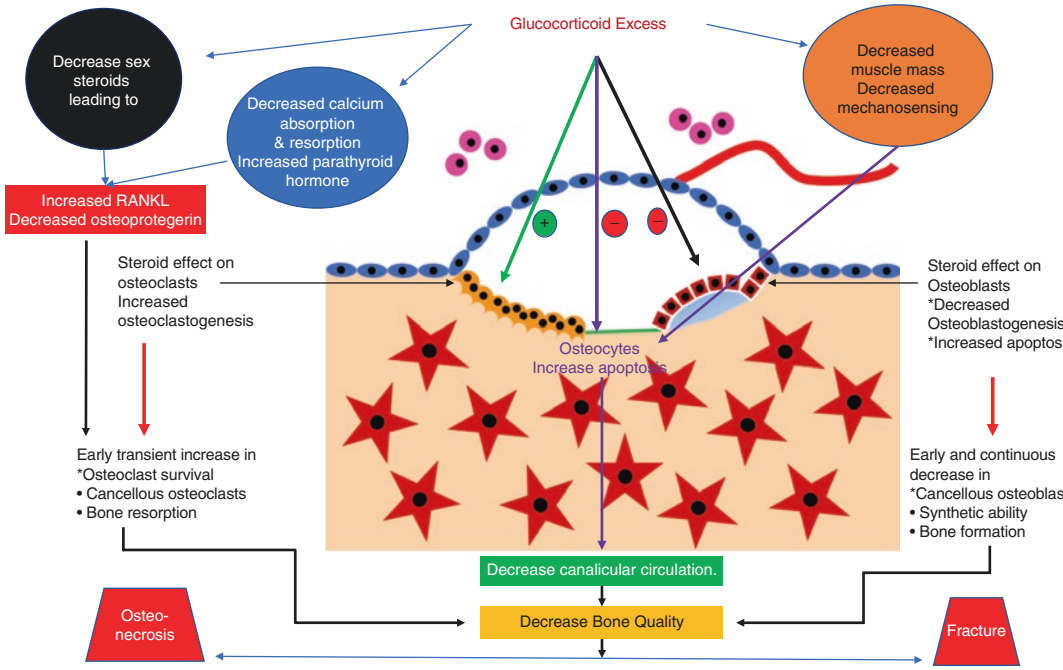

Fig. 31.3 Pathophysiology of glucocorticoid-induced osteoporosis: Excessive amounts of systemic glucocorticoids lead to clinically significant adverse effects on the musculoskeletal system by inducing a state of inappropriate bone remodeling through direct and indirect mechanisms and muscle atrophy that contributes to osteoporosis and fractures. Early bone loss is driven by changes in hormone levels mainly estrogen and parathyroid hormone which stimulate receptor activator of nuclear factor-κB ligand (RANKL)–induced osteoclastogenesis. Osteocyte and osteoblast apoptosis prevents effective mechanosensing and new bone formation

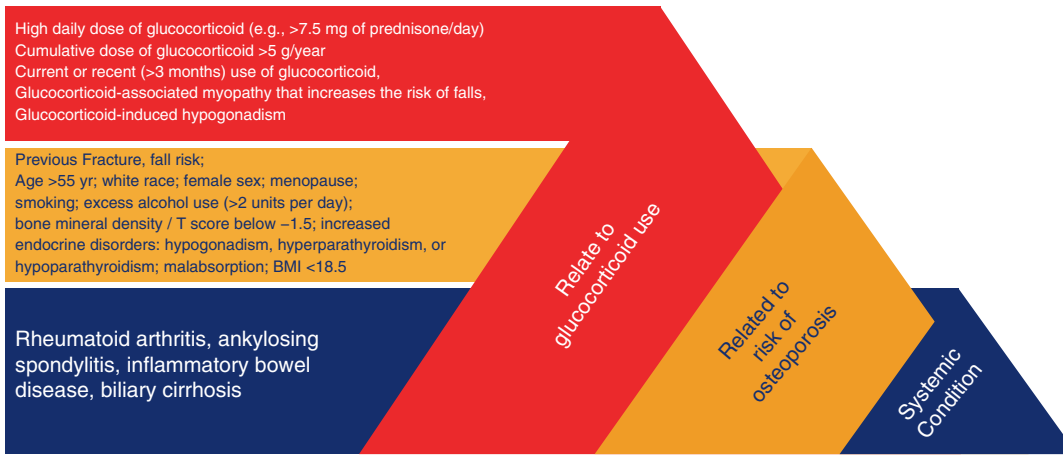

Fig. 31.4 Risk Factors for fractures in patients receiving glucocorticoids: Patients taking steroids should be assessed with care, and consideration should be given to several factors that make glucocorticoid-induced osteoporosis (GIO) a unique form of bone loss

bone loss predominates, with most marked changes not only in the lumbar spine but also in the femoral neck and other sites. The effect on bone is dose dependent, with relative risk significantly increased at daily doses higher than 2.5 mg prednisolone equivalent [25]. It is also dependent on duration, with fracture risk returning to baseline months after cessation of therapy. However, changes to bone can occur sooner than many physicians realize. One study found that a 40 mg or higher prednisone equivalent a day can result in substantial BMD loss at the lumbar spine in just 2 months [84]. Meta-analyses indicate that exposure to steroid use is associated with a relative risk of fracture of about 1.6–1.98 and is independent of gender [26, 85].

Fractures most often occur at sites enriched with trabecular (cancellous) bone, such as the lumbar spine and femoral neck. Vertebral fractures may be asymptomatic and detected only by radiographic imaging. While much of the knowledge of GIO is extrapolated from experience with postmenopausal osteoporosis, it is important to note that fractures tend to occur at higher bone mineral density in glucocorticoid-induced osteoporosis [86].

Phases of bone loss associated with glucocorticoids: GC-induced bone loss has a rapid with, as mentioned earlier, early phase of excessive bone resorption and, a slower, later phase marked by inadequate bone formation [42, 87, 88].Within the first few days of treatment, glucocorticoids transiently increase osteoclast numbers due to an antiapoptotic effect on mature osteoclasts, which probably results in early loss of bone [87]. Bone resorption may also be stimulated by higher doses of glucocorticoids [89]. In the second phase, chronic glucocorticoids excess suppresses remodeling by downregulating osteoblastogenesis and osteoclastogenesis and is characterized by depressed bone formation and turnover [88]. Studies have demonstrated that bone resorption decreases after 4 weeks of prednisolone administration to normal or below normal levels [90]. The decrease in bone formation and turnover in GIO is in contrast to the increase in bone resorption, and turnover that characterizes osteoporosis caused by a loss of sex steroids (i.e., in postmenopausal women).

The risk of fracture rapidly decreases when glucocorticoids are discontinued. A prospective study showed clinically significant improvement in bone mineral density at the lumbar spine within 6 months after discontinuation of glucocorticoids [91]. A large retrospective study showed an increased risk of a major osteoporotic fracture among patients with recent prolonged glucocorticoid use but not among those with intermittent or past use of these agents [92].

Differential sensitivity to glucocorticoid: There is great variability of glucocorticoid linked side effects among individuals, including bone loss, for largely unknown reasons. Attention has been paid to the 11 β-hydroxysteroid dehydrogenase (11β-HSD) system, which is a pre-receptor modulator of glucocorticoid action. This system catalyzes the interconversion of active/inactive cortisone, and the 11β-HSD enzyme amplifies glucocorticoid signaling in osteoblasts. Interestingly, 11β-HSD, widely expressed in glucocorticoid target tissues including bone, can be modulated and amplified by pro-inflammatory cytokines [93, 94], age, and glucocorticoid administration itself, suggesting that the mechanism could be a key regulator of the effects of glucocorticoids on bone. Individual glucocorticoid sensitivity can also be regulated by polymorphisms in the glucocorticoid receptor gene [95].

Time effect: The increase in GIO and its consequent fracture risk is immediate, as early as 3 months after the initiation of therapy and reverses sharply after discontinuation of glucocorticoids. This cannot be explained by BMD changes, but can be related to the added effects of glucocorticoids on bone remodeling previously uncoupled by the inflammation itself, and the dramatic effect on bone strength through induced apoptosis of osteocytes. Data also suggest a rapid increase in rate of falls after start of oral glucocorticoids [25]. Thus, primary prevention, after

careful assessment of the fracture risk, is recommended in high-risk patients.

Dose effect: In epidemiological studies, the increased risk of fractures is observed even at low doses of prednisone, that is, 2.5–5 mg per day. The appropriate care of patients receiving such low doses has been advised in recent guidelines, which will be discussed later in this chapter. There is a dose-dependent increase in fracture incidence. Interestingly, the fracture risk is related to the current daily dose, more than to the cumulative dose [96]; this may be attributed to the difficulty of an accurate calculation of this cumulative dose.

Prior versus current glucocorticoids use: Ever use of glucocorticoids is associated with an increased risk of hip fracture, and this justifies the assessment of osteoporosis and fracture risk in all patients. However, the risk is mainly associated with recent and prolonged glucocorticoid use, more than to remote or short courses [97].

Role of underlying disease: Persistent inflammation is associated with bone loss as shown in longitudinal studies in patients with active RA or ankylosing spondylitis (SpA). In contrast, prospective open studies show that complete control of inflammation (in parallel with clinical improvement and thus increased mobility) is accompanied by the absence of bone loss [98]. This is not only expected in spondyloarthritis in the absence of glucocorticoids but is also observed in RA of the hand, spine, and hip and in patients receiving low doses of glucocorticoids [98–100]. In the BeSt study, conducted in patients with recent-onset active RA, bone loss was limited in all treated groups, including in the group initially treated with high-dose prednisone [101]. Thus, the concept that a high level of inflammation is more deleterious for bone than a low dose of glucocorticoids, controlling this inflammation is relevant as far as surrogate markers (BMD, biological parameters) are concerned. However, there is no evidence for a reduction in fracture risk with such a strategy [102], and further epidemiological studies are important in this aspect.

Role of patient characteristics: Age, female gender, low BMI, history of falls and previous fractures, duration of menopause, and smoking are associated with fracture risk in patients with glucocorticoids, similarly to how they are in primary osteoporosis. It has been reported that the prevalence of non-vertebral fractures is a strong determinant of the risk of having vertebral fractures in patients with RA [103], implying that the individual's skeleton is already of inadequate strength to withstand the trauma of daily living. Beyond glucocorticoids use, these risk factors must be assessed in all patients, and all causes of secondary osteoporosis are added risk factors of fractures in patients on glucocorticoids therapy [104].

Glucocorticoids Pharmacologic Preparation

Most common forms of administered glucocorticoids are oral preparations. Intravenous, inhaled, injected, and transdermal preparations are also frequently encountered. However, side effects, including to bone, are not limited to oral or intravenous administrations. Injected glucocorticoids, particularly when repeated, and topical therapy may both lead to systemic effects.

Systemic (Tablets/Injections): Glucocorticoids are transported in the bloodstream bound to corticosteroid-binding globulin and albumin, in equilibrium with the biologically active free form that binds to the glucocorticoid receptor. Individual sensitivity to glucocorticoid signaling is also affected by genetic variability of the glucocorticoid receptor, with alternative splicing and polymorphisms identified [105, 106]. Furthermore, pharmaceutical preparations have differences in absorption, transport, and target affinity, and thus a varied range of potencies and duration of effects. Glucocorticoid potency ranges from lower potency such as with cortisone and prednisone, to higher potency, such as with dexamethasone and betamethasone. In general, when oral cortisol (hydrocortisone) is used as a baseline, prednisone and prednisolone have about

four times the potency, while methylprednisolone and triamcinolone are about five times the potency, and dexamethasone and betamethasone are about 25 times the potency.

Inhaled glucocorticoids: For almost two decades, inhaled glucocorticoids have been used widely in the management of chronic lung disease, mainly asthma [107]. However, the effect of inhaled glucocorticoids on bone and whether their use leads to GIO is somewhat controversial. In a meta-analysis by Richy and colleagues, inhaled glucocorticoids were associated with a 1.2–1.8-times increased risk of vertebral fracture and a 1.6-times increased risk of hip fracture [108]. This meta-analysis also demonstrated that inhaled glucocorticoids were associated with lower bone density at the spine and hip and lower levels of bone formation markers (osteocalcin and procollagen type 1 C-terminal propeptide). Vestergaard and colleagues found an increased risk of any fracture (adjusted for comorbid diseases, but not respiratory severity) associated with inhaled glucocorticoids only for daily dosages above 7.5 mg of prednisolone equivalents (equivalent to 1875 μg of budesonide/day) [109].

Fujita and colleagues examined lumbar BMD (and biochemical markers) in inhaled glucocorticoids users with no oral glucocorticoids for at least 1 year and found significant lower BMD and serum osteocalcin among the inhaled glucocorticoids users versus controls in the postmenopausal group only [110]. Wong and colleagues found a negative relationship between total cumulative dose of inhaled glucocorticoids and BMD in asthma patients [111].

Risk Stratification, Screening, and Assessment

Management of patients who start/remain on glucocorticoids is based on risk assessment and prevention of osteoporosis. The rate of screening for bone disease traditionally varies according to the medical specialty of the provider prescribing the chronic glucocorticoid therapy [112], though it can be said that awareness has increased in recent years [113]. There are several recommendations for identifying high risk of fracture in patients on glucocorticoids (Table 31.1). Screening for fracture risk should be performed soon after the initiation of glucocorticoid treatment. Currently, tools to estimate the risk of fracture among patients who are younger than 40 years of age are lacking. The risk of fracture increases, and the time to fracture decreases considerably with increasing age among patients who receive glucocorticoids [114]. The risk of fracture among patients of ages ≥40 can be estimated with the use of bone mineral density (BMD) testing and the fracture risk assessment tool (FRAX). Table 31.1 summarizes the main clinical risk factors for glucocorticoid-induced osteoporosis (GIO).

Table 31.1 Risk factors for glucocorticoid-induced osteoporosis

Clinical risk factors for glucocorticoid-induced osteoporosis
High fracture risk (FRAX score)
Imminent fracture risk (fracture in the last 2 years)
Previous vertebral fracture or low trauma appendicular fracture
Postmenopausal woman
Premature menopause at <45 year or male hypogonadism
Age >65 year
Planned or current glucocroticoids use of >6 months
Low BMI: <20 kg/m^2
Family history of hip fracture
Other systemic risk factors of osteoporosis, e.g., alcohol excess, RA, hyperparathyroidism, and thyrotoxicosis

The 2017 ACR guidelines [115] allow clinicians to evaluate fracture risk in adult glucocorticoid users of all ages. Under these guidelines, adults <40 years of age are classified as low risk unless they have prevalent fragility fracture, or are high-dose steroid users with extremely low BMD or rapid BMD loss. This risk stratification algorithm flags high-risk young adults for more aggressive care, while exempting most young people from monitoring and treatment of little benefit to them. However, it does not account for clinical GIO risk factors such as malnutrition, low body weight, thyroid and parathyroid dis-

ease, family history of hip fracture, and alcohol and tobacco use. These are common comorbidities among young patients with inflammatory conditions like inflammatory bowel disease and rheumatoid arthritis, and substantially impact individual fracture risk. Adults ≥40 years of age are risk stratified using FRAX scores, an established method that incorporates clinical GIO risk factors. However, this method has specific limitations when applied to glucocorticoid users. FRAX equations do not adequately adjust for high-dose or prolonged glucocorticoid exposure, cannot assess the BMD-independent effects of glucocorticoids on bone [26], and rely on hip BMD when glucocorticoids cause disproportionate loss of trabecular BMD, best measured at the spine.

The guideline authors address these issues by recommending annual fracture risk assessment for all patients that evaluates glucocorticoid dose, duration, and exposure pattern, screens for fall risk, frailty, and the clinical risk factors as described and assesses body mass index, muscle strength, and signs of occult fracture. The authors recommend that patients with concerning findings on this assessment undergo serial BMD testing regardless of their original fracture risk classification. The guidelines also endorse the Fracture Risk Calculator, an alternative to FRAX that incorporates spine BMD, for patients with discordant hip and spine BMD measurements (available at: https://riskcalculator.fore.org/).

Glucocorticoid-Induced Changes in BMD and Bone Microarchitecture

In postmenopausal osteoporosis, the risk of osteoporotic fractures has been shown to be doubled for each standard deviation decrease in BMD [116], but this may underestimate the fracture risk for patients treated with glucocorticoids. In glucocorticoid-treated asthmatic patients with vertebral fractures, Luengo et al. [117] found that BMD was higher compared with a group with postmenopausal osteoporosis and fractures. Similarly, Peel et al. [118] found that steroid-treated patients with RA had a 6.2-fold increased risk of vertebral fractures with only a 0.8–1.5 S.D. decrease in lumbar spine BMD. Therefore, in addition to BMD, the decision to start treatment may also depend on assessment of clinical risk factors.

Increased rates of bone loss in the hip, spine, and radius are well documented in individuals treated with glucocorticoids. Earlier studies revealed that the BMD loss is an immediate consequence of the introduction of glucocorticoids therapy and affects the trabecular bone (i.e., spine) more than it does the cortical bone (i.e., femur). According to a meta-analysis of 56 cross-sectional studies and 10 longitudinal studies, bone loss assessed by dual-energy X-ray absorptiometry can be 5–15% during the first year of treatment [24]. The main determinant of BMD at any time is the cumulative dose. The increased rate of bone loss persists in chronic glucocorticoids users, but at slower rate.

Data obtained from assessment of bone microarchitecture using high-resolution peripheral computed tomography (HRpQCT) are sparse. In a cross-sectional study of 30 postmenopausal women who had received oral glucocorticoids for longer than 3 months, despite similar areal BMD values to 60 control subjects, significantly lower total, cortical, and trabecular volumetric BMD, thinner cortices, increased trabecular separation, and reduced trabecular number were reported in the radius and tibia; whole bone stiffness, assessed using finite element analysis, was also significantly reduced in comparison with the controls [119]. Although the patients and controls were generally well matched, however, bisphosphonate use was significantly more common in the former (100% vs. 8.6%), so definite attribution of the observed differences to glucocorticoid therapy cannot be made.

Trabecular bone score (TBS) provides an indirect index of trabecular bone architecture that can be obtained from DXA images of the lumbar spine and has predictive value for fracture independent of BMD [120]. In 64 postmenopausal women who had taken prednisolone in a dose of ≥5 mg daily for >3 months, TBS was significantly lower than in a group of non-glucocorticoid-treated controls, although lumbar

spine BMD T-scores were not significantly different [121]. Similar findings have been reported in 416 individuals on long-term glucocorticoids (≥5 mg daily for 3 months), the decrease in TBS being most marked in men and in individuals with fracture [122]. These findings indicate that glucocorticoids have adverse effects on spine bone microarchitecture that are independent of BMD and which may contribute to increased fracture risk.

Monitoring BMD Changes/ Response to Therapy

It is recommended for all adults >40 years of age, and for adults <40 years of age with prevalent osteoporotic fracture or other osteoporosis risk factors, to arrange for BMD testing at the start of glucocorticoid treatment. For adults >40 years of age, serial BMD monitoring is recommended every 1–3 years for those not on anti-osteoporotic treatment, and every 2–3 years during treatment for those taking "very high dose glucocorticoids" (>30 mg/day prednisone equivalent with >5 g annual cumulative exposure), poor medication response, adherence or absorption, or other risk factors for bone loss. BMD assessment should be carried out every 2–3 years after completing treatment. For adults <40 years of age, BMD monitoring every 2–3 years regardless of treatment is recommended for those with a moderate to high fracture risk, very high dose glucocorticoid exposure, or other risk factors [123].

Fracture Risk Assessment in Individuals Treated with Steroids

The WHO fracture risk assessment tool (FRAX) (http://www.shef.ac.uk/FRAX) algorithm has been developed to estimate the 10-year risk of hip and other major fractures (clinical spine, humerus, or wrist fracture) based on clinical risk factors, with or without BMD. The risk factors included in FRAX are: age, sex, body mass index (BMI), personal history of fracture, parental history of hip fracture, current smoking, alcohol intake, glucocorticoid use, rheumatoid arthritis, and other causes of secondary osteoporosis and femoral neck (not spine) BMD. These clinical risk factors are largely independent of BMD and can thus improve the fracture risk assessment. FRAX cannot be used in premenopausal women, men aged <40 years and in subjects previously treated with anti-osteoporotic drugs.

One of the limitations of FRAX is that use of oral GCs is recorded as a dichotomous risk factor and does not take into account the dose of glucocorticoid and the duration of use. Moreover, FRAX does not take into account the difference in risk between prior and current use [97]. FRAX assumes an average dose of prednisolone (2.5–7.5 mg/day or its equivalent) and may underestimate fracture risk in patients taking higher doses and may overestimate risk in those taking lower doses. Moreover, the predictive value of FRAX has been mainly validated for non-vertebral fractures although the principal risk in glucocorticoids users is for vertebral fractures. Adjustment of FRAX has been proposed for postmenopausal women and men aged ≥50 years with lower or higher doses than 2.5–7.5 mg/day: a factor of 0.8 for low-dose exposure and 1.15 for high-dose exposure for major osteoporotic fractures and 0.65 and 1.20 for hip fracture probability [124]. For very high doses of glucocorticoids, greater upward adjustment of fracture probability may be required. Moderate risk was defined as a 10-yearr major osteoporosis fracture risk of 10–19% and a hip fracture risk of 1.1–2.9%, with both doses adjusted. Pharmacologic therapy was suggested for these two groups. Low-risk patients were defined to have a major osteoporosis fracture risk of <10% and a hip fracture risk of ≤1% in 10 years. These patients can be treated conservatively with adequate dietary calcium and vitamin D, with supplements of the latter if necessary.

Using data from the UK General Research Practice Database, Kanis et al. [125] have provided adjustments that can be incorporated into the FRAX calculations to adjust for different doses of glucocorticoids (Table 31.2). For daily doses of over 7.5 mg daily of prednisolone or

Table 31.2 Adjustment of FRAX-derived 10-year probability of osteoporosis fracture according to dose of glucocorticoids. Data from reference [128]

Daily dose of prednisolone (mg)	Average adjustment for 10-year probability of major osteoporotic fracture	Average adjustment for 10-year Probability of hip fracture
<2.5	−20%	−35%
2.5–7.5	No change	No change
≥7.5[a]	+15%	+20%

[a]Greater upward adjustment of fracture risk, may be appropriate, for high doses of prednisolone

equivalent, greater upward adjustment of fracture probability may be required. It should be noted that the duration of glucocorticoid therapy and cumulative dose are not accommodated within the FRAX algorithm. In addition, the use of total hip BMD in FRAX may result in underestimation of fracture risk in patients with differentially low spine BMD, although a correction for this discordance has been proposed [40, 41, 126, 127]. A final caveat is that the response to treatment in glucocorticoid-treated individuals selected on the basis of FRAX-derived fracture probability has not been documented.

FRAX assessment has already been included in some guidelines at different steps of the treatment decision. The American College of Rheumatology (ACR) has created guidelines addressing management of GIO, last updated in 2017 [115]. Adult patients are risk stratified by age and their fracture risk as well as the steroid therapy dose. In concordance, the International Osteoporosis Foundation (IOF)–European Calcified Tissue Society [129] recommendations advised that a treatment decision for postmenopausal women and for men aged ≥50 years exposed to oral glucocorticoids for ≥3 months should be based on fracture risk assessment with FRAX adjusted for glucocorticoid use (with or without BMD testing). Treatment can be considered directly (without FRAX assessment) if patients are at high risk defined by one of the following criteria: prevalent fracture, age ≥70 years, and exposure to a glucocorticoid dose ≥7.5 mg per day or low BMD (T ≤ −2.5).

Glucocorticoid-Induced Osteoporosis in Children and Adolescents

Children represent a different approach as bone development is still critical. In children, weight gain, growth retardation, and Cushingoid features are the most frequent adverse reaction to chronic oral glucocorticoid use, but a recent meta-analysis that included a total of 6817 children noted a 21% incidence of decreased bone mineral density [130]. Growth retardation, whether directly or through suppression of the hypothalamic–pituitary axis or of sex steroid hormone production, puts children at considerable risk of osteoporosis in adulthood, as peak bone mass is achieved in late adolescence and early adulthood. While there are few prospective randomized controlled trials, there is general consensus for ensuring adequate calcium and vitamin D intake and for avoidance of further pharmacologic means such as bisphosphonates. Bisphosphonate use should only be considered, very carefully, for children who have an osteoporotic fracture who are still continuing long-term glucocorticoid use.

For inhaled steroid use in children, commonly prescribed for asthma, most studies have not reported significant effects of inhaled steroid on bone markers [131–133], although a few have identified decreased BMD with high dose inhaled corticosteroids [134]. On the other hand, a point of argument has been raised, as better control of asthma leads to greater physical activity, which is beneficial to bone development. It is now well-accepted that no bone-specific monitoring or pharmacologic treatment is needed in intermittent or routine inhaled corticosteroid use for asthma, though "periodic" evaluations of bone density may be advised in long-term, high-dose therapies [135].

Management of Glucocorticoid-Induced Osteoporosis

In a study of a large managed care population in the United States, Saag and colleagues [136] found low rates of preventative interventions in

individuals on long-term glucocorticoid therapy. Postmenopausal women were the most likely to receive recommended interventions, yet only approximately 50% were treated with anti-osteoporotic medication. In total, 19% of postmenopausal women underwent bone mass measurements. This number dropped to <6% in women under 50 years of age as well as in men. The study also found that rheumatologists were three to four times more likely to initiate the above interventions than internists or family practitioners. Interventions carried out aiming at improving physician management of GIO have largely been unsuccessful. When physicians were randomized to receive a web-based GIO intervention (including a personalized performance-audit and feedback) versus control intervention, there was no significant increase in BMD testing (19% versus 21%) or prescription of antiosteoporotic medications (32% versus 29%) in the year following the intervention [137].

There is a mismatch between BMD data and fracture data in patients receiving glucocorticoids because of the disparity related to the alteration of bone quality. At similar levels of BMD, postmenopausal women taking glucocorticoids have considerably higher risk of fracture than controls not using glucocorticoids [96]. There is a debate on the appropriate T-score threshold to be considered a risk and as an indication for treatment in patients with glucocorticoids: the same diagnostic criterion as in postmenopausal women has been suggested ($T \leq -2.5$), but a higher threshold (i.e., $T \leq -1.5$) has been proposed for intervention, because bone loss can be 10% or more in some individuals over the first year of glucocorticoids use [138].

There is no means to provide an evidence-based threshold for treatment decisions. A practical approach is to recommend a BMD measurement in glucocorticoids users (optimally at the initiation of treatment) and to consider that patients with $T \leq -2.5$ as those who should receive the highest priority for treatment [139]. However, beyond the BMD, a more comprehensive approach of the risk and clinical judgment is recommended. This will be discussed in further details later in this chapter.

Management of steroid-induced osteoporosis can be stratified into general measures and pharmacological measures.

General Measures

At the initiation of glucocorticoid treatment, clinical assessment should be carried out to assess for: measurement of the patient's height, as height loss in the follow-up could be related to asymptomatic vertebral fractures. Biological tests are performed to screen for other causes of bone diseases. There is no indication for assessment of biochemical markers of bone remodeling either at baseline or during follow-up, as bone turnover is not reliable for interpretation on individual basis among and is consistently low in glucocorticoid users [104].

A number of life-style measures may mitigate the harmful skeletal effects of glucocorticoids, although the evidence base for this approach is weak and requires extrapolation from studies in non-glucocorticoid-treated individuals. The risk of falling should be assessed in particular in elderly patients, patients with painful joints of the lower limbs, and patients with massive doses of glucocorticoids. Fall risk should be assessed at baseline and preventive measures instituted wherever appropriate. Exercise, tailored to the individual patient, and good nutrition with adequate dietary calcium intake should be advocated with avoidance of smoking and alcohol abuse. Maintenance of an adequate vitamin D status should also be advised.

As the daily dose of glucocorticoids is a determinant of fracture risk, attention should be paid to keep the dose of glucocorticoids to a minimum. This must be constantly reviewed by considering both the reduction of the dose to the minimally active, considering alternative administration such as intra-articular injections., or the use of steroid-sparing drugs such as methotrexate or azathioprine or alternative routes of administration (e.g., inhaled or topical) where appropriate. Topical therapy (such as inhaled glucocorticoids or glucocorticoid enemas for asthma or bowel disease, respectively) is pre-

ferred over enteral or parenteral glucocorticoids whenever possible. Nonsteroidal therapies should be used when possible to maintain remission, once achieved. However, it is also important to maintain suppression of the underlying disease, since this will prevent the adverse skeletal effects of inflammation and other effects of increased disease activity.

Nutrition/Calcium and Vitamin D Supplementation

Attention to nutrition must be paid to prevent protein and calcium intake deficiencies. Calcium and vitamin D have been used for decades in GIO, although there are controversies about their effect on BMD. In 66 patients with RA receiving prednisone, 1000 mg/day of calcium carbonate and 500 IU/day of vitamin D3 induced a positive change of 0.63% per year at the lumbar spine, versus a decrease of 1.31% per year in the placebo group; there was no effect at the femoral neck [140]. No benefit was observed in another study with a 3-year follow-up [141].

However, it is reasonable to consider that any deficiency in calcium and vitamin D could be deleterious in patients beginning or receiving glucocorticoids. For calcium, the recommendation is to have an intake of 1000–1500 mg/day, and supplementation should be prescribed only to patients whose dietary intake does not provide this adequate quantity. Glucocorticoid-treated patients may seldom be outdoors and thus exposed more than the general population to vitamin D deficiency. Vitamin D Supplementation is considered adequate in the range of 800–2000 IU per day. There is no evidence of an advantage using calcitriol or alfacalcidol, as there is a large variability of outcomes with these vitamin D metabolites over plain vitamin D [104].

Pharmacologic

Anti-resorptives and teriparatide have been assessed in prevention and treatment of GIO (Fig. 31.5). There are a number of issues regarding their efficacy. In contrast to BMD, which was considered as the main end point, fracture inci-

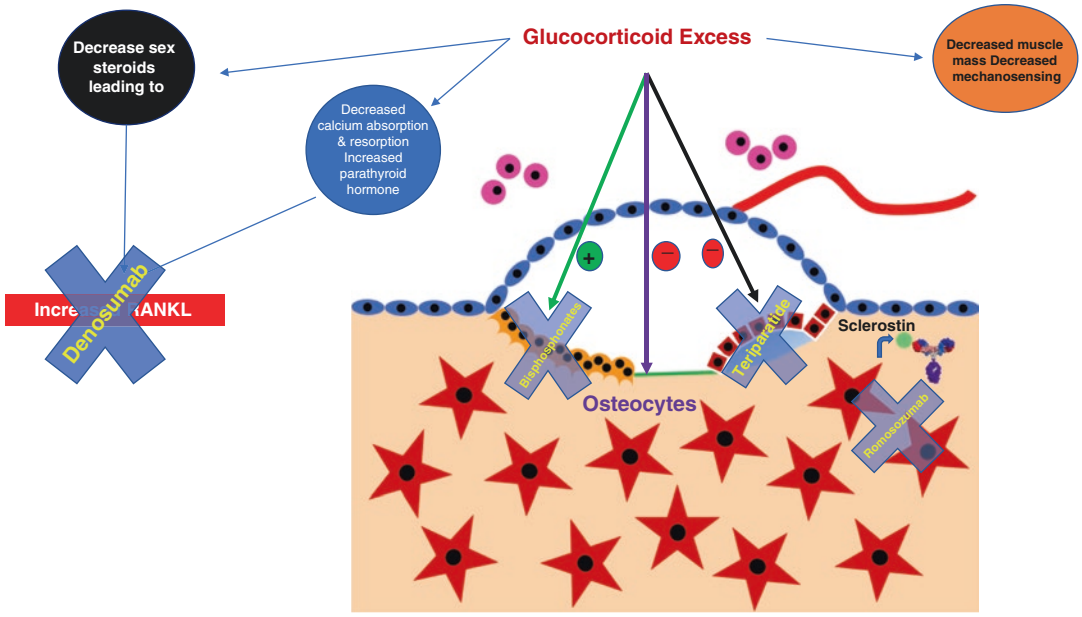

Fig. 31.5 Management of glucocorticoid-induced osteoporosis: counteracting the negative impact of glucocorticoids on the bone: Mechanism of action of the antiresorptive (bisphosphonates and denosumab) or anabolic agents (teriparatide, abaloparatide, and romosozumab) on bone

dence has not been a primary end point of any study. Furthermore, the duration of the studies tends to be short (1 year on average), and the number of men and premenopausal women in these studies is low. Thus, the efficacy on fracture(s) prevention in patients treated with glucocorticoids is mainly based on bridging data between the short-term change in BMD, and the long-term change in BMD and reduction of fracture risk in postmenopausal patients diagnosed with osteoporosis.

In addition, there is inevitable heterogeneity in glucocorticoid-treated trial populations, with respect to age, underlying disease, comorbidities and co-medications, dose and duration of glucocorticoid therapy, and the timing of bone protective therapy. Furthermore, the duration of most treatment studies has been relatively short and this, combined with smaller trial populations, reduces the strength of the safety database [142].

Antiresorptive Agents

Bisphosphonates

Bisphosphonates are the most popular anti-osteoporotic medication. Alendronate (oral 5 or 10 mg once daily, or 70 mg once weekly), risedronate (oral 5 mg daily or 35 mg one weekly), and zoledronate (intravenous infusion 5 mg once yearly) are all approved for this indication. All have been shown to have beneficial effects on lumbar spine and hip BMD in people treated with glucocorticoids [143–150], and for alendronate and risedronate, there is also evidence from post hoc analyses for a reduction in the rate of vertebral fractures [148, 149].

Alendronate was assessed in a placebo-controlled study in 477 men and women over 48 weeks. There was a 2.1% and 2.9% increase at the lumbar spine in the 5 and 10 mg alendronate groups, respectively, and a 0.4% decrease in the placebo group. At the femoral neck the changes were +1, +1.2, and −1.2%, respectively. Interestingly the decrease of BMD in the placebo group (receiving calcium and vitamin D) was driven by the duration of glucocorticoids: −2.9, −1.4, +0.8 in patients receiving GCs for less than 4 months, 4–12 months, and more than 12 months, respectively [151]. In a follow-up study in a second year, performed in 208 out of the 477 patients, there were fewer patients with new vertebral fractures in the treated group (0.7%) than in the placebo group (6.8%) [152].

Two 1-year studies were performed with risedronate, one for prevention in patients beginning glucocorticoids and one for treatment of GIO in patients chronically treated with glucocorticoids. Data from pooling these two studies suggest a reduction of fractures in the first year of therapy: 16% of placebo patients and 5% of those on risedronate 5 mg/day [153–155].

In a comparative double blind randomized study, zoledronic acid (1 injection) induced a higher BMD increase than risedronate (daily) in treatment (+4.06 vs +2.71%) and prevention (+2.6 vs 0.6%) subgroups over 1 year at the lumbar spine [156].

The number of non-vertebral and hip fractures has been insufficient in individual trials to assess an impact of bisphosphonates. However, data from cohort studies provide some evidence for efficacy at these sites. In an observational cohort study of women aged >65 years taking alendronate or risedronate, Thomas et al. [157] studied the baseline incidence of clinical fractures in the first 3 months after starting glucocorticoid therapy and the fracture incidence in the following 12 months. Compared with the baseline incidence, both clinical vertebral and non-vertebral fracture incidence were significantly lower. Treatment within the first 90 days of glucocorticoid use was associated with a significant reduction in clinical fractures (including vertebral) of 48% at 1 year and 32% at 3 years when compared with nonuse. Finally, in three matched cohorts derived from healthcare administrative data from Ontario, Canada, Amiche et al. [158] reported that in individuals initiating long-term glucocorticoids, therapy within the first 6 months with alendronate or risedronate was associated with a decrease in incident hip fracture (alendronate 0.49 (0.34–0.69), risedronate 0.58 (0.36–0.90). The results confirmed a reduction in vertebral fracture risk with etidronate, alendronate, and

risedronate, but no decrease in risk of forearm or humerus fractures for any bisphosphonate. The analysis was limited to oral bisphosphonates, and zoledronic acid was not considered. Overall, therefore, these studies would be consistent with a beneficial effect of bisphosphonates both on vertebral and non-vertebral fracture, including hip fracture.

The safety profile of bisphosphonates in glucocorticoid-induced osteoporosis has been less well studied than in postmenopausal osteoporosis because of the small number of participants included and shorter duration of the trials. Attention has been paid recently to osteonecrosis of the jaw and atypical femoral fractures such as side effect of long-term administration of antiresorptive drugs in osteoporosis; these events are very rare [159, 160] but glucocorticoids use is one of the identified risk factors. Buccal hygiene procedures should be implemented to prevent any local increased risk of infection. Whether these rare events can change the duration of antiresorptive treatments in long-term glucocorticoids users; this requires further studies. Because of comorbidities and co-medications, people taking glucocorticoids may be more susceptible to side effects [161, 162].

Bisphosphonates should be used cautiously in premenopausal women, as they cross the placenta; appropriate contraception must be used if necessary and preference given to a short bone half-life bisphosphonate [142].

Denosumab

Denosumab inhibits bone resorption by binding to RANKL and interfering with the development of osteoclasts. A non-inferiority trial comparing denosumab with risedronate in patients who were beginning to receive glucocorticoids and in those who had received these agents long-term showed superiority of denosumab with respect to increases in bone mineral density at the spine at 12 months and non-inferiority with respect to rates of fracture [163].

A systematic review and meta-analysis of four randomized-controlled trials evaluating the efficacy and safety of denosumab for the prevention and/or treatment of GIO [164] revealed that treatment with denosumab provided significantly greater increments in lumbar spine and total hip BMD, compared with bisphosphonate therapy or placebo. There was no difference in fracture incidence; however, the total number of reported fractures across trials was low, and the studies were not powered to detect fracture differences between treatment groups. In a previously published meta-analysis excluding GIO studies [165], denosumab likewise increased spine and hip BMD greater than that observed with bisphosphonate therapy. Fracture wise, denosumab was associated with significantly fewer fractures at 24 months, when compared with alendronate (risk ratio 0.51, 95% CI 0.27–0.97).

A third previously published meta-analysis of 11 studies using denosumab to treat postmenopausal women with osteoporosis indicated an increased risk of serious adverse events related to infections [166]. However, the meta-analysis carried out by Yanbeiy and Hansen [164] did not detect a difference in the frequency of infections between denosumab and control groups. Rates of adverse events and serious adverse events were also similar between denosumab and control groups. In summary, denosumab represents a reasonable therapeutic choice for patients with GIO.

Anabolic in the Management of Glucocorticoid-Induced Osteoporosis

The predominant role of reduced bone formation in glucocorticoid-induced osteoporosis provides a rationale for the use of anabolic agents in its treatment. In an active comparator controlled, randomized, double blind study the effects of 18-month treatment with subcutaneous teriparatide, 20 μg/day, or oral alendronate 10 mg/day, were compared in 428 men and women with glucocorticoid-induced osteoporosis [167]. Teriparatide therapy resulted in significantly greater increases in spine and hip BMD, and this was seen in both premenopausal and postmenopausal women and in men [167]. In another mul-

ticenter, randomized, double-blind study of teriparatide 20 microg/day versus alendronate 10 mg/day in patients with GIO (277 postmenopausal women, 67 premenopausal women, 83 men) [168], at 18 months, mean percent increases from baseline in lumbar spine BMD were significantly greater in the teriparatide versus alendronate group in postmenopausal women (7.8% versus 3.7%, $p < 0.001$), premenopausal women (7.0% versus 0.7%, $p < 0.001$), and men (7.3% versus 3.7%, $p = 0.03$). Radiographic vertebral fractures occurred in one teriparatide (one postmenopausal) and ten alendronate patients (six postmenopausal, four men), and nonvertebral fractures occurred in 12 teriparatide (nine postmenopausal, two premenopausal, one man) and eight alendronate patients (six postmenopausal, two men). The proportion of patients reporting adverse events in teriparatide versus alendronate groups was consistent across subgroups. The magnitude of increase in BMD was somewhat less than that seen in nonglucocorticoid-treated postmenopausal women in another study [169], possibly as a result of the opposing actions of intermittent PTH and glucocorticoids on osteoblastogenesis, and osteoblast and osteocyte apoptosis [170–172]. Although fracture was not a primary end-point of the study, in concordance with the results of the study carried out by Langdahl et al. [168], there were significantly fewer new vertebral fractures occurred in the patients treated with teriparatide when compared with those treated with alendronate (0.6% vs. 6.1%; $p = 0.004$). The incidence of non-vertebral fractures was similar in the two treatment groups. In a study carried out by Saag and colleagues [173], results after 36 months of treatment demonstrated a continued increase in spine and hip BMD in the teriparatide-treated group, with superiority over alendronate at the 24- and 36-month time points. A lower incidence of new vertebral fractures was also seen in the teriparatide group at 36 months (1.7% vs 7.7%, $p = 0.007$), with a similar incidence of non-vertebral fractures in the two groups. Interestingly, measurements of TBS in a subpopulation of this study demonstrated a significant increase after 36 months in teriparatide-treated patients, but no significant change in those treated with alendronate [122]. While the long duration of this study is unique among treatment trials for glucocorticoid-induced osteoporosis, it should be noted that the participant discontinuation rate at 36 months was 44%.

However, bone loss and fractures occur rapidly after teriparatide is discontinued; therefore, after discontinuation, an antiresorptive agent such as bisphosphonate or denosumab should be initiated. Initial treatment with an anabolic agent such as teriparatide or abaloparatide, followed by an antiresorptive agent, may be considered for treatment of severe osteoporosis (bone mineral density T score below −2.5 in patients with a history of fracture).With regard to safety, increased pre-dose serum calcium levels were significantly more common in the teriparatide than alendronate-treated group (21% vs. 7%), but no other concerns were identified [174].

Romosozumab

Romosozumab is a monoclonal antibody against sclerostin, a protein secreted by osteocytes that inhibits bone formation through regulation of osteoblasts. Through its mechanism of action through which it blocks the repressive effect of sclerostin on the Wnts pathway, romosozumab acts as a potent bone forming stimulator. Furthermore, since sclerostin promote the formation of osteoclasts through a RANKL-dependent mechanism, the inhibitory effect of romosozumab on bone resorption gives romosozumab the dual function effect on bone, i.e., stimulate bone formation and inhibit bone resorption, which gives promising positive implications for the management of GIO. Earlier studies on glucocorticoid-treated rats revealed that sclerostin-antibody treatment resulted in marked improvements in bone mass across the rats' skeleton and in osteocyte viability, resulting in decreased bone fragility [175]. However, like abaloparatide, sclerostin antibodies have not been studied in patients on chronic steroids; however, they have shown benefit when administered subcutaneously in postmenopausal women and men. In postmenopausal women specifically,

romosozumab increased BMD when compared with placebo and teriparatide and decreased the incidence of fractures when compared with placebo and alendronate [176–180]. There is currently an ongoing study to assess the efficacy of romosozumab versus denosumab for osteoporosis in long-term glucocorticoid users in an open randomized parallel group-controlled trial (https://www.smartpatients.com/trials/NCT04091243#locations).

Third-Line Agents

Treatment either with raloxifene (a selective estrogen-receptor modulator) in postmenopausal women should be reserved for patients in whom other treatments are contraindicated or in whom such treatments have failed. Raloxifene is approved by the Food and Drug Administration for the prevention and treatment of glucocorticoid-induced osteoporosis in postmenopausal women. One trial showed that in postmenopausal women who received glucocorticoids, raloxifene significantly increased absolute bone mineral density (measured in grams per square centimeter) at the lumbar spine by 1.3% from the baseline measure, as compared with calcium and vitamin D supplementation, which decreased the absolute bone mineral density [181].

However, there was no difference in bone mineral density at the femoral neck between the treatment groups, and trials assessing rates of fracture among patients who have received both glucocorticoids and raloxifene are lacking. Although raloxifene has been shown to reduce the risk of estrogen receptor-positive breast cancer [182], potential adverse effects include hot flashes, leg cramps, venous thromboembolism, and fatal stroke [183].

Follow-Up

In cases of a fracture occurring ≥18 months after initiation of oral bisphosphonate therapy or significant bone loss (≥10%/y) after 12-months of therapy, it is recommended to treat with oral bisphosphonate. Alternatively, an intravenous bisphosphonate can be considered, if absorption or adherence problems are suspected. Another class of osteoporosis medication (teriparatide and denosumab) can be prescribed in case of intolerability or lack of efficacy to first line of management [115].

For patients who have completed 5 years of oral bisphosphonate therapy and are expected to continue glucocorticoid treatment, further treatment for osteoporosis is recommended and may include continuing oral bisphosphonate for 7–10 years or switching to a different class of osteoporosis medication. When glucocorticoid therapy is discontinued, fracture risk should be reassessed. If the fracture risk is deemed to be low, it is recommenced to withhold osteoporosis therapy. Otherwise, treatment should be continued [104, 115].

Algorithm for Assessment and Management of GIO

Undertreatment of glucocorticoid-induced osteoporosis has been widely recognized [21, 184]. In a population-based study of adults age ≥20 years, rates of BMD testing and prescription of bone protective medication between 1998 and 2008 were studied in individuals prescribed systemic glucocorticoids for 90 days or longer [185]. Overall, in the first 6 months after initiation of glucocorticoid therapy, only 6% had BMD testing, 22% received therapy, and 25% had both interventions.

Undertreatment was greatest in younger people and men, and primary care physicians had lower prescription rates than rheumatologists. Similar results have been reported using information from a national public health-insurance database in France, with only 8% undergoing BMD testing and prescriptions of calcium ±vitamin D alone or together with bisphosphonates were issued in 18% and 12% respectively [186]. In a large cohort from Canada of men and women aged 66 years or over who were initiating long-term glucocorticoid therapy, Amiche et al. reported that only 13% were prescribed bone protective therapy [158]. The problem of under-

treatment is compounded by poor persistence with bisphosphonate therapy, particularly in younger people, those with comorbidities, and those in whom BMD measurements have not been made [187].

According to the 2017 guidelines by the American College of Rheumatology [115], glucocorticoid-treated patients can be classified into the following fracture risk categories:

High Fracture Risk

- All adults with prior osteoporotic fracture.
- Men aged ≥50 years and postmenopausal women with hip or spine bone mineral density T-score ≤ −2.5.
- Adults aged ≥40 years with a glucocorticoid-adjusted Fracture Risk Assessment Tool (FRAX) 10-year risk for major osteoporotic fracture or hip fracture of ≥20% or ≥3%, respectively.

Moderate Fracture Risk

- Adults aged ≥40 years with a glucocorticoid-adjusted FRAX 10-year risk for major osteoporotic fracture of 10%–19% or risk for hip fracture of >1%–<3%.
- Adults aged <40 years with a hip or spine bone mineral density Z-score of <−3 or rapid bone loss of ≥10% at the hip or spine over 1 year and glucocorticoid treatment at ≥7.5 mg/d for ≥6 months.

Low Fracture Risk

- Adults aged ≥40 years with a glucocorticoid-adjusted FRAX 10-year risk for major osteoporotic fracture of <10% and risk for hip fracture of ≤1%.
- Adults aged <40 years with none of the above risk factors other than glucocorticoid treatment.

Figure 31.6 shows an algorithm to for assessment and management of GIO. Stages of assessment and management can be split into three sections:

Initial fracture risk assessment: A clinical fracture risk assessment includes obtaining a history with full details of glucocorticoid use (dose, duration, and pattern of use), an evaluation for falls, fractures, frailty, and other osteoporosis risk factors (malnutrition, significant weight loss or low body weight, hypogonadism, secondary hyperparathyroidism, thyroid disease, family history of hip fracture, and history of alcohol use [at ≥3 units/day] or smoking) and other clinical comorbidities, in addition to a physical examination including measurement of weight and height (without shoes), testing of muscle strength, and assessment for other clinical findings of undiagnosed fracture (i.e., spinal tenderness, deformity, and reduced space between lower ribs and upper pelvis) as appropriate given the patient's age. The risk of major osteoporotic fracture calculated with the FRAX tool (https://www.shef.ac.uk/FRAX/tool.jsp) should be increased by 1.15 and the risk of hip fracture by 1.2, if the prednisone dose is >7.5 mg/day (e.g., if the calculated hip fracture risk is 2.0%, increase to 2.4%). It is recognized that in some cases, bone mineral density (BMD) testing may not be available.

Reassessment of fracture risk: A clinical fracture risk reassessment carried out as above. Very high dose of glucocorticoids treatment was defined as treatment

with prednisone ≥30 mg/day and a cumulative dose of >5 gm in the past year. Reliability of FRAX (https://www.shef.ac.uk/FRAX/tool.jsp) after osteoporosis treatment is debated, but FRAX calculation can be repeated in adults age ≥40 years who have not received treatment.

Pharmacologic treatment for adults: Recommended doses of calcium and vitamin D are 1000–1200 mg/day and 600–800 IU/day

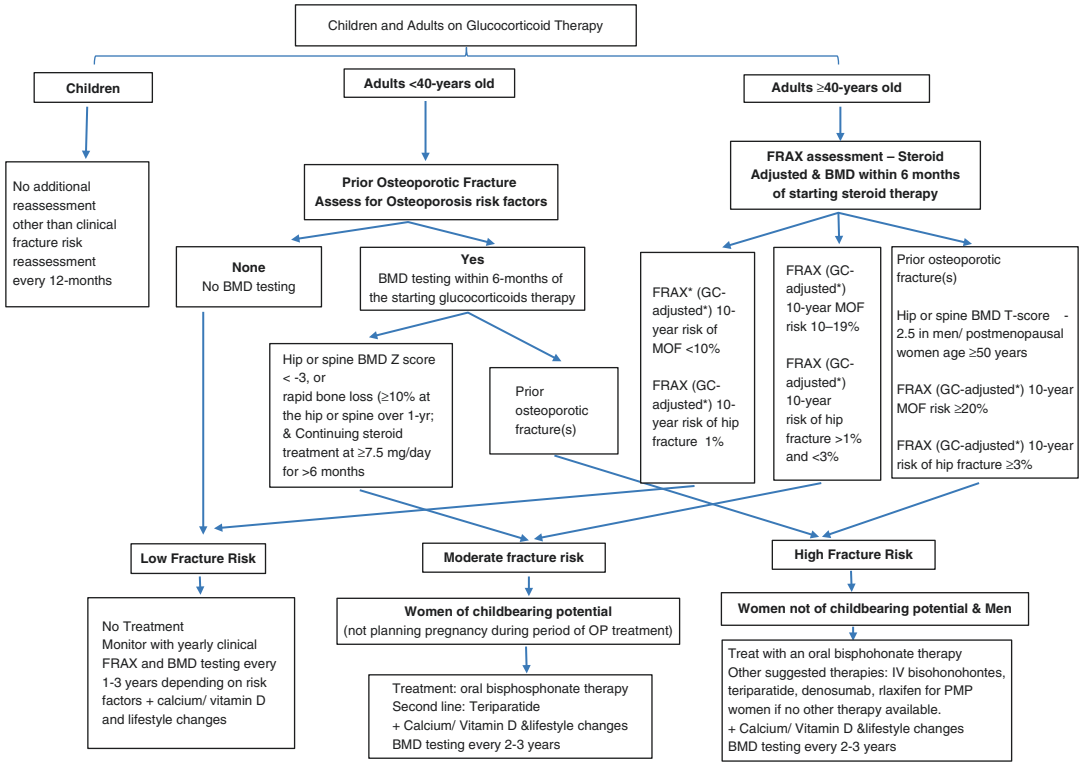

Fig. 31.6 An algorithm for assessment and management of glucocorticoid-induced osteoporosis

(serum level ≥20 ng/ml), respectively. Lifestyle modifications include a balanced diet, maintaining weight in the recommended range, smoking cessation, regular weight-bearing and resistance training exercise, and limiting alcohol intake to 1–2 alcoholic beverages/day. Very high-dose glucocorticoid treatment was defined as treatment with prednisone ≥30 mg/day and a cumulative dose of >5 gm in the past year. The risk of major osteoporotic fracture calculated with the FRAX tool (https://www.shef.ac.uk/FRAX/tool.jsp) should be increased by 1.15 and the risk of hip fracture by 1.2, if the prednisone dose is >7.5 mg/day.

Table 31.3 shows a comparison of the main guidelines published regarding the treatment indications for glucocorticoid-induced osteoporosis.

In conclusion, there have been significant advances in our understanding of the mechanisms by which glucocorticoids affect bone and increase fracture risk. Yet, the clinical management of glucocorticoid-induced osteoporosis remains suboptimal. Use of glucocorticoid for a duration of over 3 months leads to decreased bone mineral density, primarily through osteoblast suppression, as well as through increasing osteoclast life span. Awareness of osteoporosis risk mandates the stratification of patients into low, moderate, and high risk categories. Fracture risk should be assessed in all patients at the initiation of prolonged glucocorticoids therapy. All patients should maintain adequate intake of calcium and vitamin D, while those in moderate and high risk categories should initiate bisphosphonate therapy, or if bisphosphonates are contraindicated, use of alternative agents such as teriparatide or denosumab.

Table 31.3 A comparison of the four main guidelines published regarding the treatment of glucorticoid-induced osteoporosis

	IOF-ECTS (2012) [188, 189]	JSBMR (2014) [190]	NOGG (2017) [191]	ACR (2017) [115]
Previous fracture	Recommend to treat	Recommend to treat	Recommend to treat	Recommend to treat
DXA score/ Bone mineral density	Treat is BMD <70% of the Young Adult Mean (age 20–44 years)	Treat at T-score ≤ −1.5	DXA scan not indicated	≥40-years old: treat if T-score ≤ −2.5 <40-years old: Treat if Z-score < −3.0
FRAX (glucocorticoid adjusted)	Not indicated	Treat if above the individual country specific thresholds	Treat if above the age-dependent threshold[a]	>40-years: treat if FRAX (GC-adjusted[a]) 10-year MOF risk >20% FRAX (GC-adjusted[a]) 10-year risk of hip fracture >3% <40-years: treat if rapid bone loss (>10% at the hip or spine over 1-yr
Glucocorticoid dose	Treat if ≥7.5 prednisone or equivalent	Treat if ≥7.5 prednisone or equivalent	Treat if ≥7.5 prednisone or equivalent	<40-years: consider treatment if treatment at ≥7.5 mg/day for >6 months >40-years: adjust FRAX score if steroid dose above ≥7.5
Older adults	Treat if ≥65 years	Treat if ≥70 years	Treat if ≥70 years	Treat as >40-years (no specific consideration for age)

IOF/*ECTS* International Osteoporosis Foundation/European Calcified Tissue Society,, *JSBMR* Japanese Society for Bone and Mineral Research, *NOGG* National Osteoporosis Guideline Group (UK), *ACR* American College of Rheumatology, *FRAX* fracture risk assessment tool, *MOF* major osteoporotic fracture

[a]Example: ≥20% Major osteoporosis fracture if age ≥65 years, or ≥15% major osteoporosis fracture if age ≥60 years

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Osteonecrosis of the Jaw

32

Yasser El Miedany

Introduction

Osteonecrosis of the Jaws: A Review and Update in Etiology and Treatment

Osteonecrosis was first described as a consequence of ionizing radiation used in the treatment of malignant tumors 1. The main presentation was in the form of persistent pattern of nonhealing exposed alveolar bone in the oral cavity and, consequently, it was given the name osteoradionecrosis (ORN). This clinical presentation was initially called "avascular necrosis." Later, it was noted that, regardless of medical history, comorbidities, dental procedures, or other potential confounders and risk factors, bisphosphonate was the only factor shared by all patients with this condition [1, 2]. This bisphosphonate-associated condition has been named "bisphosphonate-related ONJ osteonecrosis of the jaw (BRONJ)," which reflects a state of "jaw-bone death" without specifying underlying cause or risk factor associated. Later, an association between osteonecrosis of the jaw (ONJ) and medications other than bisphosphonate, such as denosumab and antiangiogenic drugs in the treatment of malignancy, has been reported with an increased incidence of bone necrosis being related to these medications [3]. In 2014 and to accommodate the growing number of osteonecrosis cases involving the maxilla and mandible associated with other antiresorptive (denosumab) and antiangiogenic therapies, the American Association of Oral and Maxillofacial Surgeons (AAOMS) suggested that the nomenclature be changed from bisphosphonate-related ONJ (BRONJ) to medication-related osteonecrosis of the jaw (MRONJ) (Fig. 32.1) [2, 4].

It is worth noting that in contrast to osteonecrosis at other skeletal sites with respect to epidemiology, etiopathogenesis, risk factors, clinical manifestations, diagnosis, and treatment, ONJ is unique. An example is the osteonecrosis of diaphyseal or endochondral long bones (e.g., femur and tibia), which mainly affects men in their third to fifth decades of life (exception are systemic lupus patients who are characterized by a female predominance), and is attributed to known risk factors such as corticosteroid or alcohol use in nontraumatic cases [5]. On the other hand, osteonecrosis of the membranous or flat craniofacial bones (e.g., maxilla and mandible) affects both men and women and, however, is more prominent in women who are more prone to develop osteoporosis and more likely to receive antiresorptive therapy for bone thinning. Osteonecrosis in such cases usually occurs in the fifth decade of life or higher and is linked to dental risk factors and oral trauma [6, 7].

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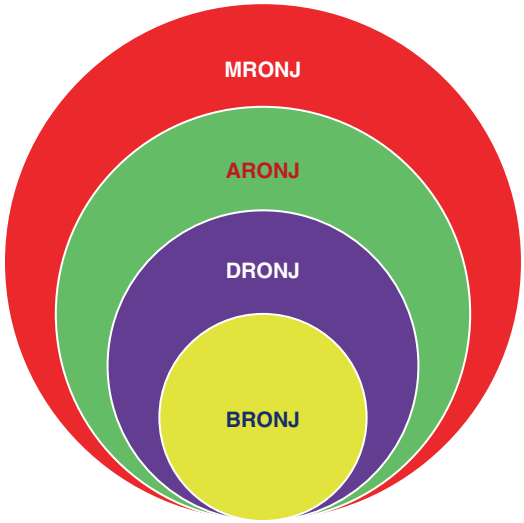


Fig. 32.1 The evolving concept of medication-related osteonecrosis of the jaw nomenclature. BRONJ bisphosphonate-related osteonecrosis of the jaw (ONJ), DRONJ denosumab-related ONJ, ARONJ antiresorptives ONJ, MRONJ medication-related ONJ

This chapter will focus on the medication-related osteonecrosis of the jaw. It will start by defining the disease, its incidence, pathophysiology, stages of the disease, and its risk factors and approaches to diagnosis both radiology and laboratory. It will expand to discuss measures to predict the disease prognosis and approaches to prevention and treatment.

Definition

In comparison with the radio-induced osteonecrosis, which is defined as exposure of necrotic bone that persists for over 3 months in a previously irradiated area receiving ionizing radiation above 50 Gy and is not caused by tumor recurrence [8], the American Association of Oral and Maxillofacial Surgeons [2] reported that a confirmed case of MRONJ is defined if the following characteristics are present: (1) current or previous treatment with antiresorptive or antiangiogenic agents, (2) exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than 8 weeks, and (3) no history of radiation therapy to the jaws or obvious metastatic disease to the jaws. The addition of "probed bone" to the case definition is of clinical significance since frank exposed bone is not always seen, even though it is notably necrotic and radiographically has a similar pattern. In addition to these requirements, common features may also include pain, soft tissue swelling, ulceration, erythema, and suppuration [3, 9, 10].

A suspected case of MRONJ is defined as an area of exposed jawbone for less than 8 weeks in a patient with a history of antiresorptive therapy and no current or past history of radiotherapy to the head and neck. However, it is estimated that up to 30% of MRONJ cases may initially present without clinical evidence of exposed jawbone or characteristic signs and symptoms. Clinical manifestations without bone exposure, such as deep periodontal pocket, loose tooth, trismus, hypoesthesia/numbness of lower lip (Vincent's symptom), and non-odontogenic pain could be classified as nonexposed MRONJ [11].

Furthermore, although the majority of cases of MRONJ occur following a dental intervention, which impacts on bone, some can occur spontaneously. Signs and symptoms include delayed healing following a dental extraction or other oral surgery, pain, soft tissue infection and swelling, numbness, paraesthesia, or exposed bone. Patients may also complain of pain or altered sensation in the absence of exposed bone. However, some patients may be asymptomatic at presentation, with MRONJ lesions seen as an incidental finding. A history of antiresorptive or antiangiogenic drug use in these patients should alert practitioners to the possibility of MRONJ [10].

Incidence of MRONJ

MRONJ has been observed in patients being treated with antiresorptive or antiangiogenic drugs for management of solid tumor cancers,

e.g., breast cancer, prostate cancer, and cancers of the blood, e.g., multiple myeloma. Due to the rare nature of MRONJ, the estimates of incidence and prevalence vary widely. In cancer patients, the MRONJ risk ranges from 0% to 12% (0–1200 cases per 10,000), compared with a risk of 0–0.02% (0–2 cases of ONJ per 10,000) in cancer patients exposed to placebo in clinical trials [12–15]. However, it is worth noting that estimates toward the higher end of this range tended to come from studies with small sample sizes, which can overestimate the risk of low frequency events.

In patients being treated with oral antiresorptive drugs for osteoporosis, the risk of MRONJ is lower than the risk for patients being treated for cancer. Estimates range from 0% to 0.1% (0–10 cases per 10,000) [16, 17]. One study estimated the incidence to be "more than 1 in 10,000 and less than 1 in 1000" [18]. Another study estimated that the incidence of alendronate-associated osteonecrosis of the jaw in this patient group is 4.3 per 10,000 drug patient years (0.043%) [19]. There is some weak evidence that the risk appears to increase with increasing drug duration [20]. The risk of MRONJ in patients with osteoporosis given a once yearly intravenous infusion of bisphosphonates appears to be no greater than that in patients taking the drugs orally, with one study identifying one case of MRONJ in a sample of around 6000 patients (0.017%) [21].

There is less evidence to base an estimate of incidence in those patients prescribed denosumab. The Summary of Product Characteristics (SmPC) for Prolia®, the denosumab formulation indicated for treatment of osteoporosis, reports that 13 cases of MRONJ were observed in 4450 patients (0.3%) over 7 years of an extended phase III clinical study [22].

In summary, MRONJ is a rare condition in the osteoporosis patient group, while the risk in cancer patients is up to 100 times greater. The risk of MRONJ should be discussed with patients, but it is important that they are not discouraged from taking antiresorptive or antiangiogenic drugs or from undergoing dental treatment [23].

Characteristics of the Jawbone

Osteonecrosis occurs only in the jawbone, but not in other bones such as long bone and cranium due to the following reasons that are related to the anatomical and physiological characteristics: (1) Teeth erupt from the jawbone by breaking the oral epithelium; thus, sources of infection can readily reach the bone directly from the affected teeth through the epithelium. (2) The jawbone is covered only with thin oral mucosa, which is susceptible to injury from everyday actions such as mastication, and infection due to mucosal injury can directly spread to the jawbone. (3) Over 800 types of bacteria are present in the mouth as sources of infection at concentrations of 1011–1012/cm^3. (4) Inflammation can readily spread to the jawbone through dental infections (caries, pulpitis, apical periodontitis, and periodontal disease). (5) The jawbone is directly exposed to the interior of the mouth and thus susceptible to infection, as a result of invasive procedures such as tooth extraction or implant therapy [24].

The jawbone is more susceptible to infection compared with bones in other parts of the body, and such unique environment plays a crucial role in the pathogenesis of MRONJ. In this context, Cardemil et al. [25] reported that the expression levels of ossification markers and bone resorption markers are different between the jawbone and tibia; such differences may reflect bone remodeling capability and affect the process of osteonecrosis. The jawbone is stimulated by teeth during mastication, and its remodeling occurs at a higher rate compared with other bone in the body.

Pathophysiology

Since the first report of ONJ cases published in 2003 and 2004, and although significant progress has been made in our understanding of the disease, still our understanding of the ONJ pathophysiology is not fully clear and much more work needs to be done to completely explain how it develops [10, 11]. Many hypotheses have been proposed, which have sparked empirically based

treatment modalities. Since it is unlikely that one single hypothesis can explain the pathophysiology of ONJ, as it is indeed multifactorial, it is also unlikely that one treatment modality will be successful in all patients. Moreover, more clinical and preclinical evidence becomes available, the proposed hypotheses and treatment approaches will need to be continuously modified. Reviewing the literature, there are five main hypotheses for the ONJ pathophysiology:

Hypothesis 1: Bone Remodeling Inhibition

One important note is that osteonecrosis of the jaws occurs only in alveolar bone of the maxilla and mandible [20]. This raised the suggestion that alveolar bone may demonstrate an increased remodeling rate as compared with other bones in the axial or appendicular skeleton, which may explain the ONJ predilection in the jaws [21, 22]. However, earlier studies have failed to confirm differences in bone turnover between the mandible and femur by bone scintigraphy, while the maxilla did show increased bone turnover; administration of BP or denosumab did not change the turnover rate of any bones [23, itself]. Interestingly in mice, fluorescent-labeled bisphosphonates demonstrate preferential accumulation in sites of tooth extraction or dental disease, where bone turnover is increased. This is why increased uptake may predispose such sites to higher bisphosphonate doses and increase susceptibility to bisphosphonate effects. Although this may not demonstrate a general increase in bone turnover in the jaws, it does show a localized increase in potentially future ONJ sites [24]. The increased bone resorption in the setting of dental disease, coupled with the thin overlying mucosa and a direct pathway through the periodontal ligament with the external environment, make the jaws a suitable breeding ground for ONJ to develop.

The socket left in the gum after a tooth extraction passes through three stages as it heals. The first stage is the inflammatory phase. The gum becomes inflamed, a blood clot forms inside the socket and granulation tissue forms over the wound. New tissue usually replaces the clot within a week after the procedure. Following this process is the proliferative phase, when the wound begins to close. The final stage is the maturation phase. The cells in the site form new structures and bony networks, and connective tissue, called collagen, which populates the healing area. Bone resorption plays an important role in the process of healing after tooth extraction. After tooth extraction, bundle bone appears to be the first bone to be absorbed and replaced with woven bone [26–28], whereas alveolar bone is gradually absorbed throughout life [29, 30]. The remodeling process results in a ridge morphology reduced in vertical height and more palatal in relation to the original tooth position (Fig. 32.2) [31–35].

Since both bisphosphonates and denosumab share the same mechanism of action, i.e., inhibit osteoclast function, it is not surprising that altered bone remodeling is the leading hypothesis for ONJ development [36–39]. This has been supported by the studies outcomes showing that the ONJ prevalence in patients receiving bisphosphonates and denosumab is not significantly different [40–42]. Moreover, animal studies reported that when rodents with periodontal or periapical disease or tooth extractions are treated with zoledronate as compared with RANKL inhibitors, they demonstrate a similar rate of periosteal bone deposition, histologic necrosis, and bone exposure [43–45]. In summary, these human and animal studies confirmed the central role of bone remodeling suppression.

On another front, earlier studies revealed similarity in the prevalence of ONJ in patients treated with bisphosphonates or denosumab [46, 47]. However, the mechanism of antiresorptive effect differs. While bisphosphonates bind to exposed hydroxyapatite and incorporate into the bone matrix, where they are retained with a half-life of many years [48–50], denosumab does not incorporate into the bone matrix, but inhibits RANKL with significantly much shorter half-life of 32 days maximum [51, 52] and rapid reversibility of its antiresorptive effects [53]. An animal study

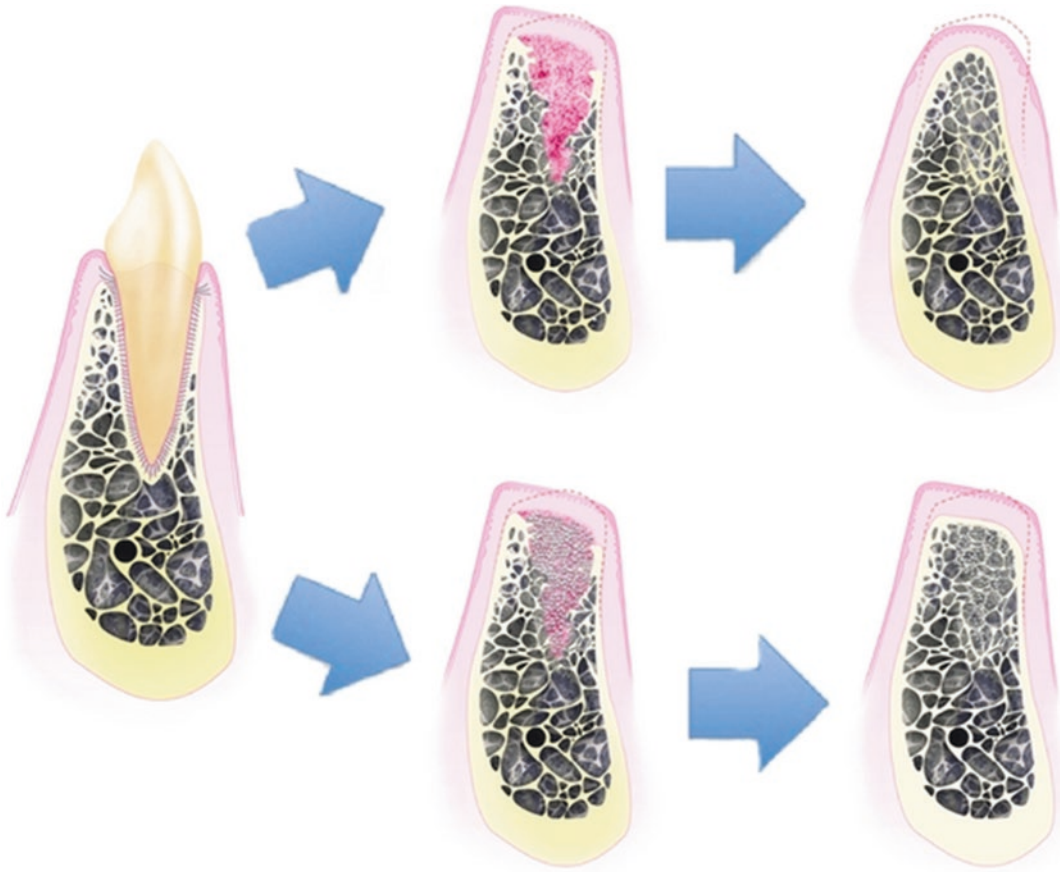


Fig. 32.2 Healing of the extraction socket with and without socket grafting. When socket grafting is not adopted, major alveolar ridge resorption occurs. In a first phase, initially the blood clot, subsequently the granulation tissue and later the provisional matrix and the woven bone fill up the alveolus. The bundle bone is completely resorbed causing a reduction in the vertical ridge. In a second phase, the buccal wall and the woven bone are remodeled causing the horizontal and further vertical ridge reduction. When socket grafting is adopted, the first phase and vertical bone reduction still occur; however, the second phase and the horizontal contraction are reduced. (Quoted from Pagni et al. [35] under open access scheme under the CC BY-NC-ND license (Commons Attribution (CC-BY) license (http://creativecommons.org/licenses/by/4.0/))

demonstrated faster normalization of TRACP-5b levels after discontinuation of RANKL inhibitor OPG-Fc, a surrogate to denosumab, as compared with zoledronic acid [54]. In addition, radiographic and histologic indices of ONJ returned to levels of control animals after withdrawal of OPG-FC, whereas zoledronate-treated mice still demonstrated ONJ features. If these data can be validated in controlled clinical studies, they may support the rationale for drug holidays in the management of ONJ patients. They may also demonstrate that discontinuing denosumab vs. bisphosphonate therapy prior to surgical intervention offers faster recovery of normal bone homeostasis [55].

Another factor that points to the central role of osteoclastic bone resorption in ONJ pathophysiology is the effect of parathyroid hormone (PTH). Several case reports revealed that administration of parathyroid hormone appeared to exert beneficial effects as it improved the healing of extraction sockets and ONJ lesions, by directly stimulating osteoblastic function and indirectly increasing osteoclastic bone resorption [56–59].

Hypothesis 2: Inflammation, Infection, and the Biofilm

The fact that a percentage (0.8–12%) of the patients diagnosed to have malignant diseases and treated with systemic antiresorptives develop ONJ [60–64], although this may be underestimated [65, 66], suggests that additional inciting factors, beside antiresorptives, might play a role and contribute to ONJ development. Data collected from ONJ patients and their coexisting risk factors, revealed that tooth extraction is generally the most common inciting event associated with ONJ. However, in adults, teeth are almost always extracted because they have periapical or periodontal infections or inflammation [67, 68]. Animal models of inflammation and infection have been developed to mimic the clinical presentation of ONJ with associated dental pathology and have consistently shown that both inflammation/infection and administration of a systemic antiresorptive are sufficient for the development of ONJ [69–73].

While local inflammation is a part of the healing process after tooth extraction, the combination of Inflammation/infection has been thought to play a role in ONJ. The occurrence of infection on top of the underlying inflammatory process may induce a state of advanced dental disease or around teeth with periodontal or periapical infection [65, 68, 74]. In multiple myeloma and metastatic cancer patients, reduction of the ONJ incidence was reported in the patients who were subjected to an aggressive dental hygiene therapy [75, 76]. Furthermore, assessment of histologic specimens taken from the necrotic bones did report the presence of bacteria on the exposed bone, including *Actinomyces* species [77, 78]. However, one question remains to be answered. Did the bacteria induce the infection and exposed the underlying bone, or did the exposed bone develop a bacterial biofilm? Studies have shed light on the complexity of biofilm, which include fungi and viruses in addition to the bacterial species [79, 80]. These multiorganism biofilms present challenges to therapy and may require complicated strategies to eradicate the infection [81–83].

Hypothesis 3: Angiogenesis Inhibition

Bone becomes necrotic without adequate blood supply, as do most tissues, even in pathologic processes. Based on this fact, antiangiogenic therapies have been developed and are currently widely used to inhibit tumor invasion and metastases, targeting vascular signaling molecules such as vascular endothelial growth factor (VEGF) [84]. Zoledronic acid has been found being able to reduce circulating VEGF levels in cancer patients in vivo and reduce angiogenesis in vitro [85–87]. Zoledronic acid inhibits proliferation and interferes with adhesion and migration of human endothelial cells [85, 86], which is thought to interrupt tumor invasion and metastases [85, 88]. In addition, all bisphosphonates, particularly nitrogen-containing bisphosphonates, induce a statistically significant decrease in microvessel density in vivo [89].

Studies have revealed that ONJ was reported in patients receiving antiangiogenic therapies such as tyrosine kinase inhibitors and antivascular endothelial growth factor (VEGF) monoclonal antibodies [90–93]. In multiple myeloma patients, the ONJ prevalence was reported to be the highest, which has been attributed to the concomitant antiangiogenic medications and steroids [94, 95]. However, even though there is some evidence that antiangiogenesis is involved in the ONJ disease process, histopathologic studies have shown normal vasculature in postmortem specimens. Furthermore, denosumab has not been associated with antiangiogenesis [96]. Therefore, although unlikely to be central in the development of ONJ, antiangiogenesis is thought to be a significant contributor to the disease process.

Hypothesis 4: Soft Tissue Toxicity

An early hypothesis in ONJ pathophysiology was a bisphosphonate direct soft tissue toxicity [97]. Exposure to bisphosphonates, particularly the nitrogen-containing ones, induces apoptosis or decreased proliferation of cervical, prostate, and oral epithelial cells in vitro [89, 97–101]. In vitro

studies also demonstrate that nitrogen containing BPs localize to epithelial tissue and bone [102]. In addition, oral alendronate is associated with esophageal irritation, requiring special precautions for patients during administration [103]. However, this hypothesis has become less likely due to the lack of soft tissue toxicity reported with denosumab.

Hypothesis 5: Innate or Acquired Immunity Dysfunction

Suggestions have been raised regarding a possible link between altered immunity and its impact on the development of ONJ. This was based on earlier findings, e.g., the fact that tumor pathogenesis is often associated with an impaired immune function [104], and animal studies have implicated immune deficiency in the development of ONJ, while infusion of mesenchymal stem cells or T-regulatory cells prevents and alleviates ONJ-like lesions [105]. In addition, the highest prevalence of ONJ in patients with multiple myeloma, who receive steroids and antiangiogenics as part of their chemotherapy regimen further points to a role of immune dysfunction in ONJ pathogenesis [86]. Additionally, in many animal models of ONJ, incidence and severity of disease increases with the presence of chemotherapy or steroids [57, 62, 105, 106]. In patients on oral BPs, steroids are also a risk factor for ONJ [68]. This points to the potential significant contribution of immunomodulators in the pathophysiology of the disease.

In conclusion, the pathophysiology of ONJ is multifactorial. Human and animal studies point to a combination of mechanisms, interacting with each other to increase the development and severity of the disease. Figure 32.3 summarizes the different factors involved in ONJ pathogenesis.

Diagnosis and Stages of MRONJ

The diagnostic criteria for MRONJ developed by AAOMS are based on pharmacological history and clinical and radiographic features [107–111]. A patient can be diagnosed with MRONJ if both of the following criteria are fulfilled: (1) a history or ongoing treatment with antiangiogenic agents or antiresorptives such as bisphosphonate and denosumab and (2) exposed or nonhealing bone that can be probed through a fistula in the maxillofacial region persisting for more than 8 weeks and no history of radiation therapy to the head and neck region or obvious metastatic disease of the jaws [2, 107, 111, 112].

MRONJ staging system was developed in 2006 by Ruggiero et al. and subsequently adopted by the AAOMS and updated in 2014 [2, 107] (Table 32.1).

The addition of stage "0" category in the latest classification seems to be a valid disease category

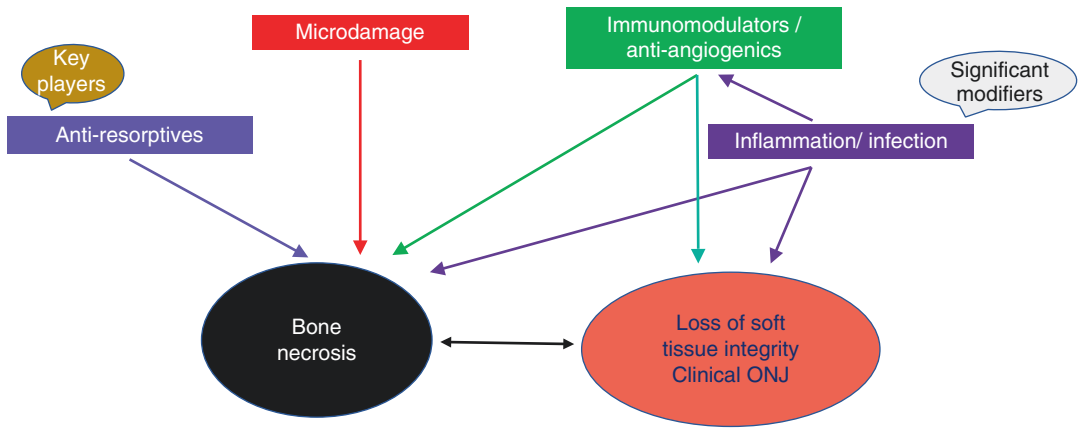


Fig. 32.3 ONJ pathophysiology: the potential synergy of multiple pathways of ONJ

Table 32.1 Medication-related osteonecrosis of the jaw staging system as updated by American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2014

Stage	Clinical findings
At-risk category	No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates
Stage 0	No clinical evidence of necrotic bone, but nonspecific clinical findings, radiographic changes, and symptoms (Fig. 32.4)
Stage 1	Exposed and necrotic bone, or fistulae that probe to the bone in patients who are asymptomatic and have no evidence of infection (Fig. 32.5)
Stage 2	Exposed and necrotic bone, or fistulae that probes to the bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone, with or without purulent drainage (Fig. 32.6)
Stage 3	Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in the mandible, maxillary sinus, and zygoma in the maxilla) resulting in pathologic fracture, extraoral fistula, oral-antral/oral-nasal communication or osteolysis extending to the inferior border of the mandible of sinus floor (Fig. 32.7)

IV intravenous, *MRONJ* medication-related osteonecrosis of the jaw, *AAOMS* American Association of Oral and Maxillofacial Surgeons

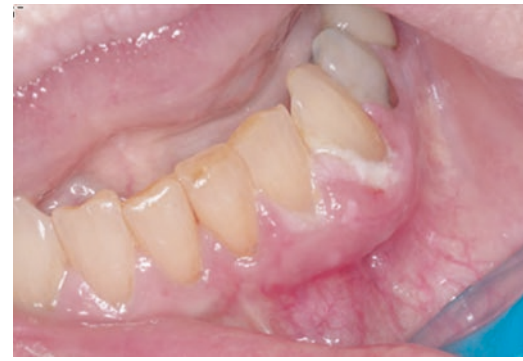


Fig. 32.5 A 71-year-old Caucasian female with a four-year history of oral ibandronate use for osteoporosis, presenting with an asymptomatic area of exposed bone and associated granulation tissue involving the lingual surface of the left posterior hemimandible (stage 1 MRONJ). (Quoted with permission from *Osteonecrosis of the Jaw*)

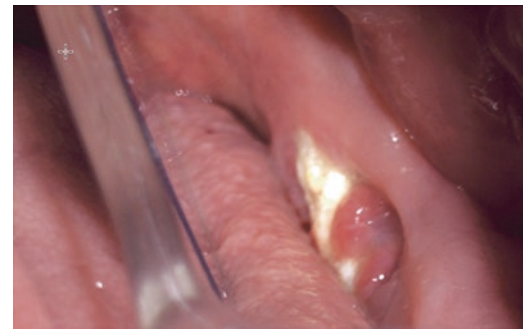


Fig. 32.6 A 78-year-old Caucasian male with a six-year history of oral alendronate use for osteoporosis, presenting with a painful area of exposed and infected bone involving the right hemimaxilla (stage 2 MRONJ). (Quoted with permission from *Osteonecrosis of the Jaw*)

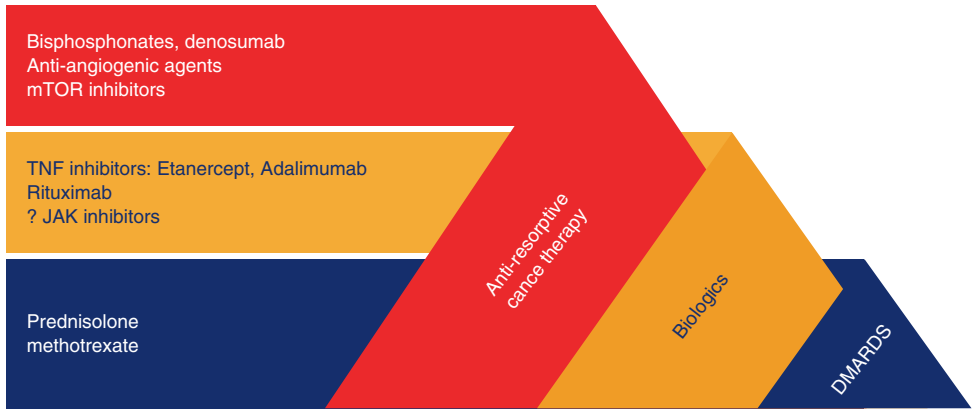


Fig. 32.4 A 76-year-old Caucasian female on denosumab therapy for osteoporosis for 2 years, presenting with loose teeth and swelling of the left mandibular anterior gingiva and purulent crevicular exudate from the periodontium, but no overt evidence of exposed bone (stage 0 MRONJ). (Quoted with permission from *Osteonecrosis of the Jaw*)

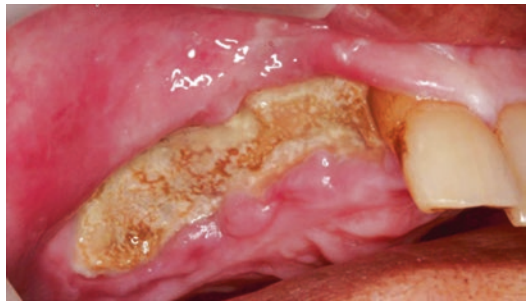


Fig. 32.7 A 69-year-old male with diffuse facial/mandibular swelling, pain, and cutaneous sinus tract formation consistent with a stage 3 MRONJ with a cutaneous 2 sinus tracts from the mandible MRRONJ lesion

as it helps to captures those patients with prodromal disease (nonspecific symptoms or clinical and radiographic abnormalities that might be due to exposure to an antiresorptive agent). Earlier studies revealed that up to 50% of patients with stage 0 have progressed to stage 1, 2, or 3 [113, 114]. Therefore, stage "0" has been considered as a separate category. As these patients have no clinical evidence of necrotic bone but present with nonspecific symptoms or clinical and radiographic findings, it is important to consider the early manifestations of this stage which is shown in Table 32.2. It has to be noted that these nonspecific findings, which characterize this unexposed variant of ONJ, can occur in patients with a history of stage 1, 2, or 3 disease who have healed and have no clinical evidence of exposed bone [2].

Table 32.2 Features of stage "0" in the ONJ staging, which helps to identify those patients with prodromal disease

Symptoms	Clinical findings	Radiological findings
Odontalgia not explained by an odontogenic cause Dull, aching bone pain in the jaw, which may radiate to the temporomandibular joint region Sinus pain, which may be associated with inflammation and thickening of the maxillary sinus wall Altered neurosensory function	Loosening of teeth not explained by chronic periodontal disease Periapical or periodontal fistula that is not associated with pulpal necrosis caused by caries, trauma, or restorations	Alveolar bone loss or resorption not attributable to chronic periodontal disease Changes to trabecular pattern—dense bone and no new bone in extraction sockets Regions of osteosclerosis involving the alveolar bone or surrounding basilar bone Thickening or obscuring of the periodontal ligament (thickening of the lamina dura, sclerosis, and decreased periodontal ligament space) [115]

Risk Factors for MRONJ

In addition to recognizing the signs and symptoms of MRONJ, healthcare professionals need to be aware of the risk factors that may contribute to the development and severity of the condition, although the available data are inconclusive. Risk factors can be stratified into three main categories: medication related, personal factors, and local risk factors.

Medications Exposure to denosumab or bisphosphonates is the primary risk factor for MRONJ (Table 32.3), although it has been established that MRONJ can arise following the use of other cancer therapies (e.g., inhibitors of angiogenesis, tyrosine kinase inhibitors) (Fig. 32.8) [116–119]. The risk of developing MRONJ with these treatments increases with more frequent administration, a higher dose per administration (e.g., doses used in the metastatic setting versus in the osteoporosis setting) and a longer duration of treatment [119–122]. Data do not support any difference between denosumab and bisphosphonates in time to onset of MRONJ if cumulative exposure and potency are accounted for [123].

Local The development of MRONJ generally follows a local infection or trauma to the bone (usually surgical trauma or pressure sores) or soft tissue. Typical events that might precede MRONJ

Table 32.3 Incidence of ONJ cases reported for different antiresorptive agents as well as cancer therapies

Bisphosphonates	RANKL inhibitor	Antiangiogenic agent	mTOR inhibitors
Zoledronate (67.1%)	Denosumab (6.9%)	Bevacizumab (4.1%)	Temsirolimus (0.2%)
Alendronate (42.7%)		Sunitinib (2.4%)	Everolimus (0.5%)
Pamidronate (30.7%)		Sorafenib (0.5%)	
Risedronate (4.8%)		Pazopanib (0.1%)	
Ibandronate (4.6%)			
Clodronate (0.2%)			
Etidronate (0.2%)			

mTOR inhibitors tyrosine kinase inhibitors

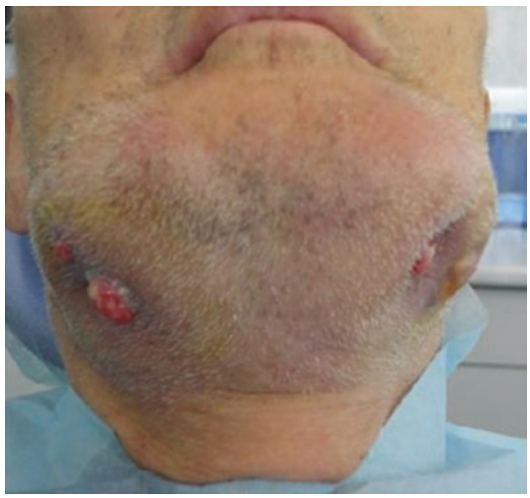


Fig. 32.8 Medication-related osteonecrosis of the jaw: In addition to the antiresorptives and antiangiogenic therapies, some drugs for RA (DMARDs, Biologics) may compromise healing and be associated with oral lesions identical to those of the ONJ. Steroids can increase the risk of ONJ. *mTOR-kinase* tyrosine kinase inhibitors

include significant periodontal inflammation, pressure sores from ill-fitting prostheses and invasive procedures (e.g., tooth extraction), and other dentoalveolar surgery (Fig. 32.9) [119, 124, 125]. In one study, signs of peri-implantitis were found in 93% of patients (14/15) with peri-implant MRONJ, and this may contribute to the etiology of the condition; nearly all implants (95%) had been placed before patients commenced antiresorptive treatment [125]. Of note, approximately one-third of MRONJ cases occur spontaneously without any identifiable initiating event; in these cases, subclinical trauma is a likely cause [119]. Clinical observation has shown an association between the occurrence of MRONJ and dental extractions and infection, although the underlying mechanism of how these events lead to osteonecrosis remain poorly understood and more high-quality evidence is required [119, 124, 126, 127].

Personal risk factors Many additional factors have been reported in the literature as being associated with accelerated development and/or increased severity of the condition, but for most of these, it remains unclear whether or not they are causative factors [118, 128–130]. They include the use of corticosteroids, the presence of concomitant diseases or conditions (e.g., preexisting dental infections, anemia, diabetes-mellitus, and immunosuppression or renal failure), poor oral hygiene, and smoking (Table 32.4) [118, 128, 129]. The role of genetic factors in MRONJ is also being investigated in order to help to identify patients at increased risk of MRONJ; however, a robust association between MRONJ risk and a specific genetic variant has not yet been identified [131]. In general, further research is required to elucidate the role of different potential risk factors in the development of MRONJ.

Differences in Antiresorptive Functions Between Bisphosphonates and Denosumab

The antiresorptive mechanisms of BPs and denosumab are completely different. Bisphosphonates are usually buried in the bone matrix, get incorporated into osteoclasts during the process of bone breakdown, and consequently disrupt the

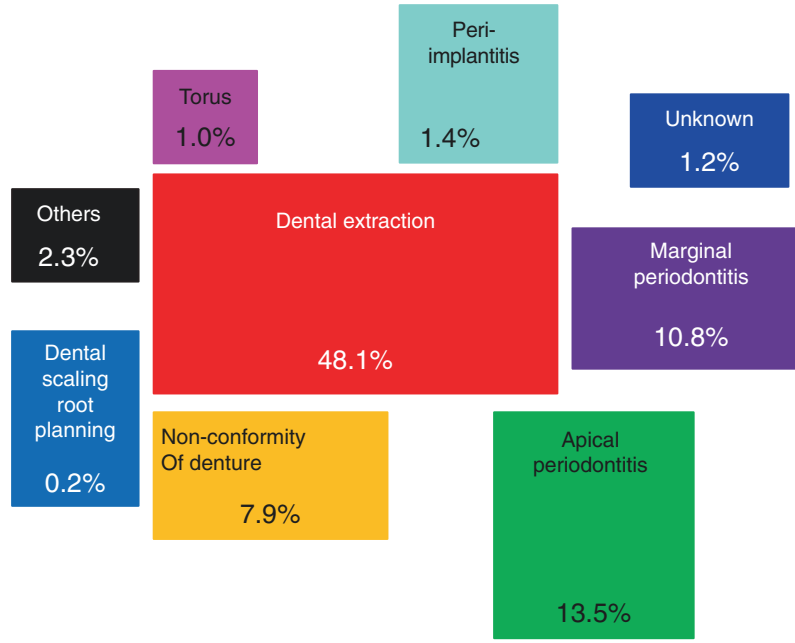


Fig. 32.9 Triggers for BRONJ onset: The commonest trigger for onset of BRONJ was tooth extraction (48.1%), followed by apical periodontitis (13.5%). (The data are taken from the published paper (Shibahara et al. 2019 [24]))

Table 32.4 Personal risk factors predisposing for ONJ

ONJ risk factors
Personal/dental factors
Dental surgery, dental extraction (tooth extraction) [major risk factor]
Local trauma from ill fitted dentures, ill fitted implants
Periodontal (gum) disease or other oral conditions, poor oral hygiene
Dental infection
Smoking
Medications
Antiresorptives or antiangiogenesis therapy (risk increases with higher doses and longer duration of antiresorptive therapy)
Glucocorticoids use
Immunosuppressants, e.g., methotrexate and azathioprine
Associated comorbidities
Diabetes mellitus, autoimmune diseases, anemia, cancer, hematological diseases, HIV
Radiotherapy to head and neck

functions of the cytoskeleton and accelerate apoptosis, thus suppressing resorption through osteoclast dysfunction. Denosumab, on the other hand, suppresses the function of the molecule RANKL, which is essential for osteoclast differentiation and function, thus inhibiting resorption through suppression of osteoclast differentiation, function, and survival. The fact that these two drugs with differing antiresorptive mechanisms induce ONJ suggests that the decrease in the bone turnover rate may represent a risk factor for ONJ. Thus, among patients treated with a powerful antiresorptive drug, ONJ is readily triggered by infections or other causes. From the pharmacokinetics of bisphosphonates and denosumab, it is conceivable that jawbone disorders due to bisphosphonates may be irreversible, but those due to denosumab may be reversible [24].

Duration of Medication Therapy as a Risk Factor for MRONJ

Regardless of indications for therapy, the duration of bisphosphonates or antiresorptive therapy continues to be a risk factor for developing MRONJ. In patients with cancer exposed to zoledronate or denosumab, the incidence of developing MRONJ was, respectively, 0.6% or 0.5% at 1 year, 0.9% or 1.1% at 2 years, and 1.3% or 1.1% at 3 years, with the risk for MRONJ in denosumab-exposed patients plateauing between years 2 and 3 [133]. In a study by Saad et al., [134] the investigators combined three blinded

Table 32.5 Comparison of dosage and outcome in ONJ of zoledronate/denosumab/alendronate in cancer and osteoporosis

Parameter	Zoledronate IV	Alendronate (oral)	Denosumab SC
Dosage in osteoporosis	5 mg IV/year for 3–6 yr	70 mg/week for 3–5 yr	60 mg SC/6-months for 5–10 years
Dosage in prevention of skeletal-related events	4 mg IV/month for 3 yr	NA	120 mg SC/month for 3-years
ONJ in cancer	1.3%	NA	1.8%
ONJ in osteoporosis	0.017–0.35%	0.02–0.1% (<4 years) 0.21% (>4 years)	0.04–0.3%

phase-3 trials and found similar results, including a plateau after 2 years for patients exposed to denosumab. In patients with cancer exposed to zoledronate or denosumab (n = 5723), the incidence of developing MRONJ was, respectively, 0.5% or 0.8% at 1 year, 1.0% or 1.8% at 2 years, and 1.3% or 1.8% at 3 years [133].

For patients receiving oral bisphosphonates therapy to manage osteoporosis, the prevalence of MRONJ increases over time, from nearly 0% at baseline to 0.21% after at least 4 years of bisphosphonates exposure. The median duration of bisphosphonates exposure for patients with ONJ and ONJ-like features was 4.4 years (Table 32.5). For patients without MRONJ, the median exposure to oral bisphosphonates s was 3.5 years [20, 107].

Compared with patients with cancer receiving antiresorptive treatment, the risk of MRONJ for patients with osteoporosis exposed to antiresorptive medications is approximately 100 times smaller. shows a screening questionnaire to identify patients at risk of developing medication related osteonecrosis of the jaw.

Imaging and Diagnosis

Once a patient suffers from a MRONJ, typical findings are necrotic (alveolar) bone, inflammation of the surrounding tissues (in some cases), and fistulas. Depending on inflammation and the involvement of nerve structures, MRONJ is often painful and will reduce the quality of life. Therefore, it is important to try to prevent MRONJ. Once the clinical picture shows typical MRONJ features, imaging is necessary to determine the size of the lesion. Exposed bone is not always painful [10, 11], therefore a thorough clinical examination and radiological imaging are essential when MRONJ is suspected. Imaging can be split into two main categories: anatomical and functional imaging (Table 32.6). This was reviewed in an article published by Berg et al. [132]. Each of these imaging modalities has its characteristic morphological, anatomical, and physiological criteria. These were discussed by Tsuchimochia and Kurabayashib in a symposium [9] and summarized in Table 32.7.

Table 32.6 Different Imaging modalities of MRONJ

Anatomical imaging	Functional imaging
Radiographs	Bone scan
Computed tomography (CT)	18F-FDG positron emission tomography/computed tomography
Cone-beam computed tomography (CBCT)	Fluorescence-guided bone resection
Magnetic resonance imaging (MRI)	

Imaging in Patients with Bisphosphonate-Associated Osteonecrosis of the Jaws (MRONJ)

Anatomical Imaging

Morphological anatomical imaging including panoramic radiographs, cone-beam computed tomography (CBCT), computed tomography (CT), and magnetic resonance imaging (MRI) will be discussed in this section. Functional imaging includes nuclear imaging techniques and

Table 32.7 A comparison of the characteristics of each of the imaging modalities used for assessment of MRONJ

	Anatomical tissue		Physiological tissue characteristics				
	Bone	Soft tissue	Bone marrow	Bone remodeling	Bone blood flow	Edema	Adipose tissue
Panoramic Radiograph	++	–	–	–	–	–	–
Cone beam CT	+++	–	–	–	–	–	–
CT	+++	++	±	–	++	+ (soft tissue)	+
MRI	+	+++	++	–	++	++ inflammation	++
Bone scan	–	–	±	+++	++	–	–
SPECT/CT	±	–	±	+++	++	–	–
PET/CT	±	+	–	–	–	++ inflammation	–

fluorescence imaging/visually enhanced lesion scope.

Panoramic Radiographs

In a daily routine, a clinical examination and a radiograph are the least examinations required in order to detect lesions and to provide data for a follow-up appointment. Marx et al. [68] noted that panoramic imaging is the image of choice for a routine dental assessment in these patients. Panoramic radiographs are able to distinguish ONJ from metastatic lesions (except if the lesion is osteolytic). For the lesion to be seen in the plain X-ray films, it is required to have a least a 30% loss of bone before detection is made.

Arce et al. [135] noted that although conventional anatomic imaging is easily accessible, bone changes and radiographic findings can have a lag time of up to 2 weeks. Rocha et al. were able to show that patients who "are treated with zoledronate presented a statistically significant increase in the number of radiographic abnormalities compared with the control group" [136]. Phal et al. found in their study that all patients showed osseous sclerosis. The alveolar margin was involved in two-thirds of the patients. Lamina dura thickening, full-thickness sclerosis, poor/nonhealing extraction sockets, widening of the periodontal ligament space, osteolysis, and sequestra, fistula, soft tissue thickening, and periosteal new bone formation were also found and described [137]. Patients who received follow-up imaging showed progressive sclerotic changes leading to possible narrowing of the mandible canal. A study published by Torres et al. [138] was able to show that in panoramic radiographs, the "mean mandibular inferior cortical bone thickness (MICBT) of patients with bisphosphonate osteonecrosis of the jaw (BRONJ) was significantly higher compared with patients without BRONJ taking bisphosphonates, and mean mandibular inferior cortical bone thickness (MICBT) of patients without BRONJ taking bisphosphonates was higher than that of controls". They could also show that "among patients taking zolendronate, there was a correlation between MICBT and cumulative dose". However, a prospective study carried out by Stockmann et al. [139] revealed that detectability of MRONJ lesions was 54% for panoramic radiographs, 96% for CT, and 92% for MRI scans. Stockmann et al. concluded that "even if BONJ lesions can be detected on panoramic radiographs, an adequate assessment of the extent of BONJ is not possible," and therefore panoramic imaging is usable, but in severe cases must be followed by further diagnostics (Figs. 32.10a, 32.11a, and 32.12a).

Cone-Beam Computed Tomography (CBCT)

Cone-beam computed tomography (CBCT) has the advantage of exposing the patient to a lower radiation than conventional CT. It provides better

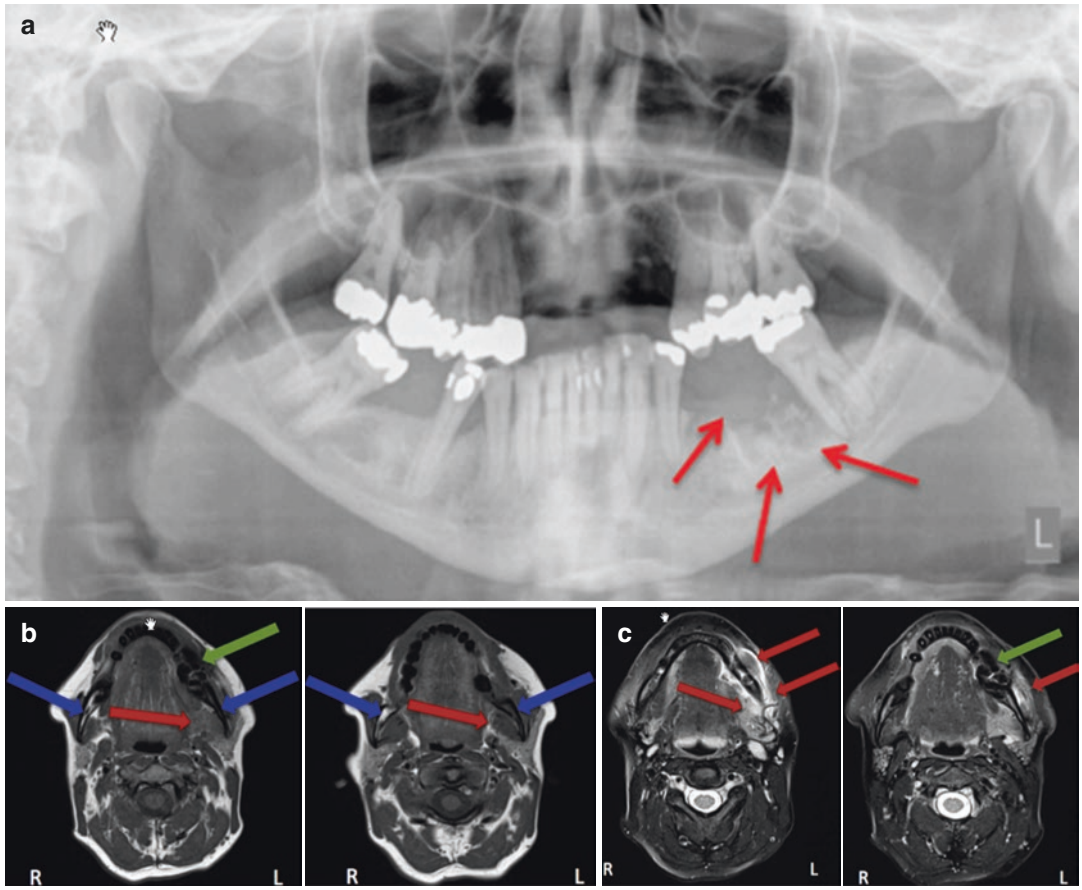
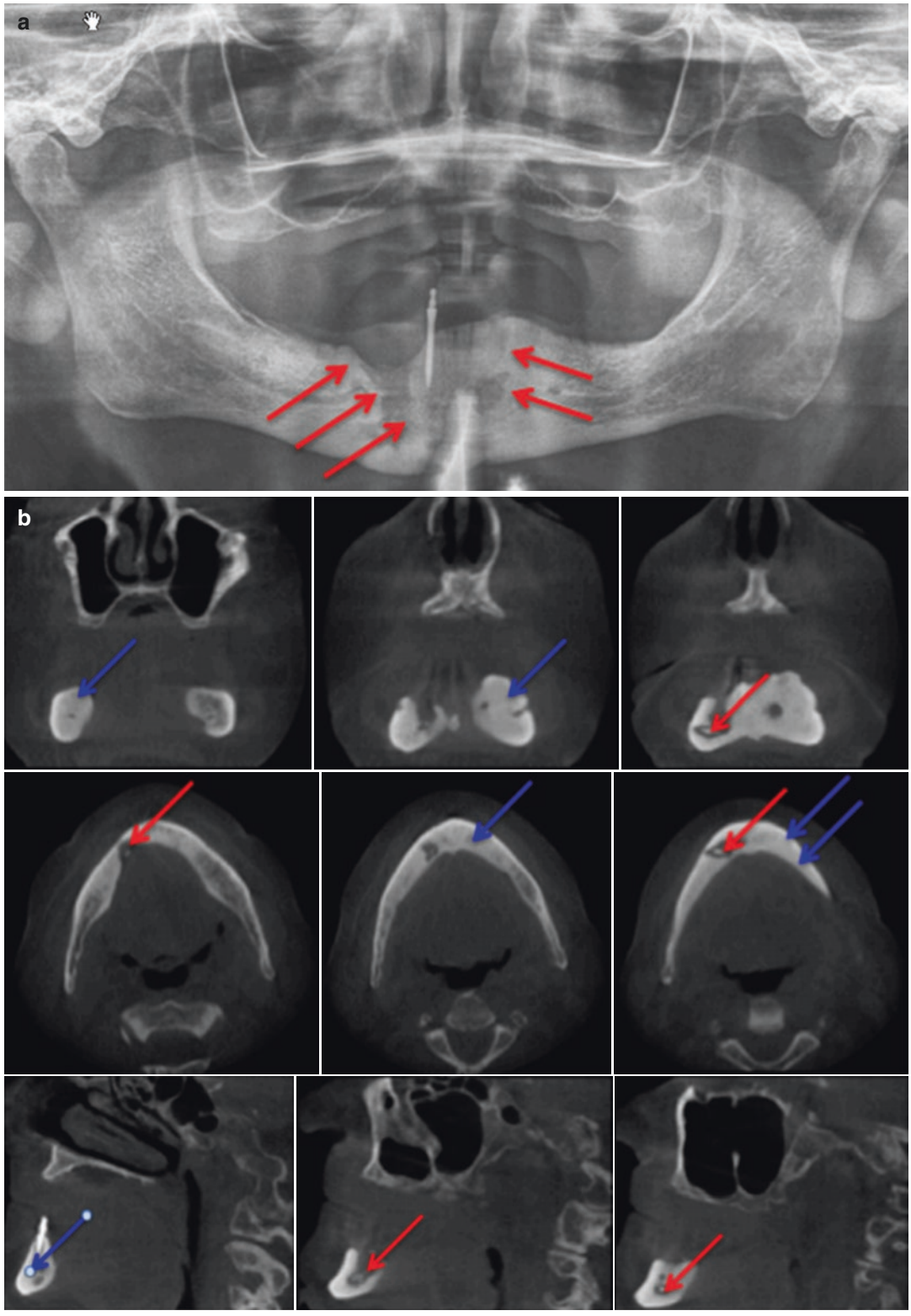


Fig. 32.10 (**a**) Panoramic radiograph: Patient: 48 years old, female, metastatic breast cancer, zoledronic acid. Red arrows point to the necrotic area. American Association of Oral and Maxillofacial Surgeons (AAMOS) staging: stage 2. (Quoted from Berg et al. [132] under open access scheme under the CC BY-NC-ND license (Commons Attribution (CC-BY) license (http://creativecommons.org/licenses/by/4.0/)). (**b**) Magnetic resonance imaging (Siemens, Avanto, 1.5T, Sequence: T1 tse tra) of the same patient: 48 years old, female, metastatic breast cancer, zoledronic acid for 2 years (panoramic radiograph Fig. 32.7a). Green arrow showing the MRONJ necrosis, red arrows showing the oedema, blue arrows showing the differences between the right side, normal fatty bone marrow, and left side: signal loss, due to loss of fat. AAMOS staging: stage 2. (**c**) Magnetic resonance imaging (Siemens, Avanto, 1.5T, Sequence: T2 tse tra) of the same patient: 48 years old, female, metastatic breast cancer, zoledronic acid for 2 years (panoramic radiograph Fig. 32.7a). Green arrow showing the MRONJ necrosis: hypointense bone marrow, red arrows showing the oedema. Pair of screenshots. AAMOS staging: stage 2. (Quoted from Berg et al. [132] under open access scheme under the CC BY-NC-ND license (Commons Attribution (CC-BY) license (http://creativecommons.org/licenses/by/4.0/))

Fig. 32.11 (**a**) Panoramic radiograph: Patient: 77 years old, male, metastatic prostate cancer, ibandronic acid and later another antiresorptive drug: denosumab. Red arrows point to the necrotic area. There is an artifact that attributed to the thyroid shield. AAMOS staging: stage 2. (**b**) Cone-beam computed tomography (Carestream CS 9300) of the same patient: 77 years old, metastatic prostate cancer, ibandronic acid and later another antiresorptive drug: denosumab. For panoramic radiograph, see Fig. 32.2. First row, coronary view; second row, axial view; and third row, sagittal view. Red arrows: sequester; blue arrows: sclerotic region. AAMOS staging: stage 2. (Quoted from Berg et al. [132] under open access scheme under the CC BY-NC-ND license (Commons Attribution (CC-BY) license (http://creativecommons.org/licenses/by/4.0/))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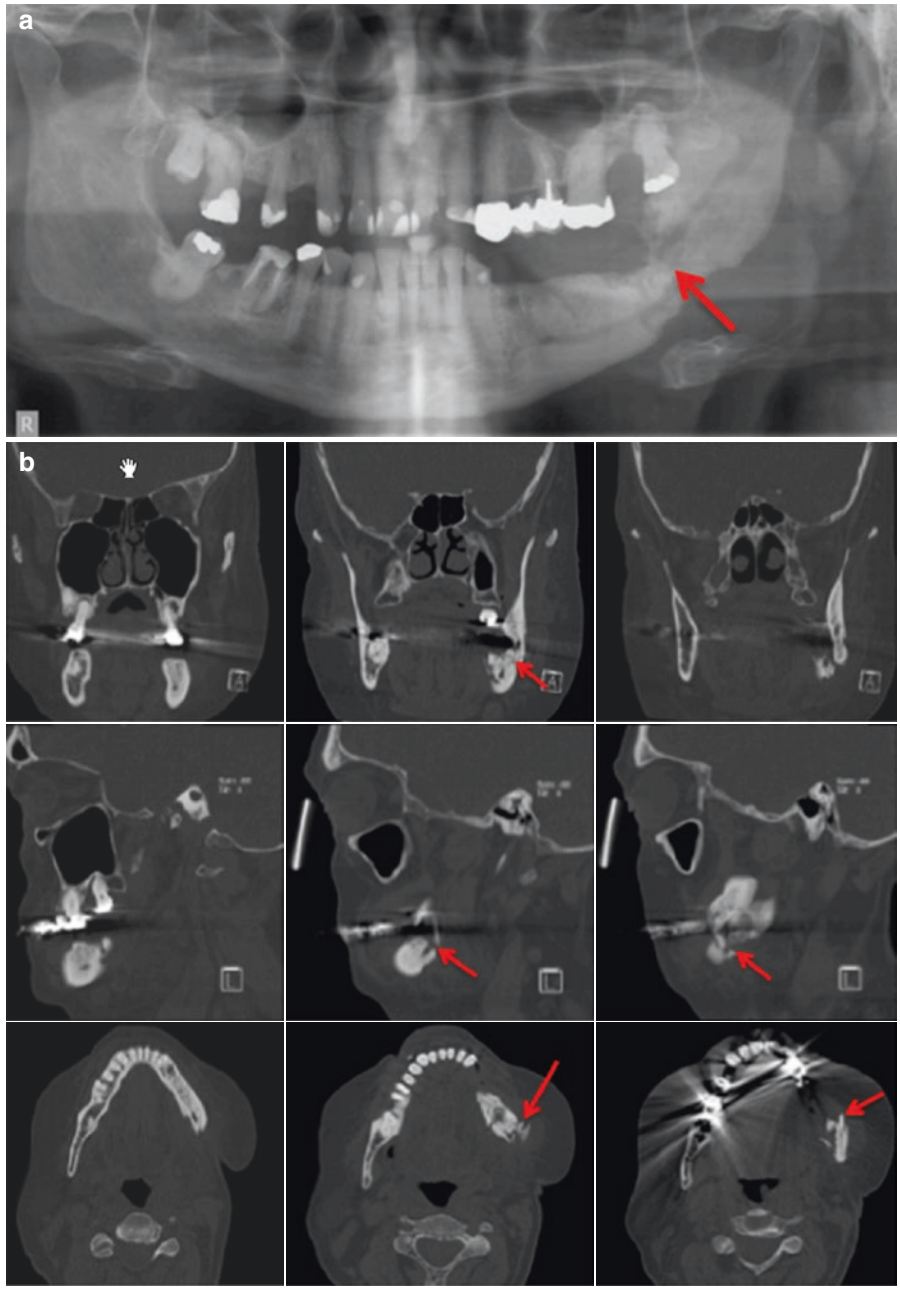

Fig. 32.12 (**a**) Panoramic radiograph: Patient: 66 years old, male, secondary osteoporosis due to castration, alendronate. Red arrow indicates the almost invisible fracture. AAMOS staging: stage 3. (**b**) Computed tomography (Siemens, Sensation 64) of the same patient: 66 years old, male, secondary osteoporosis due to castration, alendronate. Red arrow points in the direction of the fracture due to the bisphosphonate necrosis. AAMOS staging: stage 3. (**c**) Planar scintigraphy (Siemens, Symbia) Blood pool phase. Of the same patient: 66 years old, male, secondary osteoporosis due to castration, alendronate. AAMOS staging: stage 3. (**d**) Technetium-99m-3,3-diphosphono-1,2-propanodicarboxylicacid (99Tcm-DPD) SPECT/CT (Siemens, Symbia) of the same patient: 66 years old, male, secondary osteoporosis due to castration, alendronate. First row sagittal, second row axial view; 4.5 h after injection (bone phase). The uptake in the left mandible is clearly visible (red arrow). AAMOS staging: stage 3. (Quoted from Berg et al. [132] under open access scheme under the CC BY-NC-ND license (Commons Attribution (CC-BY) license (http://creativecommons.org/licenses/by/4.0/))

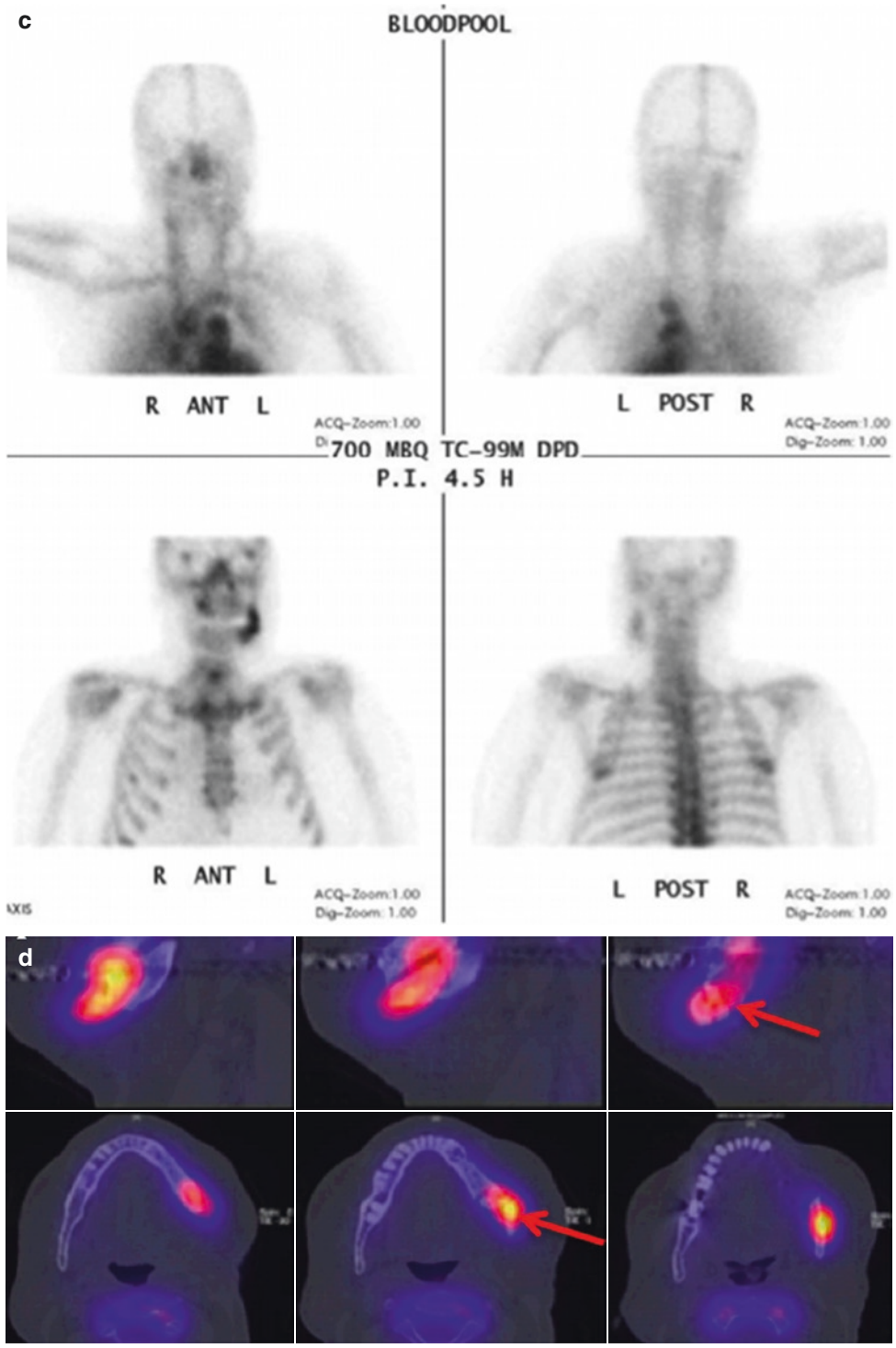

Fig. 32.12 (continued)

image quality beside little limited for discrimination of soft tissue, and in the meantime, it provides detailed information about cortical thickness and integrity, marrow involvement, irregularities after tooth extraction, and cancellous BMD.

In comparison with MRI and CT, there are fewer papers about imaging of MRONJ with CBCT. In their review, Yalcin and Gungormu's reported that typical findings in CBCT and CT are "pathologic fractures, narrowing of the marrow space and involvement of the inferior alveolar canal" [140] (Fig. 32.11b).

Detecting periosteal thickening or bone density changes at an early stage before it gains clinical importance might be another indication [140, 141] for the use of CBCT. Wilde et al. stated that the two most common findings in CBCT for MRONJ are "destruction of the trabecular structure of the cancellous bone and erosion of the cortical bone" [142]. Treister et al. described CBCT as superior at detecting fragmentation and sequestra in comparison with panoramic radiographs [143]. Since Cankaya et al. [144] found in their rat model that "the extent of the BONJ lesions assessed from CBCT scans did not differ significantly from the intraoperative situation, and a significant correlation between CBCT measurements and intraoperative measurements was found," and radiation dosage a low as just 3 μSv (effective dose 5 × 5 cm adult exam) are commercially published [145], CBCT might gain even greater relevance in the future.

Computed Tomography

The appearance of ONJ at radiography and CT is variable and includes ill-defined areas of lucency or low attenuation, permeative appearance, cortical destruction, bony sequestrum, periosteal reaction, or sclerotic changes [146]. The bone changes may be mixed, predominantly lytic, or predominantly sclerotic [147–150]. The lytic areas may represent foci of bacterial infection. Persistent alveolar sockets have been described as a typical radiographic feature of ONJ. Focal medullary sclerosis with disorganized micro-trabeculae and poor corticomedullary differentiation in the suspected necrotic site has been described as a finding associated with early symptoms of tooth loosening or delayed socket healing after tooth extraction; this appearance may represent early imaging findings associated with bisphosphonate-related ONJ [147]. Periosteal reaction and bony sequestrum may be predominant in advanced stages of the disease (Fig. 32.12b) [146].

Bianchi et al. [148] assessed 32 panoramic radiographs and CT scans in detail for the following features: "structural alteration of trabecular bone, from initial change in thickness and mineral content of the trabeculae to the formation of microlacunae; cortical bone erosion; osteosclerosis; small (less than 15 mm) sequestrum; extensive (more than 15 mm) sequestrum; and presence of periosteal new bone." They found that CT was superior to dental panoramic radiographs in detecting all the radiologic signs [148]. Cortical bone erosion and trabecular bone resorption were visible to different extents.

The extended follow-up (CT scans at 3, 6, 12, 18, and 24 months) by Bedogni et al. was able to show that "CT signs of recurrent disease are apparent within 6 months after surgery and precede clinical manifestations of BRONJ" [151]. Sanna et al. stated that CT helps to differentiate between MRONJ and metastasis [152]. Elad et al. assessed 110 CT scans and stated "the mandibular canal cortex was resistant to the destructive process of the jaw, unlike in metastases" [153], but there are MRONJ cases which are still difficult to diagnose even with CT. Therefore, clinical examination is mandatory for diagnosis [154]. On another front, thickening of the sinus maxillary mucosa was also noted in MRONJ patients [148]. A study by Gallego et al. showed that MRONJ patients had greater probability of presenting sinus mucosal thickening in comparison to a healthy group. They used a thickening of >3 mm as their measurement value. In their assessment, they found that the thickening was present more in patients with "advanced-stage disease" [155].

Magnetic Resonance Imaging

At MR imaging of ONJ, signal intensity changes encompass bone and adjacent soft tissues; after contrast enhancement, the signal intensity

changes may appear more extensive than changes seen at CT [147]. MRI is considered the method of choice in assessing ONJ with high sensitivity for progressive cell death and repair (edema). It also provides detailed information about cortical thickness and integrity, marrow involvement, irregularities after tooth extraction, and cancellous bone mineral density. Variable signal intensity abnormalities on T1- and T2-weighted images have been noted, a finding possibly associated with the disease stage. ONJ is typically associated with decreased signal intensity on T1-weighted images; signal intensity changes on T2-weighted or short inversion time inversion-recovery (STIR) images and contrast-enhanced images show greater variability [146, 156, 157].

In the study carried out by Guggenberger et al., all MRONJ foci "showed markedly decreased signal on T1-with increased signal on T2-weighted images. Contrast uptake of affected bone and surrounding tissue was noted in all patients who had foci of bisphosphonate ONJ" [158]. Furthermore, the authors described that contrast-enhanced MR imaging shows more extensive changes in comparison to the clinical examination and CBCT imaging. In their study, Stockmann et al. stated that "MRI has a high detectability for BONJ lesions" [139], but limitations were found concerning the extent of the detection. Bedogni et al. assessed in their study 11 MRI scans performed on MRONJ patients [41]. Gadolinium (intravenous) was used as a contrast agent. These images showed two patterns of bone disease: "Exposed areas showed a low signal in T1- and T2-weighted and inversion recovery images, which suggests low water content and is histopathologically correlated with paucity in cells and vessels (osteonecrotic pattern). Unexposed diseased bone was characterized by T1 hypointensity and T2 and IR hyperintensity, which suggests high water content and inflammation, associated with hypercellularity, osteogenesis, and hypervascularity (osteomyelitic pattern)" [159]. Hypointensity in T1 was also seen in MRI scans performed on our patient (Figs. 32.5 and 32.6). Krishnan et al. described early MRI findings of MRONJ in their publication. This includes at the early stage "the loss of the normal T1 hyperintensity of fatty marrow in the mandible and maxilla." "Bone destruction, soft tissue edema and enhancement, inferior alveolar nerve thickening, and pterygoid muscle swelling and enhancement" are findings of more advanced stages [160] (Fig. 32.10b, c).

Functional Imaging

Functional imaging has gained increased attention over the past years. Functional imaging modalities may have an important role in the diagnosis of MRONJ. Functional imaging bone includes two main items: scintigraphy and positron emission tomography (PET).

Bone Scan (Skeletal Scintigraphy)

In functional imaging of bone diseases, a skeletal scintigraphy is one of the basic imaging modalities. Radionuclide bone imaging is not specific, but its excellent sensitivity makes it useful in screening for many pathologic conditions. Bone scintigraphy with technetium-99m–labeled diphosphonates is one of the most frequently performed of all radionuclide procedures. These compounds accumulate rapidly in bone, and by 2–6 hours after injection, about 50% of the injected dose is in the skeletal system. Single photon emission computed tomography (SPECT) is a nuclear medicine tomographic imaging technique using gamma rays. Information from a planar scintigraphy is displayed in a two-dimensional form in contrast to SPECT. In SPECT imaging, the distribution of the radionuclide is monitored in multiple two-dimensional images and from multiple angles. From these datasets, a three-dimensional image is then calculated. If anatomical imaging should be added, hybrid SPECT/CT scanners are available. SPECT-CT is very similar to conventional nuclear medicine planar imaging, using a gamma camera, where the images or pictures from two different types of scans are combined together; hence, it is possible to provide true 3D information.

MRONJ should not show an uptake in the necrotic zone, but due to the associated infection, a nuclide uptake may be seen.

In a case analysis by Chiu et al., 10 out of 13 patients showed focal abnormal activity (increased radionuclide uptake with central decrease) in scintigraphy imaging [161]. O'Ryan et al. [162] published a retrospective study on MRONJ patients who had received whole-body planar bone scintigraphy. They used the following scoring system for the jaw: "score 0, no visual evidence of increased uptake was present; score 1, uptake was mild and equal to that in the sternum; and score 2, uptake was intense and greater than that in the sternum" [162]. The comparison with the sternum uptake was based on a paper published by Kakhki et al. [163]. Kakhki et al.'s paper, a study on 334 patients who had no diseases of the sternum/chest wall or malignancy, assessed the normal uptake in a sternum considering the age of the patient.

Thomas et al. assessed the impact of bone scintigraphy in patients with metastatic castration-resistant prostate cancer who had received bisphosphonates. Their focus was on early prediction of clinically asymptomatic MRONJ. MRONJ was significantly more often developed in patients with a pathological tracer uptake [164]. Ristow et al. investigated the bone turnover in the jaw of breast cancer patients who had received no antiresorptive medication, bisphosphonates, or denosumab. Interestingly, they found that "there was similar turnover of bone in the mandible compared with other skeletal sites (such as the femur), while the maxilla showed significantly higher turnover." Since the majority of MRONJ lesions occur in the mandible, the bone turnover role of the MRONJ pathogenesis must be further reviewed [165] (Fig. 32.12c).

18F-FDG Positron Emission Tomography/Computed Tomography (PET/CT)

Fludeoxyglucose F18 (18F-FDG) PET/CT combines anatomical imaging and functional imaging. Infected bone tissue is expected to show increased glucose metabolism, reflecting an increased uptake, in comparison to necrotic areas. This is the main reason for imaging in suspected necrotic areas, where no blood flow and hypermetabolism occurs, is used. Therefore, abnormal mandibular enhancement on PET scan is not necessarily an indicator of MRONJ, but rather a reflection of an inflammatory process [166]. Consequently, early detection and assessment of an inflammatory process is possible if this imaging is available. This is of vital importance as the inflammatory phase is one of the risk factors for the development of a MRONJ and as expected, early diagnosis might prevent the progression of the disease. Fleisher et al. retrospectively analyzed the PET/CT scans from 23 patients (treated with bisphosphonate and/or denosumab) and concluded that PET/CT can be a helpful tool since their results showed that "FDG PET/CT detects local and diffuse metabolic changes that may not be represented by plain radiography" [167]. For evaluation a normal reference has to be taken: "normal bone of the contralateral side of the jaw, the cervical vertebrae, and the skull base can be considered as the normal reference" [158]. However, PET imaging cannot identify osteonecrosis that is not associated with infection (i.e., aseptic necrosis) or a reactive or reparative process [167] (Fig. 32.12d).

Fluorescence-Guided Bone Resection/Visually Enhanced Lesion Scope (VELscope®)

Fluorescence-guided bone resection is a precisely described way of imaging in combination with surgery in MRONJ patients. This method is published: preoperatively, the patient receives 100 mg doxycycline twice a day for 10 days. The viable bone will have a doxycycline uptake and will present a "greenish" light when illuminated by the VELscope® (LED Dental, White Rock, BC, Canada). The fluorescence of vivid bone will be visualized "under blue excitation light of 400 to 460 nm" [168], and "it should be noted that the green fluorescent filter fitted to the handpiece is an essential component that separates the doxycycline fluorescence from the bright exciting light of the lamp" [168]. Necrotic bone will not have an uptake therefore no/very little fluorescence is shown. In a study by Pautke et al.,

"bleeding of the bone during resection did not correlate with any bone fluorescence signal" [169]. In cancellous bone regions, bone bleeding can occur, suggesting viable bone, but fluorescence is not seen. This technique might offer a way to standardize the surgical procedure. In a study performed by Assaf et al. [170], 20 patients were included in a prospective study. Except in one case, necrotic lesions were visible using the VELscope®. Even in a patient who received only a single 100 mg shot of doxycycline 1 hour preoperatively, it was possible to distinguish between necrotic and healthy bone using the VELscope®. Based on these findings and their own observations, Ristow and Pautke published a study on eight patients using autofluorescence of healthy bone without doxycycline/tetracycline labeling. Using the VELscope® Vx, vivid bone showed an autofluorescence. Necrotic bone shows an altered fluorescence pattern (pale or no fluorescence). Thus, it is suggested that autofluorescence of bone might be of similar use during the surgical therapy of MRONJ [171].

Clinical Application of MRONJ Imaging

Defining the Area of Inflammation

MRONJ is basically osteomyelitis associated with bone necrosis [172]. Severe infiltration of inflammatory cells is seen on histopathological examination, particularly in nonexposed bone, whereas actinomyces species are often found in necrotic lesions. In the early stage of the disease, MRI shows a decrease in bone marrow signal intensity on T1-weighted images, whereas increased signal intensity is seen on T2-weighted images and short T1 inversion recovery (STIR) images. Inhomogeneous gadolinium enhancement reflects soft tissue inflammation. In advanced diseases, in necrotic areas, the bone marrow signal intensity of T2-weighted images and STIR can decrease, whereas in non-necrotic areas, an increasing intensity can be seen [173]. These high signal intensities reflect inflammation of the bone marrow, edema, and circulatory disturbances in bone. Tomographic information depicting inflammation of the soft tissue is also observed. FDG PET/CT is also used to diagnose MRONJ [174]. FDG PET/CT is useful for diagnosing osteomyelitis and also helpful for diagnosing inflammation in MRONJ patients [175].

Monitoring of the Disease Course

It is critical to closely monitor MRONJ patients by imaging modalities for the assessment of spread or remission. Repeat imaging examinations might be required as it provide important information to select the appropriate treatment option and evaluate the response to therapy. When the lesion is confined to the alveolar bone, periodic intraoral X-ray imaging and panoramic examination are useful for assessing changes in the alveolar bone surrounding teeth with caution of excess radio exposure. In stage II, III, or advanced stage I, CBCT, CT, MRI, and bone scintigraphy can offer additional and more precise information to monitor the patients. MRI and FDG PET/CT are useful for evaluating the state of inflammation. Bone scintigraphy is well suited to reflect changes in bone metabolism during the disease course and after surgery. FDG PET/CT can be available to evaluate the treatment response after surgery [176].

Providing Useful Imaging Findings for Surgery

Although conservative treatment has been widely accepted, surgical intervention can also play an important role in the disease management and result in improved outcomes, [177–179]. Patients may undergo surgical procedures including debridement, marginal resection, partial resection, en-bloc or segmental resection of the mandible, hemi-mandibulectomy, maxillectomy, or excision of the whole mandible, depending on the severity of MRONJ. The success rate of surgery varies from 15% to 100% [177]. Complete excision of sequestered and nonregenerative bone is mandatory to improve the success rate. Total coverage of the viable bone by soft tissue and improvement in symptoms are important to maximize the patient's quality of life. To ensure successful surgical excision of the nonviable bone CT, CBCT, MRI, and bone scintigraphy

provide useful information to set a surgical margin. Sclerosing bone and tissues that indicate negative regenerative capacity can be identified by CT and CBCT, and the status of inflammation in the bone and soft tissue can be assessed by MRI. Bone scintigraphy clearly demarcates the bone lesion boundaries. Sufficient blood supply is necessary for bone repair and regeneration. Three-phase bone scintigraphy (vascular phase, blood pool phase) or measurement of the blood flow index may help to assess blood circulation [180, 181]. Fluorescence imaging-guided debridement is also reported for MRONJ treatment [182].

Predicting Disease Prognosis

MRONJ often develops after tooth extraction. Advanced periapical and marginal periodontitis is a common cause of extraction. Intraoral x-ray examination and panoramic radiography are the standard imaging techniques for detecting periodontitis. However, it is difficult to predict the future onset of the disease by imaging among people with antiresorptive therapy because periodontitis is very common. To reduce the possible risk of future development of the osteonecrosis of the jaw, early detection and treatment of dental diseases is vital. Particularly for nonsymptomatic intravenous bisphosphonate users, intraoral X-ray examination and panoramic radiography should be carried out routinely because of the high occurrence rate of the disease. In oral bisphosphonate users without MRONJ symptoms, close examination of intraoral and panoramic X-ray images also must be studied. Patients who have received bisphosphonate therapy for more than 4 years are at high risk of developing the disease. Bone scintigraphy is useful for predicting the onset of the disease [182–185]. O'Ryan et al. reported that bone scintigraphy showed positive uptake before the development of MRONJ in 67.5% of patients who had no clinical evidence of osteonecrosis [186]. Radiopharmaceuticals including methylene diphosphonate (MDP) and hydroxymethylene diphosphonate (HMDP), used for bone scintigraphy, have a P C P bond in their chemical structures, which is the same basic structure as that in bisphosphonate drugs. These radiotracers are thought to accumulate in identical sites in the bone as bisphosphonate drugs concentrate. When radiotracers show high uptake in the alveolar bone (suspected periodontitis), bisphosphonate drugs accumulate at high concentrations in the same region, in contrast to the normal uptake region, which may induce higher toxic damage to osteoclasts than in non-high-uptake cases. Radiotracers accumulate increasingly in tooth extraction sites. Bisphosphonate use may be postponed for nonsymptomatic patients with increased uptake in jaws on bone scintigraphy until a decrease to normal uptake levels is observed [187, 188].

Lab Investigation: Bone Markers in MRONJ

The maxillary and mandible bones concentrate a greater proportion of BPs than other bone tissues due to their relatively higher bone turnover ratio [189]. This remodeling rates cause an alveolar bone cortical thickness [190]. Antiresorptive medications inhibit the resorptive activity of osteoclasts when used in therapeutic doses, while they stimulate osteoblasts. However, the use of high doses of the bisphosphonates results in the formation of intracellular calcium in both osteoblasts and osteoclasts causing cytotoxic effect. As a result, the mechanism of bone regeneration is impaired, and necessary remodeling cannot take place. Serum parameters associated with bone metabolism and reflecting the state of bone remodeling can be measured [191, 192].

A total of seven biomarkers were identified and classified into three groups: bone turnover biomarkers (i.e., bone alkaline phosphatase (BAP), c-terminal telopeptide cross-link of type I collagen (CTX), deoxypyridinoline (DPD), N-telopeptides of bone type I collagen (NTX), osteocalcin (OC)), endocrine biomarkers (i.e., parathyroid hormone (PTH)), and angiogenesis markers (i.e., vascular endothelial growth factor (VEGF)). The systematic reviews of Dal Prá et al. [193] and Enciso et al. [194] revealed that bone turnover biomarkers present a series of individual and inherent limitations. Bone alkaline phosphatase (BAP) has a low sensitivity and

specificity in the study of bone metabolic disease and is not useful in patients with hepatic disorders. Osteocalcin appears altered in states of liver failure. CTX and NTX do not exclusively measure bone metabolism but all the tissues that contain type I collagen. Finally, DPD is currently considered a non-discriminatory marker in bone pathology. In the study of osteoporosis as well as MRONJ, the current gold standard biomarker is CTX [195].

Bone Markers as Predictors of MRONJ

Reliable prediction of medication-related osteonecrosis of the jaw (MRONJ) occurrence and its consequences is one of the most challenging tasks for clinicians. Given the low incidence, severe complications, and lack of effective treatment of MRONJ, developing efficient predictive and preventive strategies becomes all the more necessary, although none such strategy has so far gained wide acceptance [196]. Personalized medicine is currently being tested across several clinical fields to predict risks, prevent complications, and optimize outcomes [197]. Most incidences of MRONJ occurred following an invasive dental procedure (IDP). Over the last decade, preoperative serum level of C-terminal telopeptide cross-link (CTX), a by-product of bone remodeling, has been presented as a predictor of the risk of developing post-operative MRONJ [198], and a prognostic factor [199]. Furthermore, a preoperative drug holiday of 3–6 months has been recommended for patients with a 3 year or greater history of bisphosphonate use [200, 201].

C-terminal telopeptide cross-link (CTX) is a product of bone remodeling that can be measured in blood. Early reports suggested that serum levels of CTX progressively decline with antiresorptive treatment and recover after the treatment stops. Therefore, it can be used to predict the occurrence of osteonecrosis following a dental procedure in patients on antiresorptive medications [198].

The study suggested that the risk of MRONJ following a dental procedure in patients on bisphosphonates was high if the CTX level was below 100 pg/ml, moderate at 100–150 pg/ml, and low above 150 pg/ml [198, 202, 203] (Table 32.8). Based on these studies and others, many clinicians all over the world performed CTX routinely before any dental procedure in patients on antiresorptive treatment. Serum levels of CTX were also used to monitor the condition of bone remodeling during drug holiday and to determine the appropriate duration of such holiday before a procedure can be safely performed. The practice continues despite multiple subsequent studies questioning the practice [204, 205].

Table 32.8 CTX serum level as a predictor of MRONJ

CTS serum level	ONJ risk
<100 pg/ml	High
100–150 pg/ml	Moderate
>150 pg/ml	Low

In a clinical practice statement, The American Academy of Oral Medicine stated that, despite the need for predictive biomarkers, there was not enough evidence to justify dependence on CTX in predicting the risk of MRONJ following a dental procedure, especially in patients on intravenous bisphosphonates or denosumab [206]. Another study [207] reported that serum levels of CTX by itself are not reliable as a predictive or preventive measure for such complications. Data also suggested that a drug holiday of 5 months was not helpful in preventing osteonecrosis-related complications in patients on intravenous bisphosphonates.

Association Between Periodontitis and ONJ

Periodontal disease is an infectious inflammatory condition that affects the teeth-supporting tissues (i.e., gingiva, periodontal ligament, cementum, and alveolar bone). Periodontal disease initiation and propagation are related to an oral dysbiosis, which reflects changes in the microbial communities in the mouth.

Human oral microbiome consists of both symbionts and pathobionts. Deviation from symbiosis among the bacterial community leads to "dysbiosis," a state of community disturbance. This shift causes major dysbiosis-related diseases in humans, namely, periodontitis, irritable bowel syndrome, chronic vaginosis, etc. Among them, periodontal disease depicts a major dysbiotic

condition due to the diversity of genera involved in normal and periodontal microbiome [207]. Oral dysbiosis produces a secondary impaired host response, triggering inflammation [208].

Periodontal disease is an epidemiologically ubiquitous disease that affects 20–50% of the global population [209]. The presence of this local low-grade inflammatory disease has been considered as a MRONJ risk factor. Keystone periodontopathogens have been isolated from MRONJ sequestra [210]. The link between periodontal disease and MRONJ has been explored in several animal models. The onset of MRONJ-like lesions can be achieved by injecting high doses of bisphosphonates or monoclonal antibodies (mABs) in the presence of experimentally induced periodontal inflammation, and likewise, the absence of periodontal disease-related inflammation ameliorates MRONJ-like lesions outcomes after tooth extraction in mouse models [211, 212].

A systematic review [213] assessed the hypothesis that there may be a relationship between periodontal disease and MRONJ. Meta-analysis showed that subjects affected by MRONJ are more than twice as likely to have periodontal disease than nonaffected individuals. Löe [214] suggested a plaque index is a measure of the state of oral hygiene, and a higher plaque index was reported to represent an accentuated risk for periodontal disease in some individuals.

The biological rationale that underlies this relationship has mainly been studied in animal models [210–212]. Oral dysbiosis can trigger an inappropriate host response, in which cytokines, reactive oxygen species, and matrix metalloproteinase are generated. These molecular patterns impede the proper functioning of defense mechanisms such as antioxidant mechanisms or tissue inhibitors of metalloproteinases.

This self-sustaining pathogenic cycle results in periodontal tissue destruction [215, 216]. Nonetheless, antiresorptives can affect this mechanism due to their ability to diminish osteoclastic activity, therefore limiting bone resorption and remodeling. This phenomenon prolongs bone exposure to a periodontal disease-related microenvironment, where bone is subjected to oxidative stress, endotoxaemia and the release of a large number of growth factors and mediators of inflammation, therefore precipitating cellular and molecular toxicity and ultimately the onset of local necrosis [210, 211]. The tandem effect of local trauma (i.e., tooth extraction) and this low-grade inflammatory response make up the current MRONJ etiopathogenic model [217–220]. Moreover, the spreading of local bacterial and the dissemination of proinflammatory cytokine from periodontium can exert antiangiogenic mechanism through the OPG/RANKL/RANK system, reinforcing bone necrosis, and this biological plausibility has been ascertained in vivo and in vitro [210, 221].

Prevention, Management, and Treatment of MRONJ

MRONJ can be managed effectively with respect to symptom control and QoL, and the risk of developing the condition can be substantially reduced if preventive measures are taken. To achieve the best outcomes for patients with MRONJ, a multidisciplinary approach is required involving healthcare professionals dealing with osteoporosis therapy, oncologists, dentists, nurses, primary care physicians, oral and maxillofacial surgeons (OMFSs), and the patient. In addition, educational programs need to be adapted/implemented to improve interdisciplinary collaboration and understanding of the benefits and side effects of bone-modifying agents across dental and medical specialties. These initiatives should be tailored specifically to the role of each healthcare professional in the prevention and management of ONJ.

The AAOMS stresses that priority should be given to the oncological treatment for patients with cancer and bone metastases at risk of developing MRONJ [2]. Physicians need to balance the risk of MRONJ with the benefit of bisphosphonates or denosumab in reducing the substantial risk of SREs [222]. A case-based review and application of recommendations from the 2015 guidelines of the International Task Force on ONJ [223] have advocated preventive measures to minimize the risk of MRONJ. A combination of preventive measures taken both before and

during treatment with denosumab or bisphosphonates, as described below, can significantly reduce the risk of MRONJ [224, 225]. For example, in a case series of 1243 patients receiving pamidronate, zoledronic acid or denosumab in a malignant setting, the incidence of MRONJ was reduced from 4.6% to 0.8% by the implementation of regular dental check-ups and improved oral hygiene [226].

Preventive Measures Taken Before Antiresorptive Therapy

Paper: Medication-related osteonecrosis of the jaw: Prevention, diagnosis, and management in patients with cancer and bone metastases.

Discussing Medication-Related Osteonecrosis of the Jaw with Patients

When patients are being considered for treatment with denosumab or bisphosphonates, it is important that the risk of developing MRONJ is clearly explained by HCPs in the context of maintaining skeletal health. Skeletal-related events can cause considerable pain and reduce mobility and quality of life [227–229], and the results of discrete-choice studies suggest that both patients and physicians consider that the benefits of the treatments outweigh the risk of developing MRONJ [230, 231]. An analysis of the number of patients that would need to be treated with denosumab instead of zoledronic acid to prevent one additional skeletal-related events (seven patients), compared with the number that would need to be treated to induce one additional ONJ event showed that the benefits of using denosumab substantially outweighed the risk of ONJ [123]. There are no data to suggest that prevention of ONJ should be different between similarly dosed bisphosphonates or denosumab, and the implementation of preventive strategies is identical with both types of therapy.

In addition to explaining the risk of MRONJ, preventive measures should be discussed with patients. The involvement of specialist nurses (e.g., osteoporosis or oncology/urology nurses) should be considered when discussing MRONJ with patients to increase the opportunity to disseminate advice. If materials for patient education are available, these should be provided.

Oral Assessments and Other Preventive Measures

When in consultation with patients about the use of denosumab or bisphosphonates, it is essential that physicians carry out an oral examination and take a brief dental history. In particular, it is important to identify local dental infections, especially those that involve the bone, such as marginal periodontitis and apical periodontitis. Other considerations might include the general status of a patient's dentition and, if there are dentures, whether these are ill-fitting and for how many years they have been worn. If a patient is undergoing chemotherapy, oncologists should briefly look for exposed bone when assessing for chemotherapy-induced oral mucositis.

If the patient has any of the risk factors, it is advisable that before initiation of denosumab or bisphosphonates, patients should have dental assessment, with a thorough examination of the oral cavity and radiographic assessment (e.g., panoramic radiographs). It is the dentist's responsibility to identify an individual at risk and prevent dental infection through good oral hygiene and regular dental checkups. In patients at high risk of developing bone metastases or likely to require chemotherapy (i.e., advanced stage or clinically aggressive disease), a dental check at the time of diagnosis of a cancer that typically spreads to the bone may also be prudent [232]. In cases where antiresorptive therapy is likely to be needed at some time during the course of the patient's management, this would result in less time pressure for dentists and oro-maxillofacial surgeons and less likelihood of a delay in antiresorptive therapy if/when urgently required at a later date. Nevertheless, formal cost-benefit assessments of such an intervention are currently lacking.

Preventive Measures Taken During Antiresorptive Therapy

Several approaches can be taken during treatment with bisphosphonates or denosumab to prevent MRONJ. A key strategy is to encourage patients

to maintain good levels of oral hygiene and to undergo six monthly dental checkups. Both patients and healthcare professionals need to remain vigilant for the signs and symptoms of MRONJ throughout treatment. All but the most minor dental procedures warrant the seeking of expert advice and the threshold for referral to oro-maxillofacial surgery should be low in case of any uncertainty about the risk of MRONJ. In several cases, treatment will be suspended for major dental procedures (e.g., extraction and other procedures involving osseous injury). It should be noted, however, that evidence to support the practice of interrupting treatment in order to reduce the risk of ONJ development following dentoalveolar surgery is lacking. Taking a drug-holiday before any invasive procedure remains a controversial issue. In this case, a drug holiday can be defined as the temporary termination of drug administration before dentoalveolar surgery to minimize the risk of bone necrosis [233]. If considering treatment interruptions, it is relevant to note that denosumab does not become physically bound to the bone matrix and consequently is associated with low levels of accumulation [234]. Compared with bisphosphonates, which may remain covalently bound to the bone for many years [235], due to its mode of action, the effects of denosumab are reversed faster on suspension of treatment [236].

Patients undergoing surgical extraction or any other dentoalveolar surgery with a history or current bisphosphonate use through an oral route of administration for less than 4 years with no clinical risk factor have a low risk of developing MRONJ and require no alteration in the planned procedure. However, patients should be informed about the risk of developing ONJ. Their physician should be involved in the decision making and possible dose alteration or drug holiday [210].

Patients on oral bisphosphonate therapy longer than 4 years, or less than 4 years in duration but with concomitant use of an antiangiogenic medication or corticosteroids, will experience a synergistic effect of these therapies on their bone. The physician should suggest the discontinuation of bisphosphonate therapy for at least 2 months before dentoalveolar surgery only if the systemic condition of the patient permits it; the holiday should be continued until osseous healing and full mucosal coverage are achieved [2].

Managing Oral Infections Before and During Antiresorptive Therapy

Dental infections are associated with MRONJ [72]; therefore, timely diagnosis and resolution of an underlying dental infection is a priority to prevent the condition. Furthermore, resolving infection may reduce the need for dental extraction, which is also associated with MRONJ.

Dental extraction can be considered if the tooth is preventing resolution of the infection. Extractions should be carried out with the minimum level of trauma possible or be performed in a surgical setting according to published protocols to reduce the risk of subsequent MRONJ, which has a reported incidence of approximately 4% [124, 237]. Tooth extractions in patients receiving denosumab or bisphosphonate treatment, especially in the oncological setting, should be performed under antibiotic prophylaxis (e.g., amoxicillin/clavulanic acid) and accompanied by smoothening of sharp bony edges and closure of the wounds, and then monitored until complete mucosal healing is achieved [124].

Treatment

Asymptomatic Patients

Asymptomatic Patients Receiving IV BP or Antiangiogenic Drugs for Cancer

Maintaining good oral hygiene and dental care is of paramount importance in preventing dental disease that may require dentoalveolar surgery. Procedures that involve direct osseous injury should be avoided. Nonrestorable teeth may be treated by removal of the crown and endodontic treatment of the remaining roots [142]. Placement of dental implants should be avoided in the oncologic patient receiving IV antiresorptive therapy or antiangiogenic medications. There are no data regarding the risk of ONJ associated with implant placement in patients receiving antiangiogenic medications.

Asymptomatic Patients Receiving Antiresorptive Therapy for Osteoporosis

Patients receiving oral antiresorptive therapy for osteoporosis are at risk for developing MRONJ, but to a much lesser degree than those treated with IV antiresorptive therapy 87,105. MRONJ can develop spontaneously or after minor trauma. In general, these patients seem to have less severe manifestations of necrosis and respond more readily to stage-specific treatment regimens [198, 238]. Elective dentoalveolar surgery does not appear to be contraindicated in this group. It is recommended that patients be adequately informed of the very small risk (<1%) of compromised bone healing. The risk of developing MRONJ associated with oral BPs, although exceedingly small, appears to increase when the duration of therapy exceeds 4 years [2]. Therefore, management can be stratified into:

1. For patients who have taken an oral bisphosphonate or denosumab subcutaneous injections for less than 4 years and have no clinical risk factors, no alteration or delay in the planned surgery is necessary. This includes any and all procedures common to oral and maxillofacial surgeons, periodontists, and other dental providers.

   It is suggested that if dental implants are placed, informed consent should be provided related to possible long-term implant failure and the low risk of developing ONJ if the patient continues to take an antiresorptive agent. These concerns are based on recent animal studies that have shown impaired long-term implant healing [239]. Such patients should be placed on a regular recall schedule. In addition, it is advisable to contact the provider who originally prescribed the antiresorptive therapy and suggest monitoring such patients and considering alternate dosing of the medication, drug holidays, or an alternative to the bisphosphonate therapy.
2. For those patients who have taken antiresorptive therapy for less than 4 years and have taken corticosteroids or antiangiogenic medications concomitantly, the prescribing provider should be contacted to consider discontinuation of therapy (drug holiday) for at least 2 months before oral surgery (for denosumab 6 months, discontinuation is advised), if systemic conditions permit. The antiresorptive should not be restarted until osseous healing has occurred. These strategies are based on reports that corticosteroid and antiangiogenic agents, in combination with antiresorptive therapy, may increase the risk of developing MRONJ and that a drug holiday may mitigate this risk. Long-term prospective studies are still required to establish the efficacy of drug holidays in decreasing the risk of MRONJ for these patients.
3. For those patients who have taken an antiresorptive therapy for longer than 4 years with or without any concomitant medical therapy, the prescribing provider should be contacted to consider discontinuation of the antiresorptive for at least 2 months before oral surgery, if systemic conditions permit. The antiresorptive therapy should not be restarted until osseous healing has occurred. The risk of long-term oral BP therapy requires continued analysis and research [2].

Patients with Established MRONJ

Management is based on the stage of ONJ, the size of the lesions, the presence of the contributing drug therapy, and medical and pharmacological comorbidities.

Conservative therapy of ONJ focuses on improving oral hygiene, treating active dental and periodontal diseases, topical antibiotic mouth rinses, and systemic antibiotic therapy [17, 240, 241]. There are several case reports of the successful treatment of ONJ with teriparatide, which are encouraging; these reports may be considered to facilitate wound healing [242, 243]. Teriparatide is contraindicated in individuals who have had skeletal radiation and may not be a useful intervention approach for those with malignancy and a prior history of skeletal irradiation.

Experimental treatment approaches require further validation (Table 32.9). These treatment approaches include topical ozone [244], bone

Table 32.9 showing different treatment modalities of established MRONJ

Treatment Modality	Comments	References
Medical management		
Prophylactic antibiotics before or immediately after surgery	Antibiotics significantly decrease the rate of recurrence	[256–260]
Nonsurgical long-term antibiotics	Success was reported in some studies with antiseptic rinse, smoothing, and removal of necrotic bone with tweezers; no difference between it and surgical care with respect to remission; some trials with antibiotic-only approach without surgery had limited success	[261–263]
Nonsurgical antiseptic rinse	Success was demonstrated in some studies with long-term antibiotics, smoothing, and removal of necrotic bone with tweezers	[261]
Antimicrobial rinse (IV)	Success was reported in combination with surgery; longer-term antimicrobial therapy before surgery more effective; in some trials, not as effective as primary treatment or with surgery	[246, 250, 264, 265]
Surgical management		
Surgical debridement	Very successful technique, often in combination with antimicrobial rinsing, with minority requiring subsequent sequestrectomy	[257, 264, 266, 267]
Bone resection	Several studies reported excellent efficacy in healing ONJ, in combination with antibiotics; however, not all trials demonstrated high cure rates following surgery	[250, 253, 268–270]
Sequestrectomy	Often successful in combination with antibiotics	[258, 271–273]
Experimental		
Erbium YAG laser therapy	Er/YAG laser therapy was reported to be effective in most, but not all, trials	[247, 274–276]
Neodymium YAG laser	Nd/YAG laser has induced complete healing in several studies; also other studies have shown significant improvement in symptoms	[277, 278]
Low-level laser therapy	Used primarily for reduction in pain, however, also for improving the defect size, edema and in the presence of pus and fistulas; often in combination with medical or surgical therapy	[108, 251, 279, 280]
Hyperbaric oxygen therapy	Usually used as an adjunctive management tool to other therapies such as antibiotics, antiseptics, and surgery; often for symptomatic relief; not always found to have clinical impact	[260, 270, 281]
Ozone therapy	Some supporting studies used concomitant antibiotics; germicidal and analgesic effects	[139, 157–159, 244, 282–284]
Plasma rich in growth factor therapy	Reported to be very successful in combination with surgery	[108, 285]
Autologous platelet-rich plasma	80% success in one trial when used during partial bone resection of patients who failed conservative therapy; used with laser therapy as well	[152, 286]
Platelet-derived growth factor	With bone resection	[287]
Recombinant human bone morphogenetic protein type 2 therapy	A study reported healing of all patients after 1 year	[288]
Alpha-tocopherol and Pentoxifylline therapy	With adjunct antimicrobial therapy	[246]
Mesenchymal stromal cell therapy	Positive outcomes animal studies and case reports in humans	[289, 290]

Table 32.10 A summary of the patients with MRONJ management tailored to their disease stage

Stage	Clinical manifestations	Management
Stage 0	Symptoms: Jaw pain, sinus pain, Signs: unexplained loosening of teeth, periapical or periodontal fistula (not associated with pulpal necrosis caused by caries, trauma, or restorations) Radiology: alveolar bone loss, changes in the trabecular pattern, thickening or obscuring of the periodontal ligament	Symptomatic treatment to control pain and infections, in addition to close monitoring
Stage 1	Asymptomatic Exposed and necrotic bone or a fistula that probes to bone Radiographic changes stated in stage "0," which are localized to the alveolar region	Conservative therapy—improve oral hygiene. Treat active dental and periodontal disease, topical antibiotic mouth rinses
Stage 2	Symptomatic: pain, adjacent or regional soft tissue inflammatory swelling or secondary infection Exposed and necrotic bone or a fistula that probes to bone with associated infection Radiology: findings stated in stage "0" localized to the alveolar bone region	As in stage 1, symptomatic treatment, systemic antibiotics if infection is suspected, consider surgical debridement
Stage 3	As above + one or more of the following: exposed necrotic bone extending beyond the region of the alveolar bone, pathological fracture, extra-oral fistula, oral antral or oral nasal fistula, or radiographic evidence of osteolysis extending to the inferior border of the mandible or the floor of the maxillary sinus	As in stage 1 also surgical debridement, resection including jaw reconstruction if necessary

marrow stem cell intralesional transplantation [245], and addition of pentoxifylline and tocopherol to standard antibiotic regimens [246]. Laser therapy has also been proposed to be of benefit [247, 248]. Localized surgical debridement may be indicated; some authors have reported success with larger resections compared with limited debridement or conservative therapy [249, 250]. Enhanced healing has been observed in a retrospective survey of patients undergoing antibiotic therapy in addition to surgery followed by low-level laser therapy [251]. Surgery, together with platelet-derived growth factor applied to the local site, has achieved good results in stage 2 ONJ cases [252]. Hyperbaric oxygen in combination with surgery has been investigated with encouraging results [253, 254]. Further research is required with these new strategies.

In the absence of debilitating ONJ lesions, it is recommended that conservative therapy consisting of optimal oral hygiene, topical antibiotic rinses, and systemic antibiotics be initiated [255]. Nonresponsive cases should be considered for surgery including osteotomy of the affected area with resection margins extending into adjacent normal appearing bone. Soft tissue closure should be completely tension free with no underlying sharp edges of bone that could lead to mucosal breakdown. Microvascular composite tissue grafting at the time of surgical resection may be considered in the presence of a pathological fracture or ONJ if the extension is to the sinus or the inferior border of the mandible. It may also be of value if the osteotomy to healthy tissue leads to a discontinuity defect. This is a rapidly growing area of investigation and further recommendations would be available in the future.

Stage-Specific Management Approach

MRONJ management protocol remains challenging and is case dependent. Treatment approach should be set up according to the condition stage and symptoms [2]. Multiple treatment approaches have been introduced to control ONJ, including conservative treatment, surgical debridement, and resection of the lesions or the use of other adjunctive treatments such as oxygen therapy or, recently, the use of mesenchymal cells to regenerate the damaged bone. Management of patients with MRONJ tailored to their disease stage is summarized in Table 32.10. This includes the following:

- Stage 0: Since this stage represents a prodromal period with no specific symptoms, the treatment objective is only symptomatic treatment to control pain and infections, in addition to close monitoring for any sign of progression in the clinical state or radiographic image.
- Patients with established ONJ are treated differently; the treatment objectives are mainly focused on controlling pain, infection, and the progression of the bone necrosis.
- Stage 1: In this stage, the patient is asymptomatic, but with evidence of bone exposure. The treatment is chlorhexidine mouthwash 0.12% and regular follow-up appointments. Neither antibiotic nor surgical intervention is required in this stage.
- Stage 2: In this stage, due to evidence of necrosis and associated infection, an antibiotic regimen with an antimicrobial mouthwash is the treatment of choice.
- Stage 3: Surgical management is indicated in combination with an antibiotic regimen in this stage. The surgical approach varies between debridement to complete resection with possible immediate reconstruction with plates or obturators.

Teriparatide as a Treatment Modality of MRONJ (PTH in OJN)

The anabolic characteristic of teriparatide has prompted us to use this peptide for ONJ patients. Recently, many clinical studies have been published with favorable results in treating MRONJ [291–298]. Basically, teriparatide can enhance bone formation before the stimulation of bone resorption process, and using teriparatide may promote bone repair in and around the defect of the lesions. In fact, MRONJ is a complication of long-term antiresorptive therapy blocking the action of osteoclasts but the target of the teripatatide therapy is to activate osteoblstic action.

Teriparatide has clinically demonstrated greater regaining of alveolar bone defects and accelerated osseous wound healing in the oral cavity of chronic periodontitis [16]. From teriparatide therapy, improvement of suppressed bone markers was presented in some of the literatures [292, 293, 298], and this finding provided potential roles to facilitate bone healing. The treatment duration of teriparatide may vary depending on the decision of prescribing physicians. In fact, there is no generally accepted treatment course. In one study, 1–3 months of teriparatide therapy was provided along with the surgical debridement [293]. In another study, 6 months of teripratide therapy was carried out for the MRONJ patients who were unresponsive to conventional treatments [292]. Longer administration of teriparatide (about 6 months) would be beneficial to the healing of the lesions, but financial burden to the patients might be an obstacle in a real clinical situation. Along with surgery, short-term teriparatide therapy might be reasonable in terms of the initial healing promotion of the lesions after the surgical debridement. However, in a letter, a nonresponsive case to teriparatide was presented, and antirheumatic drugs were attributed to one possible reason because of their effect on healing impairment [294].

In contrast to bisphodphonates, which have an antiangiogenic action [299–303], which can be considered as one of the etiologic factors of MRONJ, it was suggested that teriparatide enhance angiogenesis, implying that teriparatide therapy may be also beneficial for the healing via increased angiogenesis activity [304]. However, in some animal studies, experimentally induced MRONJ-like lesions did not show the angiogenesis defects [305, 306]. Recombinant human monoclonal antibody like bevacizumab shows antitumor effects via binding to vascular endothelial growth factor, thus inhibiting angiogenesis, and it was recently reported to be possibly associated with MRONJ cases [92]; however, teriparatide therapy for those patients is inappropriate.

In the one of the studies about the application of teriparatide to MRONJ patients, the researchers found that the serum vitamin D level at the baseline was thought to be an influencing factor. In the study carried out by Kim and coauthors, better clinical outcome was noted in a group showing a higher level of serum vitamin D [292],

and this may imply that lower level of vitamin D can deter bone healing. An optimal level of vitamin D is considered important for mineralization [307]. Supplemental vitamin D with calcium may be considered for the patients presenting a markedly low level of serum vitamin D. Several studies suggest that bisphosphonates, which potentially disturb bone resorption process, may substantially affect the initial response to teriparatide [308]. Therefore, some clinicians claimed that a certain period of washout phase may be necessary before teriparatide administration [309]. Meanwhile, teriparatide and vitamin D can reverse the antiresorptive effect of bisphosphonates [310, 311].

Drug Holiday and Treatment

Opinions are divided with regard to the benefit of temporarily pausing treatment with bisphosphonates or denosumab in patients who are scheduled to receive invasive dental procedures (referred to as "drug holidays") [312]. The increased risk of SREs during drug holidays must be balanced with the reduced risk of development of MRONJ on a case-by-case basis and should be discussed by a multiprofessional team.

Though evidence to support the benefit of drug holidays is lacking, a drug holiday is believed to be one of the core components of MRONJ treatment, despite complications like osteoporotic fractures in the vertebrae, femur, and pelvis. There have been some reports showing that a drug holiday can be acceptable without a significant rise of the complication rate [313, 314]. However, the increased risk of osteoporotic fractures which may be fatal should not be ignored, because the safety issue of the drug holiday should be further investigated [315]. A Japanese study found that treatment holidays before dental extraction did not reduce the risk of MRONJ in patients receiving oral bisphosphonates [316]. An American Association of Oral and Maxillofacial Surgeons (AAOMS) position paper on MRONJ stated that a 2 month drug holiday before and after dental surgery in patients receiving oral bisphosphonates may be prudent, and an international ONJ task force recommended that treatment should be withheld after invasive dental surgery in patients receiving high-dose bisphosphonates or denosumab [317].

Though the half-life of bisphosphonates is longer than 10 years [36], there is no evidence that the discontinuation of oral bisphosphonates is necessary before dental surgery [318]. Discontinuation of intravenous bisphosphonates and subcutaneous denosumab may be considered by oncologists. However, no data are available for supporting the effectiveness of secession of intravenous bisphosphonates and subcutaneous denosumab on the prevention of ONJ. In a study, the discontinuation of denosumab was associated with reversal features of osteonecrosis in a mouse model [54]. Otto et al. suggested that any surgical intervention for ONJ needed to be suspended for at least several months after denosumab administration to avoid manifestation of ONJ [319].

Considering the possible risk of osteoporotic fractures during drug holiday, teriparatide therapy may have dual benefits for MRONJ patients, promoting bone healing of the surgical wound of MRONJ patients and increasing bone density. Therefore, concerns regarding a drug holiday can be minimized by teriparatide, which is also a therapeutic agent for osteoporosis.

MRONJ and the Need for Multiprofessional Teamwork

Although the benefits of treatment with bisphosphonates or denosumab are clearly established, MRONJ has emerged as an important safety consideration. To optimize the use of these agents in practice and to ensure appropriate focus on the risk of MRONJ, good collaboration is required among dentists, physicians, oral oncologists, oromaxillofacial surgeons, and other health care professionals involved in a patient's care (Fig. 32.13). Although it is important to be aware of MRONJ and understand which patients are most likely to be affected, dentists should also be aware of the educational materials available to them and not overestimate the risk of this condition and restrict dental care unnecessarily [312]. Moreover, lack

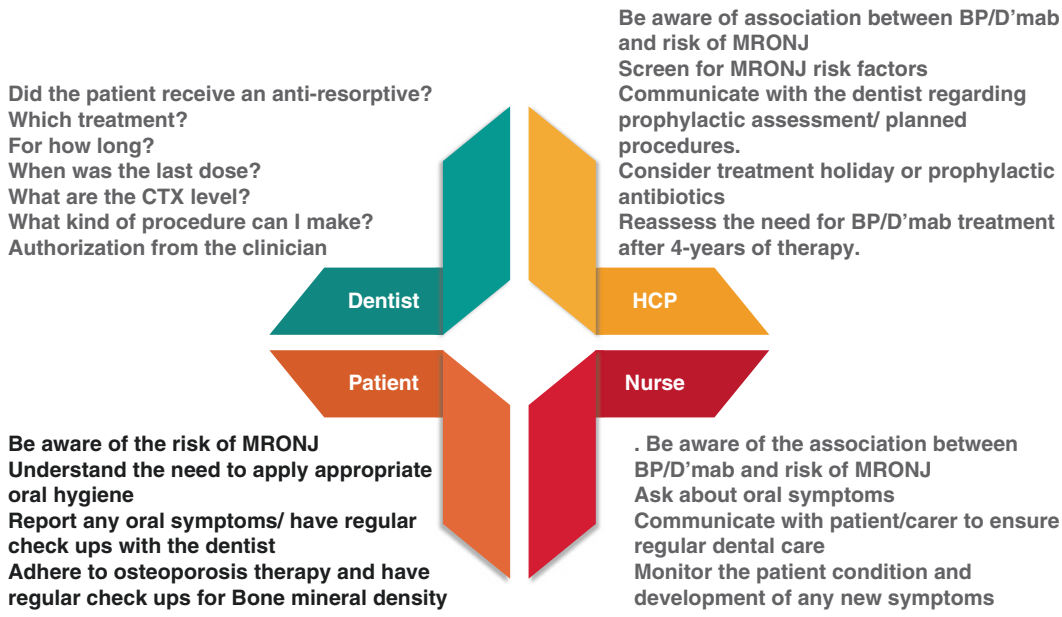

Fig. 32.13 Multidisciplinary approach to the management of MRONJ

of communication among care providers may result in misunderstandings regarding the reasons for, and the risks of, treatment with bisphosphonates or denosumab. Such misunderstandings may lead to conflicting information being given to the patient. This can ultimately jeopardize the patient's trust and adherence to the proposed treatment, leading to inferior health outcomes [320].

In conclusion, medication-related osteonecrosis of the jaw (MRONJ) is primarily an adverse side effect of denosumab or bisphosphonates (particularly when used at high doses to prevent skeletal-related events in patients with cancer and bone metastases) or possibly antiangiogenic cancer treatment. MRONJ is very unlikely event in osteoporotic patients receiving antiresorptive therapy and develops only in association with local or systemic risk factors. The development of MRONJ may compromise treatment, thereby increasing the risk of pathologic fractures in those with osteoporosis and of fractures and other bone complications in individuals with cancer. Minimizing the risk of MRONJ is critical, not only to prevent the pain and discomfort the disease can cause patients but also to maximize the benefit of treatment with bisphosphonates or denosumab. Optimizing the management of MRONJ can be challenging. Treatment protocols are complex and need to be adapted to the individual patient and the disease stage. Figure 32.14 provide a quick clinician's guide for the assessment, diagnosis, and management of MRONJ.

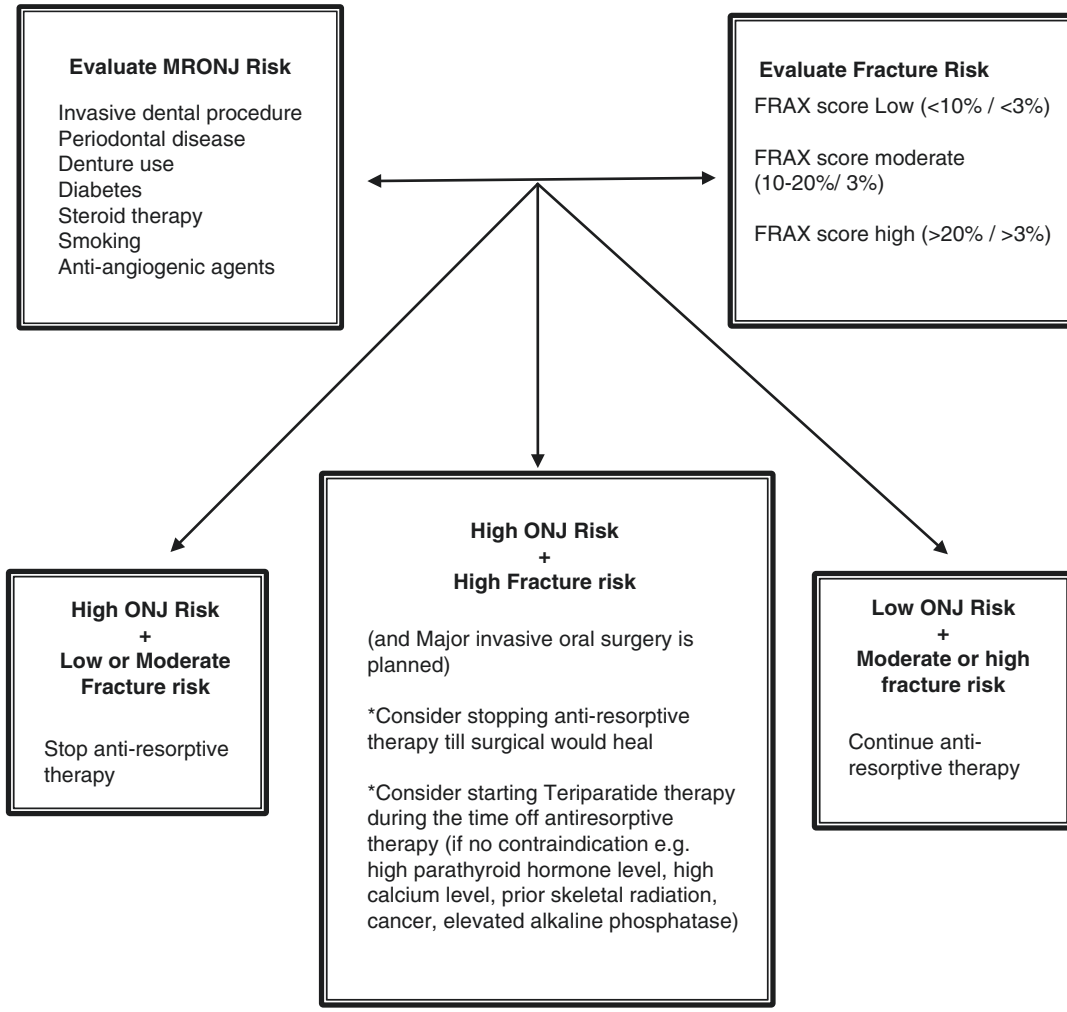

Fig. 32.14 A quick clinician's guide for the assessment, diagnosis and management of MRONJ

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