Gustavo Duque
Douglas P. Kiel
Editors

Osteoporosis in Older Persons

Advances in Pathophysiology and Therapeutic Approaches

Second Edition

Springer

Osteoporosis in Older Persons

Gustavo Duque • Douglas P. Kiel
Editors

Osteoporosis in Older Persons

Advances in Pathophysiology and Therapeutic Approaches

Second Edition

Springer

Editors
Gustavo Duque, MD, PhD, FRACP
Australian Institute
for Musculoskeletal Science
The University of Melbourne
and Western Health
St Albans, VIC
Australia

Douglas P. Kiel, MD, MPH
Department of Medicine
Beth Israel Deaconess Medical Center
and Harvard Medical School
Boston, MA
USA

Director Musculoskeletal Research Center
Institute for Aging Research
Hebrew SeniorLife
Boston, MA
USA

ISBN 978-3-319-25974-1 ISBN 978-3-319-25976-5 (eBook)
DOI 10.1007/978-3-319-25976-5

Library of Congress Control Number: 2016934851

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

To my lovely and devoted parents, Maximo and Rubiela, who always inculcated in me the humility to respect the feeble, the curiosity to understand nature and the respect for God who is the Great Architect of everything that is described in this book.

Gustavo Duque, MD, PhD, FRACP

In memory of my mother, Adrienne Kiel, who inspired me to pursue a career in medicine and to dedicate my research to the study of osteoporosis, which she lived with until she passed away following a hip fracture.

Douglas P. Kiel, MD, MPH

Acknowledgements

The Editors would like to thank Ms. Julia Megginson for her assistance in the preparation of this work. We remain grateful to Mrs. Melissa Morton from Springer for her outstanding support on this project and for her understanding that older adults suffer from a particular syndrome that must be understood and treated. Finally, we would like to thank all the authors of these book chapters who, like us, share the same interest on the subject of osteoporosis in older adults. Without their collaboration this project would have never been successful.

Foreword

The "osteoporosis" field is changing: historically being focused on the bone, but now evolving to focus on fracture risk. Such change is essential as fragility fractures are common and may have devastating consequences on quantity and quality of life. Indeed, loss of independence is a major concern of older adults, which fractures directly threaten. It is unsurprising that geriatricians are among the first to recognize that fragility fractures are not simply due to a bone disease (i.e., osteoporosis) but rather are a multifactorial geriatric syndrome resulting from low bone and low muscle mass and strength in concert with other factors that increase falls and fracture risk, e.g., diabetes, obesity, polypharmacy, osteoarthritis, neuropathy, and impaired vision, among others. It is thus appropriate that Duque and Kiel entitle this version of Osteoporosis in Older Persons as "Advances…" They have assembled an international cadre of experts to help us advance our approach to reducing fractures among the increasing numbers of older adults.

While focus on the ultimate outcome is a clinical necessity, study of the whole requires understanding of the various parts. As such, this concise work provides the reader with essential background understanding of bone biology, physiology, and genetics and overviews the animal models that have facilitated today's understanding. The importance of sarcopenia and the interrelated nature of bone and muscle are highlighted on the basic and clinical levels. The recognition that bone and muscle and critically linked, and that their joint weakness contribute to the nearly exponential increase in fracture risk with age (while clearly not a new concept) is essential. One could easily argue that the increasing recognition of sarcopenia is driving the revolution in osteoporosis understanding and ultimately in fracture risk reduction care. The "clinical" section of this work is introduced by just this concept, that osteoporosis is part of a geriatric syndrome. Subsequently, current knowledge regarding nonpharmacologic and pharmacologic therapy and the critical role of the fracture liaison service model are considered.

This work compiles a roadmap for the future of fracture risk reduction in older adults. To summarize, it reminds us of the obvious: that "osteoporosis-related" fractures are not solely the result of osteoporosis, but rather the result of a complex geriatric syndrome with multiple inputs. Reducing fracture risk, and thereby maintaining independence and quality of life, requires focus on the whole, not simply the parts. While this approach is certainly the future of

"osteoporosis" care, there is no reason that today's knowledge cannot or should not be applied now. Indeed, to quote Pope John Paul II, "The future starts today, not tomorrow."

Madison, WI, USA Neil Binkley, MD

Preface

With the aging population increasing worldwide, there is a growing interest in age-related diseases and their functional and mental consequences. Osteoporosis is a common disease in older persons with significant impact on their functionality and quality of life. Additionally, osteoporotic fractures represent an important burden to health-care budgets around the world.

Since the first description by Riggs et al. of a particular syndrome known as "senile osteoporosis," there has been a common agreement that there is a type of osteoporosis closely associated with the aging process that occurs both in men and women, and that is usually independent of serum levels of hormones. Indeed, recent advances in the understanding of bone biology and the genetics of the aging process have provided new evidence on age-related osteoporosis as a particular geriatric syndrome with specific pathophysiology, epidemiology, and treatment. In addition, new evidence showing a strong interaction between muscle and bone has demonstrated that age-related changes in one tissue would affect the other and vice versa.

The first edition of *Osteoporosis in Older Persons: Advances in Pathophysiology and Therapeutic Approach* was extremely successful in establishing the basis to understand the mechanisms of age-related osteoporosis from a *bench-to-bedside* perspective. Clinicians, researchers, and allied health professionals found in its chapters the most complete and up-to-date information on how to understand, assess, and treat osteoporosis in older persons. In this second edition, we are still following our *bench-to-bedside* approach as the stronger and unique characteristic of this project. Following the new evidence on the pathophysiology of falls and fractures in older persons, we have included a new chapter on the muscle and bone interface. From the clinical point of view, we have added new chapters on orthogeriatrics and fracture liaison services, which have significantly improved fracture care to older persons around the world.

From the bench side, we have focused the basic sciences chapters on the shift in the differentiation of mesenchymal stem cells in the bone marrow from predominant osteoblastogenesis in the young bone to increasing adipogenesis in the old bone. This process is independent of estrogen levels as demonstrated by increasing bone marrow adipogenesis in estrogen receptors knockout mice. In fact, the increasing levels of bone marrow adipogenesis starts in humans even when normal serum levels of estrogens are present in

the third and fourth decade of life, suggesting that this is an age-related process independent of sex hormones. In this book, the chapters dedicated to bone biology also illustrate the particular cellular and molecular features of osteoporosis in older persons from animal models to human biology. Additionally, the authors look at the potential role that hormones, both calciotropic and sexual, may play in the pathophysiology of this syndrome.

Concerning the predominant fractures seen in older adults, the chapters on epidemiology take a broad approach to explaining the incidence of osteoporotic fractures in the elderly. In fact, hip fractures are the predominant fracture after the seventh decade of life. This type of fracture correlates with the pathophysiology of osteoporosis since the vitality of the femoral neck area is mostly dependant on osteoblast activity, which is severely affected by the aging process in bone. By contrast, the incidence of fractures due to increasing osteoclastic activity, a typical feature of postmenopausal osteoporosis, decreases in the older population. These differences in the incidence and type of osteoporotic fractures in older persons may in part be related to genetic factors. The chapter on the genetics of osteoporosis focuses on the identification of the genes that are directly associated with osteoporosis in older adults, a field that has shown major advances since the first edition of this textbook.

A new feature of this edition is the inclusion of a new chapter on muscle and bone. Recent studies have concluded that the bone/muscle relationship goes beyond simple mechanical interaction. The identification of muscle- and bone-secreted factors, which affect both of these tissues, has revealed multiple pathophysiological and therapeutic implications that are clearly described in the chapter.

Concerning the treatment of osteoporosis, although there is increasing awareness about the importance of preventing fractures in older adults, the evidence shows that the number of patients at risk who are not receiving treatment is increasing. This lack of attention to fracture prevention is probably due to a combination of factors that include ageism, lack of evidence of the effectiveness of the treatment in old patients, and the preponderance of osteoporosis treatments directed at the regulation of osteoclastic activity that, although effective in geriatric populations, do not target bone formation, which is significantly reduced in the older population. One of the important messages throughout this book is that clinicians should be aware of the importance of treating of osteoporosis in older adults to prevent fractures, disability, and even death.

The chapter on pharmacological treatment of osteoporosis highlights very important points: first, osteoporosis once diagnosed or suspected should be treated independently of the patient's age; second, as is true of most pharmacologic agents, older individuals with comorbidities have not been included in the treatment trials that led to approval of the treatment. This makes it difficult for providers to have confidence in their efficacy. Furthermore, in some cases, treatment effectiveness in older persons is doubtful since most of the therapeutic agents regulate bone resorption

without increasing bone formation; third, the optimal therapeutic agent for osteoporosis in older individuals that decreases bone resorption while increasing bone formation has not been developed. In their conclusion, the authors state that the optimal therapeutic agent for osteoporosis in the old-old does not exist yet and that more research should be pursued in order to find the right approach to the particular features of osteoporosis in older individuals.

To reflect the most recent health-care system approaches to fracture prevention, we have included a new chapter on fracture liaison services (FLS), which support the notion that osteoporosis in older persons should be actively diagnosed and treated. FLS are the recommended approach to reduce fracture risk, establish a good communication between patients and their clinicians, and increase awareness of the importance of this disease that, although asymptomatic, has a significant impact in terms of morbidity and mortality in our older populations.

A particularly unique aspect of this book is the inclusion of two chapters on falls. This important geriatric syndrome has been historically separated from the osteoporosis syndrome because very few osteoporosis clinics considered the importance of fall prevention as a pivotal intervention to prevent fractures. As explained by the authors of the chapters, there could not be an effective preventive or therapeutic intervention for fractures in the elderly without an assessment of the risk of falls and the initiation of preventive measures. There are important links between the risk of falls and that of fractures. Probably the most relevant at this time is vitamin D, which has shown to be essential for the prevention of both, falls and fractures. Indeed, vitamin D is mentioned extensively in some of the chapters of this book as an essential intervention in the elderly population at risk. The evidence supporting this notion is reviewed in the chapters on calciotropic hormones as well as the one on the treatment of falls. Furthermore, since falls result from the interaction between multiple factors, non-pharmacological interventions are also considered in this book. In fact, we have dedicated a whole chapter to a review of the evidence on the effectiveness of non-pharmacological interventions for fall prevention.

Finally, we wanted to include two chapters on the surgical interventions for osteoporotic fractures. The new chapter on orthogeriatrics describes the most effective and evidence-based interventions to obtain the best possible outcomes in older patients undergoing surgery after hip fractures. This chapter is complemented by a comprehensive review of specific surgical interventions and techniques for osteoporotic fractures of the hip. This interesting description of surgical techniques using a simple terminology will help the clinician to interact with their surgical colleagues when treating old patients with osteoporotic fractures. Using outstanding illustrations, the authors explain in detail the characteristics of fracture stabilization in the hip and the particular challenges the surgeon faces when treating fractures in very old patients. Additionally, a review of the potential alternatives for surgical treatment of vertebral fractures was included.

In summary, this textbook has brought together experts in the field of osteoporosis in elderly persons from four continents. Our second edition has exceeded the first one in terms of new content, more evidence-based recommendations, and many practical tips and illustrations while still maintaining our *bench-to-bedside* particular approach. We have reviewed the evidence supporting the notion that osteoporosis in older persons exists as a real geriatric syndrome with a particular pathophysiology and treatment. The information included in this book will be useful to all health professionals involved in the care of our aging population in order to understand the particular features of this syndrome and the importance of its prevention.

Melbourne, VIC, Australia — Gustavo Duque, MD, PhD, FRACP
Boston, MA, USA — Douglas P. Kiel, MD, MPH

Contents

Contributors

Editors

Gustavo Duque, MD, PhD, FRACP Australian Institute for Musculoskeletal Science, The University of Melbourne and Western Health, St. Albans, VIC, Australia

Douglas P. Kiel, MD, MPH Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

Director Musculoskeletal Research Center, Institute for Aging Research, Hebrew SeniorLife, Boston, MA, USA

Authors

Eduardo L. Abreu, MD, DEng Muscle Biology Research Group-MUBIG, School of Nursing and Health Studies, University of Missouri-Kansas City, Kansas City, MO, USA

Heike A. Bischoff-Ferrari, MD, DrPH Department of Geriatrics and Aging Research, University of Zurich, Zurich, Switzerland

Geriatric Clinic, Centre on Aging and Mobility, University Hospital Zurich and City Hospital Waid, Zurich, Switzerland

Christopher M. Bono, MD Division of Spine Surgery, Department of Orthopaedic Surgery, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA

Department of Orthopaedic Surgery, Orthopaedic Spine Service, Brigham and Women's Hospital, Boston, MA, USA

Marco Brotto, BSN, MS, PhD Muscle Biology Research Group-MUBIG, School of Nursing & Health Studies and School of Medicine, University of Missouri-Kansas City (UMKC), Kansas City, MO, USA

Bone-Muscle Collaborative Sciences, College of Nursing & Health Innovation, University of Texas-Arlington, Arlington, TX, USA

Jane A. Cauley, DrPH Department of Epidemiology,
University of Pittsburgh, Graduate School of Public Health,
Pittsburgh, PA, USA

E. Paul Cherniack, MD Division of Gerontology and Geriatrics,
Department of Medicine, Geriatric Research Education and Clinical Center,
University of Miami, Miller School of Medicine, Miami Veterans Affairs
Medical Center, Miami, FL, USA

Jacqueline C.T. Close, PhD Prince of Wales Hospital,
Prince of Wales Clinical School and NeuRA, UNSW, Randwick,
NSW, Australia

Cathleen S. Colón-Emeric, MD, MHS Division of Geriatrics,
Duke University Medical Center, Durham, NC, USA

Oddom Demontiero, MBBS, FRACP Department of Geriatric Medicine,
Nepean Hospital, Penrith, NSW, Australia

Z. Elisabeth Floyd, PhD Ubiquitin Biology Laboratory,
Pennington Biomedical Research Center, Louisiana State University,
Baton Rouge, LA, USA

Louise M. Friedman, MD, MPH University of Rochester School
of Medicine and Dentistry, Rochester, NY, USA

Jeffrey M. Gimble, MD, PhD Center for Stem Cell Research
and Regenerative Medicine and Departments of Medicine,
Structural and Cellular Biology, and Surgery, Tulane University School
of Medicine, New Orleans, LA, USA

LaCell LLC, New Orleans, LA, USA

Piumali Gunawardene, MBBS, FRACP Department of Geriatric Medicine,
Nepean Hospital, Penrith, NSW, Australia

Guy A. Howard, PhD University of Miami Miller School of Medicine,
Miami, FL, USA

Geriatric Research, Education & Clinical Center, Miami, FL, USA

Research Service, Bruce W. Carter Department of Veterans Affairs
Medical Center, Miami, FL, USA

Janalee Isaacson, PhD, RN Department of Nursing,
Johnson County Community College, Overland Park,
KS, USA

David Karasik, PhD Institute for Aging Research, SeniorLife, Boston,
MA, USA

Moustapha Kassem, PhD Department of Endocrinology and Metabolism,
University Hospital of Odense, Odense, Denmark

Department of Anatomy, Stem Cell Unit, King Saud University, Riyadh,
Saudi Arabia

Ha-Yeon Lisa Kim, BHSc, MD Department of Internal Medicine, McMaster University, Hamilton, ON, Canada

Stephen R. Lord, PhD, DSc Falls and Balance Research Group, Neuroscience Research Australia, UNSW, Randwick, NSW, Australia

Paul J. Mitchell, BSc (Hons), CChem, MRSC Synthesis Medical NZ Ltd, Pukekohe, New Zealand

School of Medicine, University of Notre Dame Australia, Darlinghurst, NSW, Australia

Manuel M. Montero-Odasso, MD, PhD, AGSF, FRCPC Division of Geriatric Medicine, Department of Medicine, Parkwood Institute, University of Western Ontario, London, ON, Canada

Gait and Brain Lab, St. Joseph's Health Care Parkwood Institute Site, London, ON, Canada

Lawson Research Institute, London, ON, Canada

Mark E. Nuttall, PhD Business Development and Licensing, Department of Neuroscience, Janssen Pharmaceutical Companies of Johnson & Johnson, Titusville, NJ, USA

Alexandra Papaioannou, BScN, MD, MSc, FRCP(C), FACP Geriatric Medicine, McMaster University, St. Peter's Hospital, Hamilton, ON, Canada

Department of MedicineMcMaster University, Hamilton, ON, Canada

Paul C. Schiller, PhD Department of Orthopaedics, University of Miami Miller School of Medicine, Miami, FL, USA

Geriatric Research, Education & Clinical Center, Miami, FL, USA

Research Service, Bruce W. Carter Department of Veterans Affairs Medical Center, Miami, FL, USA

Catherine Sherrington, PhD, MPH, BAPPSC Musculoskeletal Division, Ageing and Physical Disability Program, Sydney, NSW, Australia

The George Institute, University of Sydney, Sydney, NSW, Australia

Pushpa Suriyaarachchi, MD Department of Rehabilitation Medicine, Nepean Hospital, Penrith, NSW, Australia

Bruce R. Troen, MD Division of Geriatrics and Palliative Medicine, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo – SUNY, Research Service - Western New York Veterans Affairs Healthcare Service System, Buffalo, NY, USA

Ken Watanabe, PhD Department of Bone & Joint Disease, National Institute for Longevity Science (NILS), National Center for Geriatrics & Gerontology (NCGG), Obu, Aichi, Japan

Eric Kai-Chung Wong, BSc, MD Department of Internal Medicine, McMaster University, Hamilton, ON, Canada

Jay M. Zampini, MD Division of Spine Surgery, Department of Orthopaedic Surgery, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA

Biology of Bone

1

Guy A. Howard and Paul C. Schiller

Overview

Bone is the main component of the skeleton, together with connecting tissues including cartilage, ligaments and tendons, providing mechanical and structural support for the remaining organs and systems in the body. This mechanical and structural support function is indispensable for life, both during the growth and development period as well as during adult life. However, bone also provides the unique architecture and microenvironment that preserve the niches which maintain immature stem cells. This niche aspect of bone is an inadequately recognized function, although an essential one, since stem cells are required for tissue repair and regeneration during adult life. In addition to providing mechanical support, bone contains and supports the main reservoir of cells needed to sustain tissue integrity and function throughout our lives. Thus, understanding how bone is made and maintained during life is central to developing adequate strategies to preserve a healthy skeleton as we age, so that proper mechanical support, structural integrity and tissue repair capacity are maintained.

In this chapter we will present a general overview of the process of bone formation during development, describe bone repair during adult life, review the differentiation program of bone cells, discuss the dynamic process of bone turnover, summarize the mechanisms by which specific hormones and growth factors regulate bone cell differentiation and function, and briefly describe the roles of bone cells and the skeleton in stem cell biology and the effect aging has on them.

G.A. Howard, PhD
Department of Medicine, University of Miami Miller School of Medicine, Miami, FL, USA

Geriatric Research, Education and Clinical Center, and Research Service, Bruce W. Carter Department of Veterans Affairs Medical Center, Miami, FL, USA

P.C. Schiller, PhD (✉)
Department of Orthopaedics,
University of Miami Miller School of Medicine,
Miami 33136, FL, USA

Geriatric Research, Education and Clinical Center, and Research Service, Bruce W. Carter
Department of Veterans Affairs Medical Center,
Miami, FL, USA
e-mail: P.Schiller@Miami.edu

Bone Growth and Development

The cellular events in bone maintenance, remodeling, and repair during adult life have their basis in the embryonic development of bone. The vertebrate skeleton, composed of cartilage and bone, is derived from cells of three distinct embryonic lineages. The craniofacial skeleton is formed by cranial neural crest cells, the axial skeleton is the product of paraxial mesoderm (somites), and the limb skeleton is derived from lateral plate

G. Duque, D.P. Kiel (eds.), *Osteoporosis in Older Persons: Advances in Pathophysiology and Therapeutic Approaches*, DOI 10.1007/978-3-319-25976-5_1

mesodermal cells [1]. During vertebrate embryogenesis, neural crest-derived mesenchymal cells directly differentiate into osteoblasts (bone forming cells; described in detail in next section) which will form the bones of the skull, maxilla, mandible, and the subperiosteal bone-forming layers of long bones. The bones of the skull are created as these ossification regions merge. Hence, a single bone can be formed from many smaller bones that have fused in a process called intramembranous ossification. In contrast, bones of the vertebral column, pelvis, and upper and lower limbs, are formed on an initial hyaline cartilage model, generally called an "anlagen". In this process there is an initial aggregation and differentiation of mesenchymal cells, followed by the proliferation, hypertrophy and death of chondrocytes. Bone formation then initiates in the collar surrounding the hypertrophic cartilage core that is eventually invaded by blood vessels and replaced by bone tissue and bone marrow. This process, called endo (within) – chondral (cartilage) ossification, is characterized by a defined series of events.

Early during limb development a layer of four to six cells, which surrounds a prechondrogenic core of undifferentiated cells, appears to give rise to the lineage of osteogenic cells responsible for the formation of all structural bone [2]. This bone is fabricated outside of the cartilage core, and it appears that the core is not replaced by bone, but rather by marrow and vascular elements. Bone formation is a vascular driven phenomenon, characterized by the directional nature of osteoid secretion. Analysis of the cellular and molecular events of embryonic osteogenesis, suggest that osteogenesis and chondrogenesis are independent events that are programmed early in development. Many of the molecules involved in regulating these processes during development continue to play central roles during adult life.

The exact mechanism underlying mineralization of the osteoid (predominantly a collagen matrix) has been debated for decades, although a consensus has generally been achieved by workers in the field that the process proceeds through extracellular particles called matrix vesicles. It is not yet clear how this process works, with theories and data suggesting that mineralization is initiated as an intracellular event. That is, mineral is first formed within cells (in endosomes), not in extracellular particles (matrix vesicles). It is suggested that the endosomes may provide high concentrations of phosphate and/or calcium ions as nucleation sites for mineralization. These proposed nucleation sites may be regulated by calcium and phosphate concentrations as well as by sundry proteins. At some point the endosomes are then released as matrix vesicles, becoming extracellular sites for mineralization of the matrix as anchored exosomes in the osteoid. Recent studies suggest that the matrix vesicles may in fact represent structures termed exosomes. Although exosomes exist throughout a variety of tissues, the likelihood that matrix vesicles represent a type of exosome within the skeletal milieu has been proposed. Further, it has been suggested that some aspects of cell-cell communication within the complex structure of skeletal tissue may be facilitated by exosomes (for review see [3]).

The transcription factor Sox 9 is one of the master regulators of chondrogenesis [4, 5]. Sox9 transcripts are detected in all prechondrogenic mesenchymal condensations as early as 8.5–9.5 days of mouse embryonic development, and the expression peaks in cartilage primordia at 11.5–14.5 days. This transcription factor is central to the regulated expression of the genes that define the chondrocytic phenotype and for the expression of cartilage-specific matrix proteins, including collagen II, IX, and XI, and the large proteoglycan aggrecan [6]. Soon after their formation, chondrocytes in the central region of the cartilage undergo further maturation to hypertrophic chondrocytes, which exit the cell cycle and synthesize a different extracellular matrix that is distinctly different from that of proliferating cartilage. Collagen X, a marker for hypertrophic chondrocytes, is a distinctive component of this matrix [7]. Angiogenic factors (e.g., vascular endothelial growth factor [VEGF]) secreted by hypertrophic chondrocytes induce sprouting angiogenesis from the perichondrium [8]. Subsequent to vessel formation, bone forming osteoblasts, bone resorbing osteoclasts, and

hematopoietic cells arrive, and form the primary ossification centers.

Within the primary ossification centers, hypertrophic chondrocytes undergo apoptosis, the hypertrophic cartilage matrix is degraded, incoming osteoblasts replace the degraded cartilage with trabecular bone, and bone marrow is formed. Simultaneously, osteoblasts in the perichondrium form a collar of compact bone surrounding the middle portion (diaphysis) of the cartilage. At both ends (epiphyses) of the cartilage, secondary ossification centers are created, leaving a plate of cartilage (growth plate) between the epiphysis and diaphysis. In the growth plate, a coordinated sequence of chondrocyte proliferation, hypertrophy, and apoptosis results in longitudinal growth of long bones during early development; continuing through puberty in most cases. In a coordinated fashion the growth of the epiphyses and radial growth of the diaphysis take place concurrently.

In adults, bone repair proceeds in a fashion similar to endochondral ossification. The natural healing process involves infiltration of fibroblasts, an inflammatory response, cartilage formation, vascularization, osteoblast maturation/formation, infiltration by osteoblasts and osteoclasts, and matrix remodeling. A more detailed description of the mechanisms that regulate bone cell differentiation and function will be discussed in a section below and in subsequent chapters.

Bone Cell Differentiation

Bone is dynamic connective tissue composed of an elegant assembly of functionally distinct cell populations. Their roles are to maintain the structural, biochemical, and mechanical integrity of bone as well as its central role in ion homeostasis, a calcium basin, and as a stem cell reservoir. Bone is continuously modified and reshaped throughout our lifetime by the work of osteoblasts (bone forming cells) and osteoclasts (bone cells that break down/resorb previously formed bone). A fraction of the active osteoblasts become incorporated within the newly laid down matrix and develop into specialized osteocytes within defined spaces termed lacunae. Osteocytes form a complex and organized network of interconnected cells throughout the mineralized bone matrix which supports bone structure and maintenance. Quiescent osteoblasts become flat and form a single layer of cells, called lining cells, that protects the surface of bone. Osteoblasts and osteoclasts originate from distinct cell lineages, stromal and hematopoietic (monocyte/macrophage), respectively, and the molecular processes that lead to their differentiation programs and functional development are beginning to be understood.

Osteoprogenitors, Osteoblasts, and Osteocytes

Marrow stromal cells (MSCs) can act as precursors to a variety of cell types (osteoblasts, chondroblasts, myoblasts, adipocytes, fibroblasts, etc.). Under appropriate stimulation, MSCs engage in a differentiation program leading to the production of osteoprogenitors, which in turn, give rise to osteoblasts (Fig. 1.1). Upon functional maturation, these are the cells responsible for bone matrix deposition during both intramembranous and endochondral bone formation. Osteoblastic differentiation involves an exquisite interplay of developmental cues, signaling proteins, transcription factors, and their co-regulatory proteins that support differentiation (Fig. 1.1). This refined differentiation program is reflected by the fact that within the osteoblastic lineage, subpopulations of cells can respond selectively to physiologic signals. Experimental evidence indicates that osteoblasts from appendicular and axial bone exhibit distinct responses to hormonal, mechanical, or developmental cues. It remains to be determined whether these differences reflect the inherent properties of the selected cells at different stages of osteoblastic differentiation or the local, cellular and tissue environments.

Although it is generally thought that committed precursor cells are directionally engaged in specific differentiation programs, accumulating data indicates a certain degree of plasticity.

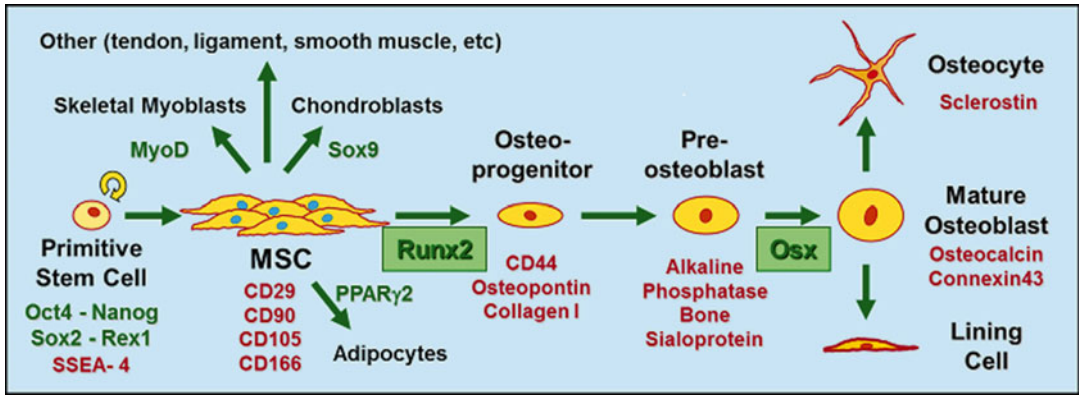


Fig. 1.1 The osteoblastic differentiation pathway. The commitment of primitive stem cells to several lineages showing their differentiation potential, with an emphasis on the osteoblastic pathway is diagramed. Some key transcription factors involved in establishing each phenotype are described (*green*) and the determinants of the osteoblastic phenotype Runx2 and Osx are *boxed*. Markers characteristic of each phenotypic stage are indicated (*red*)

Phenotypically, committed cells may dedifferentiate during proliferation and postmitotically assume a different phenotype, primarily due to effects of the local cellular environment [9, 10]. Specifically, the local environment may activate specific mechanisms, such as those involving modulation of gap-junctional intercellular communication [11], that may contribute to phenotypic determination.

The main function of the osteoblast is to synthesize bone matrix. A functionally mature osteoblast is characterized by unique morphological and ultrastructural characteristics typical of a cell engaged in the synthesis and secretion of connective tissue products. These cells show a large nucleus, enlarged Golgi, and an extensive endoplasmic reticulum. They express high levels of alkaline phosphatase and secrete an unmineralized osteoid composed primarily of type I collagen and specific bone matrix proteins. A single layer of inactive flattened osteoblasts, or bone lining cells, are observed on quiescent bone surfaces. These cells underlie the periosteum directly on the mineralized surface, as well as forming the endosteum separating bone from the marrow cavity.

Osteocytes are the terminal differentiation stage of cells in the osteoblastic lineage, and reportedly make up greater than 90 % of all the cells in the skeleton [12]. Osteocytes sense and subsequently mediate responses to support bone structure, biomechanical properties and metabolic functions. Unique features distinguishing these cells include the fact that they are strategically distributed throughout the mineralized bone matrix. For many years it was thought that osteocytes were simply osteoblasts that had been trapped in the osteoid matrix as bone continued to grow. However, more recent studies support the hypothesis that osteocytes transition from osteoblasts in an active, defined process, starting with the development of long dendritic processes. Although the exact mechanism involved in the transition of a single osteoblast into an osteocyte is difficult to observe with current methods, the development of osteocytic cell lines has helped to better understand the markers, regulatory factors, and function of osteoclasts at least *in vitro. In* vivo each osteocyte resides within a lacuna and is interconnected with other osteocytes and with osteoblasts located on the bone surface via countless cellular extensions of filopodia/dendritic processes that run through canaliculai. This extensive network of cytoplasmic interconnections contributes to osteocyte viability and maintenance of functional properties, including the expression of the protein sclerostin, which is involved in negative regulation of bone (for review see [13]). This network of cells is coupled molecularly and electrically, predominantly via intercellular communication mediated by gap junctions [14–17] comprised primarily of the gap-junction channel protein connexin 43 [18–22].

Connexin43-mediated gap-junctional communication is essential for osteoblast and osteocyte phenotypic maturation, activity, and survival [21, 23–25]. Moreover, its inhibition may affect phenotypic determination of bone cells promoting the development of an adipocytic phenotype [11].

The primary function of the osteoblast/lining cell/osteocyte functional syncytium is considered to be mechanosensory (i.e., to sense and transduce stress signals [stretching, bending] to biological activity). Osteocytes can be longed-lived; in human bone that has not undergone remodeling they can survive for decades. However, empty lacunae are observed in aged bone, indicating that osteocytes can undergo apoptosis, a scenario potentially deleterious to bone structure and integrity [26]. Interestingly, estrogens, bisphosphonates, and physiologic mechanical loading, all anti-osteoporotic regiments, inhibit osteoblast and osteocyte apoptosis [27–29].

The developmental expression pattern of transcription factors during osteoblastic maturation reflects their central roles as determinants of osteoblastic differentiation. Two transcription factors, Runx2 (Cbfa1/AML3) and Osterix (Osx; SP7) are absolutely required for osteoblast differentiation during both intramembranous and endochondral bone formation. Runx2 performs as a master regulator by mediating the temporal activation and/or repression of phenotypic genes as osteoblasts progress through stages of differentiation and cell growth [30–32]. Runx2 is a member of a small transcription factor family that shares DNA-binding domains of homology with Drosophila Runt. In homozygous Runx2-deficient mice, bone tissue is not formed. Haploinsufficiency of Runx2 causes cleidocranial dysplasia (CCD) in both mice and humans [33]. This autosomal dominant disorder is characterized by a delay in closure of cranial sutures and fontanelles, hypoplastic or aplastic clavicles, dental anomalies that include delayed eruption of deciduous and permanent teeth, and supernumerary teeth of the permanent dentition [33]. In addition to the role of Runx2 in osteoblast differentiation, Runx2 activity is also required for bone matrix deposition by mature osteoblasts [34], and some individuals with severe CCD have osteoporosis. Runx2 is targeted to the promoters and regulates the expression of several genes encoding bone specific proteins, including osteocalcin (an osteoblast-specific marker), bone sialoprotein, alkaline phosphatase, and type I collagen [30]. Interestingly, both overexpression of Runx2 and expression of a dominant-negative form of Runx2 in osteoblasts impair bone formation, revealing the complexity involved in regulation of different stages of osteoblast differentiation. Runx2 activity is modulated by phosphorylation and Runx2 interacts with other transcription factors, including signal transducer and activator of transcription-1 (STAT-1) [35], Smads 1, 3, and 5 [36–38], Hey1 [39], Menin [40], p300 [41], Grg5 [42], and Twist [43].

Analysis of Osx null mice shows that Osx is genetically downstream of Runx2. Little is known about how Osx regulates osteoblast differentiation and function. Expression of genes characteristic of mature osteoblasts is absent in cells surrounding chondrocytes in Osx null mice, and instead these cells express genes characteristic of chondrocytes. Thus, Osx may be playing a role in directing precursor cells toward the osteoblast lineage and away from the chondrocyte lineage [44, 45].

The endochondral portion of the developing clavicle is particularly sensitive to a reduction in the level of Runx2, both in mice and humans [46]. In addition, no hypertrophy develops in cartilages of the axial skeleton and the proximal limbs in Runx2 null mice. In contrast, in the distal limbs, cartilage hypertrophy is reduced, but does occur, and hypertrophy in hands and feet is initiated, but is not maintained [47, 48]. Since a low level of Runx2 expression can be detected in hypertrophic chondrocytes in wild-type growth plates, this has led to the hypothesis that Runx2, in addition to inducing osteoblast differentiation, is required or represents a limiting factor for chondrocyte hypertrophy. Furthermore, it may be required for VEGF expression and angiogenesis during endochondral ossification. Finally, Runx2 may control the expression of collagenase 3 (MMP-13) in hypertrophic chondrocytes [49, 50].

It has recently been determined that the Runx1 hematopoietic factor and the Runx3 gene (involved in neural and gut development) are also expressed in the skeleton, although their roles in bone formation are not known. Alterations in functions of various other non-bone-specific transcription factors have also been demonstrated to affect osteoblastic differentiation and function. These include activator protein-1 and its related molecules, Dlx5, Msx1, Msx2, Twist, Atf4, and nuclear steroid hormone receptors such as androgen receptors and estrogen receptors. As regulatory factors continue to be identified, the complexity of the molecular mechanisms that control gene expression in osteoblast lineage cells and drive the osteoblast maturation process are being further appreciated.

Regulators of Osteoblastic Cell Differentiation and Function

The osteoblastic differentiation program is subjected to a complex and intricate regulation by a number of growth factors, hormones and cytokines which mediate cues ranging from developmental signals to tissue homeostasis. As in other tissues, many signals simultaneously initiated by two or more of these factors have to be integrated for a unified phenotypic response. A detailed analysis of the mechanisms mediating all the osteogenic responses initiated by the action of extracellular regulators of osteoblast differentiation and bone development is beyond the scope of this section. We present here a brief overview of the main factors known to regulate osteoblastic cell differentiation and function.

Wnt Signaling Molecules

Engagement of MSCs toward osteoblastic differentiation, bone formation and skeletal development appears to be initiated by activation of the Wnt/β-catenin signaling pathway [51, 52]; β-Catenin is the downstream mediator of canonical Wnt signaling that forms transcription-regulating complexes with TCF/LEF transcription factors. Key roles for this signaling pathway have been established in embryonic skeletal patterning, fetal skeletal development, and adult skeletal remodeling [53–58]. Recent work in which β-catenin was conditionally knocked out from cells at various stages of the osteoblast lineage, suggests that β-catenin plays multiple critical roles in osteoblast differentiation [59]. Canonical Wnt signaling has also been shown to decrease osteoclastogenesis and bone resorption (see section below on "Modulators of osteoclastic cell differentiation and function").

Noncanonical Wnt signaling (i.e., pathways other than via β-Catenin) including those involving GTPase pathways and G-protein-coupled receptors appear to have a role in skeletal development. These pathways have been reported to induce osteoblastogenesis in mouse MSCs (for review see [60]).

Parathyroid Hormone

Intermittent parathyroid hormone (PTH) therapy in animals and humans induces anabolic effects on bone formation. PTH mediates its effects in cells of the osteoblastic lineage via the type 1 PTH receptor (PTH1R), which is also activated by PTH-related peptide (PTHrP). Depending on the cellular context, binding to PTH1R causes the activation of at least the adenylate cyclase/protein kinase A (AC/PKA), protein kinase C (PKC), and mitogen-activated protein kinase (MAPK) signaling pathways [61]. On the other hand, continuous administration of PTH produces bone loss due to osteoclast activation as observed in hyperparathyroidism. Different signaling pathways are activated in osteoblast precursors by intermittent or chronic stimulation, respectively, which lead to important differences in downstream gene regulation patterns. Intermittent PTH and PTHrP treatment of MSC and preosteoblastic cell lines regulates their osteogenic differentiation capacity by modulating the expression of the transcription factors Runx2 and Osx and down-regulating components of the hedgehog signaling cascade [62–64]. The stimulatory effect on osteoblastic differentiation may depend on the cell differentiation stage, exposure time and PTH dosage [19, 65].

PTH and PTHrP appear to also be involved in mechanotransduction by modulating intracellular

Ca^{2+} via mechanosensitive channels [66]. Mechanical loading and PTH have synergistic effects on osteocalcin expression *in vitro* and on bone formation *in vivo* [67]. Moreover mechanical stress induces PTHrP expression in osteoblast-like cells, suggesting that it could be a potential mediator of the anabolic effects of mechanical force on bone [68].

Vitamin D_3

Vitamin D_3 promotes osteogenic differentiation of MSCs by inhibiting proliferation and upregulating osteogenic markers such as alkaline phosphatase and osteocalcin [69, 70]. Surprisingly vitamin D_3 is not all together indispensable for normal bone development in embryogenesis as the skeleton of vitamin D receptor (VDR) mutant mice developed normally, yet they showed growth retardation, rickets, secondary hyperparathyroidism, and alopecia [71]. Vitamin D_3-bound VDR interacts with Runx2 to upregulated osteocalcin expression [72]. Overall vitamin D_3 stimulates the expression of many genes in bone cells like osteocalcin, ALP, osteopontin, CYR61 and thioredoxin reductase, and modifies osteogenic differentiation, but many of the programs induced may also be backed up by other systems (for review see [73]).

The active metabolite of vitamin D_3 responsible for the regulatory aspects described above include 1α,25-dihydroxyvitamin D_3 as the main metabolite involved in bone metabolism and bone cell functions. However, there have been reports that 24R,25-dihydroxyvitamin D_3 also has bone and bone cell metabolic actions (for review see [74]). Recent studies show that 24R,25-dihydroxyvitamin D_3 appears to be important for osteoblastic maturation/differentiation from MSC [75].

Estrogen

Estrogens have a major impact both on bone formation during growth and development and bone metabolism in adults. Bone marrow stromal cells express estrogen receptor (ER) beta (ERβ) and two splice variants of ERα suggesting they are targets of estrogen action. Furthermore, estrogens upregulate ER expression in MSCs, and when overexpressed in the marrow stromal cells, ER induced osteogenic differentiation in response to estradiol. Recently, studies in mice have shown that some effects, at least on cortical bone, do not require ERα signalling in osteoblasts or osteoclasts [76].

The estrogenic compound genistein stimulates the proliferation and osteoblastic differentiation of bone marrow MSCs by activation of the NO/cGMP pathway [77]. The differentiation-inducing effects in MSCs might be mediated by downstream induction of BMP2 and BMP6 expression. Estrogens can upregulate the expression of the osteogenic marker genes Runx2, alkaline phosphatase (ALP), collagen 1 (Col1), and TGFβ1 in MSCs. Estrogens inhibit osteoclast development and function via upregulation of osteoprotegerin (OPG) expression in osteoblasts and inhibition of cytokine expression [78]. Estrogen deficiency leads to osteoporosis in women and men [79]. Although the influence of estrogens on osteoblast function might not be the foremost function of estrogens in the maintenance of bone, estrogens are still considered to have an anti-resorptive role.

Mechanical strain and estrogens activate ERα in bone cells [80, 81]. ERα itself appears to be the mediator of such effects since ERα KO results in an impaired anabolic response to mechanical strain *in vivo* and *in vitro*. Most interesting is a recent report showing that deletion of ERα in osteoblast lineage cells has differing effects with respect to mechanical loading and bone mass in male vs female mice. Specifically, bone mass and mechanical loading were decreased in female ERα knock-out mice compared to control littermates; whereas, those same parameters were not different from control littermates in male ERα knock-out mice [82].

Bone Morphogenetic Proteins

Bone morphogenetic proteins (BMPs) are members of the transforming growth factor β (TGFβ) superfamily of signal molecules that mediate many diverse biological processes ranging from early embryonic tissue patterning to postnatal tissue homeostasis. Activation of BMP/TGFβ receptors initiates phosphorylation of the

downstream effector proteins, known as receptor-regulated Smads, leading to signal transduction [83]. While the same Smads are used by BMPs in all types of cells, association with different transcription factors accounts in part for the functional diversity of BMPs. These transcription factors are recruited by Smads to regulate the expression of specific subsets of target genes depending on the cell context. Runx2 is expressed in response to BMP/TGFβ, and acts as an integrator of BMP/TGFβ Smad signaling through the formation of Runx2–Smad complexes [84, 85]. While both BMPs and TGFβ direct Runx2–Smad interactions, only the BMP-responsive Smads promote osteoblast differentiation together with Runx2. BMPs promote bone formation by stimulating the proliferation and differentiation of osteoblasts. It has been suggested that delayed healing of non-union fractures of bone may be the result of decreased levels of BMP activity. The BMP signaling cascade is closely regulated, with the inhibitory Smads blocking the intracellular signal cascade. Predominantly BMP-2 and BMP-7 have been shown to have potent stimulatory effects on osteoblastogenesis and have proven clinical utility for bone regeneration [86–88].

Growth Hormone/Insulin-Like Growth Factor

Growth hormone (GH) is a peptide hormone secreted from the pituitary gland under the control of the hypothalamus. A large number, but not all, of its effects are mediated through insulin-like growth factor-I (IGF-I). Both GH and IGF-I play significant roles in the regulation of growth and bone metabolism and control bone mass. GH directly, as well as through IGF-I, stimulates osteoblast proliferation and activity, promoting bone formation [89]. It also stimulates osteoclast differentiation and activity, promoting bone resorption, although this effect does not appear to be via IGF-1 activity. This promotion of bone resorption results in an increase in the overall rate of bone remodeling, with a net effect of bone buildup. The absence of GH results in a reduced rate of bone remodeling and a gradual loss of bone mineral density. Bone growth primarily occurs at the epiphyseal growth plates and is the result of the proliferation and differentiation of chondrocytes. GH has direct effects on these chondrocytes, but primarily regulates this function through IGF-I, which stimulates the proliferation of and matrix production by these cells. GH deficiency severely limits bone growth and hence the accumulation of bone mass. It is also known that GH effects on target tissues involve multiple components of the IGF system including the ligands, receptors, IGF binding proteins (IGFBP), IGFBP proteases and activators and inhibitors of IGFBP proteases. Basic and clinical studies indicate a significant role for insulin-like growth factor-I (IGF-I) in determining bone mineral density (BMD). Genomic studies resulting in IGF-I deficient mice, and mice with targeted over-expression of IGF-I reinforce the essential role of IGF-I in bone development at both the embryonic and postnatal stages. Deficiency in the GH/IGF system that occurs with age has been proposed to play a major role in age-related osteoporosis. A thorough molecular dissection of the IGF regulatory system and its signaling pathway in bone may reveal novel therapeutic targets for the treatment of osteoporosis.

Leptin/β Adrenergic Receptors

Leptin was initially characterized as an adipocyte-secreted hormone that controls body weight [90–92]. KO animals for the leptin gene (ob/ob mouse) and the leptin receptor (db/db mouse) in addition to their body-mass phenotype develop a high bone mass with an increase in trabecular bone volume [93, 94]. This results from an increase in osteoblast function not number, indicating that leptin in this context has no influence on osteoblast proliferation. There is strong evidence that leptin acts centrally via hypothalamic receptors to regulate bone mass [95]. This regulatory effect appears to be via a neuroendocrine axis and the sympathetic nervous system by activating β2 adrenergic receptors on osteoblastic cells.

Leptin acts directly on human MSC by enhancing osteogenic differentiation and inhibiting the adipogenic pathway [96]. However, there are conflicting results published with respect to the local

effects of leptin on bone growth and regeneration. Some workers have argued that leptin mainly exerts a direct anabolic effect on MSC by promoting their proliferation and differentiation. Others, however point out that mice in which the leptin receptor in osteoblasts has been specifically knocked out lack a bone phenotype [97].

Glucocorticoids

Glucocorticoid effects on bone metabolism are complex and vary significantly depending on the duration, concentration and the time window of exposure [98]. Glucocorticoid receptor (GR) signalling is required during the earlier phase of osteoblastic differentiation, but dispensable in later phases. Physiologically, glucocorticoids *in vivo* are required for bone formation and stimulation of osteogenic differentiation. However, prolonged treatment at pharmacological doses induces osteoporosis *in vivo* and leads to an impairment of osteogenic differentiation *in vitro*. This impairment is mediated via enhanced expression of dickkopf-1 (Dkk-1) and secreted-frizzled related protein 1 (SFRP-1), inhibitors of the canonical Wnt signalling pathway, and may favour alternative differentiation pathways (e.g., adipogenesis) [99, 100].

Thyroid Hormone

Thyroid hormone (T_3) is essential for the normal development of endochondral and intramembranous bone and plays an important role in the linear growth and maintenance of bone mass [101]. Thyroid hormone receptors (TR) are expressed in osteoblasts, growth plate chondrocytes, and MSC [102, 103]. In MSCs three isoforms, TRα1, TRβ1 and TRβ2, are functionally expressed [104]. The effects of T_3 in osteoblastic cell lines and primary cultures are dependent upon species, cell type, anatomical origin, state of differentiation, confluence and duration of treatment, but T_3 has been implicated in the increased synthesis of osteocalcin, type I collagen and ALP, and induction of MMP13, gelatinase B (MMP9) and the tissue inhibitor of MMP (TIMP) [105, 106]. Mice expressing a non-functional TRα1 show delayed endochondral ossification and intramembranous bone formation during embryogenesis and reduced postnatal linear growth. The results from KO and transgenic mice match those seen in hypo- and hyperthyroid animals, although overall the changes in growth plate and bone morphology are very complex and not yet completely unraveled.

Our increasing understanding of the downstream targets of osteogenic developmental signaling pathways, the molecular switches directing phenotypic commitment and the network of transcription factors that regulate osteoblast differentiation are beginning to shed light on the complexity of control mechanisms for bone formation. Integration of the many osteogenic signaling pathways converges primarily through the Runx2 transcription factor, which appears to identify the specific molecular mechanisms necessary for coordinating activities from diverse developmental and physiologic signals. Simultaneously, all this information provides novel opportunities for therapeutic approaches toward potential interventions in metabolic and genetic disorders of the skeleton.

MicroRNAs

MicroRNAs (miRNAs) are small noncoding RNAs (average size about 22 nucleotides), that have been reported to play an important role in maintaining bone development and metabolism. Through the efforts of several research groups it is now clear that the process of maturation/differentiation of MSCs into mature osteoblasts and the subsequent steps in osteogenesis are all regulated in some way or another by various miRNAs. A clear understanding of the exact mechanism(s) involved in this regulation has the potential to facilitate use of miRNAs for therapeutic purposes in bone repair. In this respect it is known that specific miRNAs interact with Runx2. This is thought to be a direct interaction with its gene or perhaps by affecting other genes (e.g., BMP-2) that alter the level of Runx2 expression. Some of these miRNA interactions with Runx2 are reported to result in positive regulation, whereas others serve as negative regulators of osteogenic differentiation. The reader is referred to an extensive review of the numerous miRNAs and their respective actions on bone and bone repair that has been

recently published for a full understanding of this aspect of bone biology [107].

Monocytes/Macrophages and Osteoclastogenesis

The primary activity of osteoclasts is resorbing bone (and cartilage), and thus is required for skeletal modeling and remodeling. The osteoclast is a specialized multinucleated cell derived from cells in the monocyte-macrophage lineage (Fig. 1.2). The earliest identifiable precursor is the granulocyte-macrophage colony-forming unit (CFU-GM), which gives rise to granulocytes, monocytes, and osteoclasts. CFU-GM-derived cells differentiate to committed osteoclast precursors, which are post-mitotic cells that must fuse to form functional multinucleated osteoclasts. Osteoclasts are the principal, if not exclusive, bone-resorbing cells, and their activity has a profound impact on skeletal health. Accordingly, disorders of skeletal insufficiency, such as osteoporosis, typically represent increased osteoclastic bone resorption relative to bone formation. Prevention of pathological bone loss therefore depends on an understanding of the mechanisms by which osteoclasts differentiate from their precursors and degrade the skeleton.

Osteoclast development follows vascular invasion of cartilage during embryogenesis and requires VEGF [108]. Subsequently, osteoclastogenesis and skeletal resorption continue throughout life. Osteoclast precursors in humans are characterized by the expression of CD14 and CD11b on their surface. In addition to several transcription factors required for B cell lineage development, two transcriptional factors are important in the regulation of osteoclastogenesis: PU.1 and MITF. The myeloid and B cell tran-

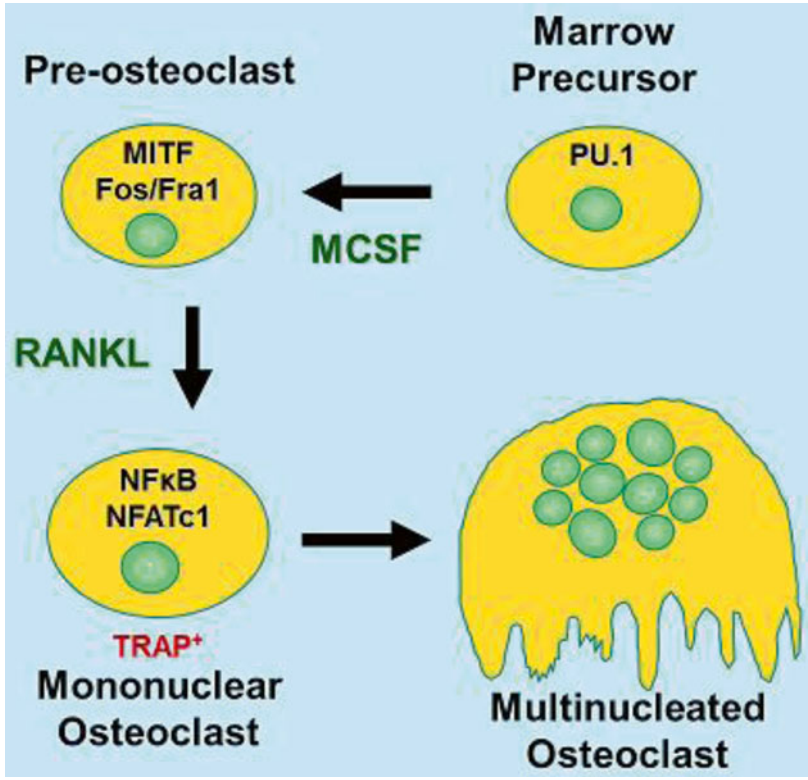


Fig. 1.2 The osteoclastic differentiation pathway. The commitment of marrow precursors to the osteoclastic pathway is diagramed. Some key transcription factors involved in establishing each phenotype are described (*black*) and the factors that induce osteoclastic determination, MCSF and RANKL (*green*) are included

scription factor PU.1 is the earliest characterized determinant of the macrophage/osteoclast lineage. Mice null for PU.1, in addition to not having B cells, lack osteoclasts and macrophages [109]. High levels of PU.1 are required for macrophage and osteoclast differentiation [110]. Downstream of PU.1, and interacting with it for osteoclast differentiation is the microphthalmia-associated transcription factor (MITF) [111].

Development of osteoclasts requires the concerted actions of several cytokines, steroids and lipids, which act directly on precursors themselves, as well as indirectly by targeting a combination of mesenchymal supportive cells and those in the lymphoid lineage. The capacity of mature osteoclasts to resorb bone is cytokine driven and depends on their ability to recognize the matrix, polarize, and secrete acid and a collagenolytic enzyme.

So far, most genetic mutations that regulate bone mass, whether natural or generated by targeted deletions, are associated with the osteoclast. Mutations can be inherent to the osteoclast and precursor, or found in proteins that are produced by lymphoid or mesenchymal tissue, which regulate the survival, differentiation and/or function of the mature bone-resorbing cell.

Modulators of Osteoclastic Cell Differentiation and Function

Osteoclastogenesis is regulated mainly by two cytokines: receptor activator of the NFκB ligand (RANKL) and macrophage colony stimulating factor (M-CSF). RANKL is a glycoprotein produced by stromal cells that belongs to the TNF ligand super family. RANKL signal is mediated through its receptor, RANK, a member of TNFR super family of type I transmembrane proteins. RANKL secreted by activated T cells and acting through the RANK receptor is able to activate the monocytic cells to differentiate into osteoclasts. RANK ligand can be inhibited by osteoprotegerin (OPG), a soluble decoy receptor that also belongs to the TNFR super family [112]. Blocking RANKL suppresses osteoclast differentiation.

M-CSF is a secreted cytokine that promotes the proliferation and differentiation of precursors of the monocyte linage. M-CSF recognizes only one receptor, the tyrosine kinase c-Fms. Transgenic mice lacking c-Fms develop osteopetrosis [113] because of their inability to produce osteoclasts.

Most factors that induce osteoclast differentiation, such as PTHrP, IL-11, and prostaglandins, do so by inducing expression of RANKL on the surface of immature osteoblasts [114]. In addition, osteoclasts produce autocrine-paracrine factors that regulate osteoclast formation, such as IL-6. Several autocrine-paracrine factors that regulate osteoclast activity include annexin-II, MIP-1α, eosinophil chemotactic factor, and osteoclast inhibitor factors 1 and 2. Most recently, the receptor for ADAM8 [115] and α9β1 integrin [116] have been shown to be involved in normal osteoclast activity. Osteoclast differentiation is controlled by exogenous hormones and cytokines as well as autocrine-paracrine factors that positively or negatively regulate osteoclast proliferation and differentiation.

As indicated above in the section on "Regulators of osteoblastic cell differentiation and function", Wnt signaling has been reported to affect osteoclastogenesis as well as osteoblastogenesis. Specifically, β-Catenin signaling in osteoclast precursors appeared to be required for their proliferation, whereas continuous activation of these same signaling pathways reportedly inhibited osteoclastogenesis [117]. Moreover, there appear to be effects on osteoclastogenesis by non-canonical Wnt signaling pathways as well. There is some evidence that Wnt ligands produced by osteoblasts may be involved in the regulation of osteoclastogenesis. The specific involvement of these factors and the direct regulatory events are yet to be determined.

In summary, bone cells from different origins, at different stages of differentiation, and with different and sometimes opposing functions, integrate into a network of cells that work together to orchestrate modeling, remodeling, and bone repair, starting very early in development. Soluble signaling cytokines, hormones, and growth factors, as well as cell-to-cell communication pathways (i.e., connexin43-gap junctional communication) play

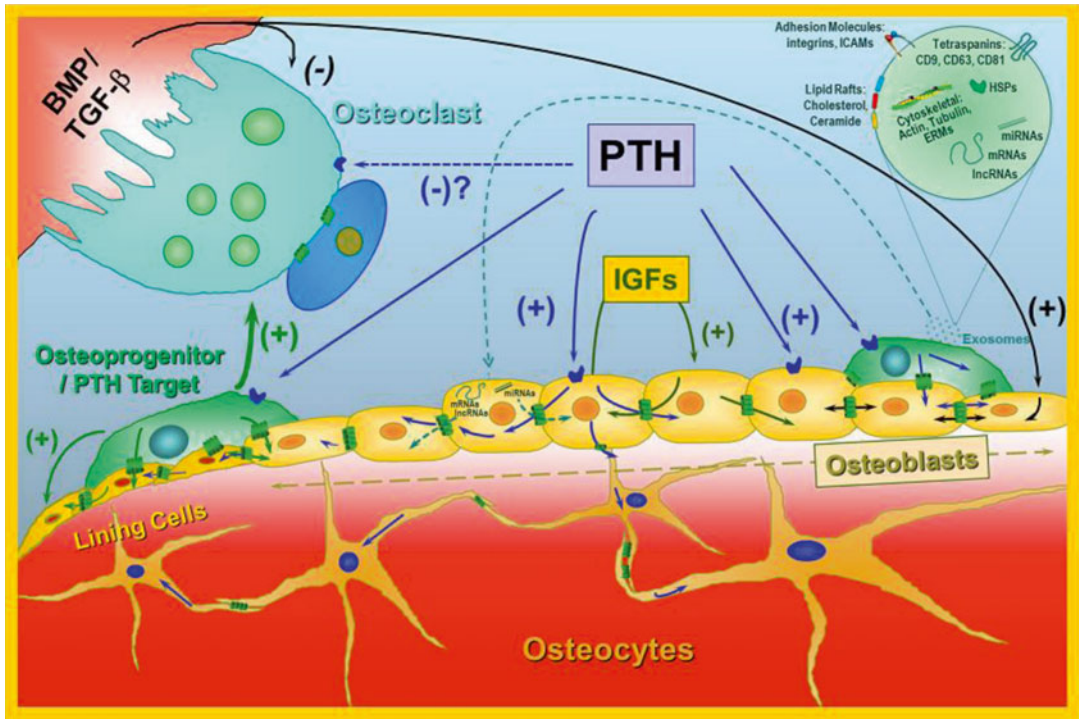


Fig. 1.3 Bone cells working in concert. Bone cells with different and sometimes contrasting functions, integrate into a network to orchestrate modeling, remodeling, and repair of bone. Some soluble signaling hormones (PTH), morphogens (BMPs), and growth factors (IGF, TGF-β) as well as cell-to-cell communication pathways (i.e., connexin43-gap junctional communication [green channels between adjacent cells or cell processes]) are included in order to describe communication pathways utilized to coordinately maintain bone integrity. Systemic, paracrine, autocrine, and coupling factors make this environment unique for bone cell differentiation and function. Cytoplasmic signaling molecules can travel through mineralized matrix (*red*) thanks to the action of osteocytes and specialized cellular structures (i.e., gap junctions)

essential roles in coordinating the maintenance of tissue integrity and appropriate skeletal mechanical support (Fig. 1.3).

Bone Turnover

Bone mass is the result of a lifelong balance between the processes of bone formation and bone resorption, and in fact, most metabolic bone diseases, including osteoporosis, are a consequence of an unbalanced (or uncoupled) bone turnover. Under normal conditions, bone resorption and bone formation in the adult bone represent not only the physiological response of the skeleton to injuries, such as fractures, but they also provide the mechanism for renewal of aging bone tissue, as well as for the remodeling of the skeletal architecture to maximize its flexibility to stress, and resistance to load.

Osteoporotic syndromes are characterized by a wide spectrum of bone turnover, ranging from accelerated to reduced remodeling rates. Although the status of bone remodeling is not a specific indication of any particular disorder, estimation of the processes of bone resorption and formation adds crucial information for the prognosis of the disease, as well as for the selection of the most appropriate therapeutic approach, thereby significantly affecting the clinical decision-making process. Higher rates of bone remodeling are, in general, associated with higher rates of bone loss, and under these conditions, an anti-resorptive treatment usually leads to better therapeutic responses than in disorders characterized by low remodeling rates.

During the process of bone resorption calcium salts are liberated from the bone, and if not reused by the osteoblasts for new bone formation, they enter the circulation and are cleared by the kidneys. Therefore, an increased bone turnover is usually associated with an increased urinary calcium output. Before current biochemical markers were introduced, urinary calcium excretion represented the only humoral index available to estimate the rate of bone turnover. Although a moderate hypercalcemia is still considered as a possible sign of increased bone remodeling rates, this parameter can obviously only provide a rough estimate of the real extent and nature of the remodeling process.

Measurement of Bone Turnover

Through the use of dual X-ray bone absorptiometry (DEXA) it is possible to measure both bone mineral density (BMD) and bone mineral content (BMC) of individuals; thus providing information on the skeleton at a specific site and at a specific point in time. Thus, while evaluation of BMD is a critical component in clinically evaluating a patient at risk for osteoporosis (and potentially for other metabolic bone diseases), BMD represents a static parameter that provides insight into the rate of bone turnover in a given patient only if repeated over time. The ability to complement the static measurement of BMD with an assessment of the dynamic process of bone turnover, enhances the ability of BMD to predict risk of subsequent fractures. However, while it has been possible to measure BMD at various skeletal sites for many years, bone turnover *per se* can only be assessed by a combination of calcium balance and isotope kinetic studies (both time-consuming and very expensive) or by tetracycline-based histomorphometry (invasive, expensive, and time-intensive). Thus, the more recent availability of biochemical markers for bone turnover represents a major methodological advance. These measurements are noninvasive, relatively inexpensive, generally available, can measure changes in bone turnover over short intervals of time, and can be assessed repetitively. As with any new technology, however, where these assessments fit into a clinical approach to patients with known or suspected osteoporosis is an evolving area.

Bone Formation Markers

The major synthetic product of osteoblasts is type I collagen; however, osteoblasts also synthesize and secrete a number of non-collagenous proteins, two of which are clinically useful markers of osteoblastic activity, and by inference, bone formation. The bone specific isoform of alkaline phosphatase (AP) is an osteoblast product that is clearly essential for mineralization. Indeed, AP deficiency, as in the disease hypophosphatasia, results in defective mineralization of bone and teeth [118]. While bone specific AP has been used for years as a clinical indicator of bone turnover, with higher levels indicative of increase bone formation (such as in Paget's disease of bone) the precise role this enzyme plays in the mineralization process remains unclear. Numerous studies have suggested that AP may increase local concentrations of inorganic phosphate, destroy local inhibitors of mineral crystal growth, transport phosphate, act as a calcium-binding protein, or some combination of these events in its role to facilitate mineralization.

Circulating alkaline phosphatase activity is derived from several tissues, including intestine, spleen, kidney, placenta (in pregnancy), liver, bone, or from various tumors. Thus, measurement of total AP activity does not provide specific information on bone formation. However, because the two most common sources of elevated AP levels are liver and bone, a number of techniques, including heat denaturation, chemical inhibition of selective activity, gel electrophoresis, and precipitation by wheat germ lectin have been used to distinguish the liver versus bone isoforms of the enzyme. Most recently, assays have used tissue specific monoclonal antibodies to measure the bone isoform which have only 10–20 % cross-reactivity with the liver isoform.

Osteocalcin (OC) another non-collagenous protein secreted by osteoblasts is widely accepted as a marker of osteoblastic activity, and hence,

bone formation. However, it should be noted that OC is incorporated into the matrix, and then released into the circulation from the matrix during bone resorption, so the serum level at any one time has a component of both bone formation and resorption. Therefore, OC is more properly a marker of bone turnover rather than a specific marker of bone formation *per se.* To complicate matters, the function of OC has not been identified, although its deposition in bone matrix increases with hydroxyapatite deposition during skeletal growth. Osteocalcin is measured in serum or plasma by radioimmunoassays, based on antibodies raised against bovine protein, which cross-react with the human molecule. Like bone-specific alkaline phosphatase, osteocalcin levels vary with age. Thus, children in active stages of bone growth have higher circulating levels than adults, with a peak around the time of puberty for both sexes. Thereafter, serum osteocalcin stabilizes, until the fifth-to-sixth decade, when a significant rise occurs in females. This phenomenon is linked to the menopausal ovarian failure, is reproduced by oophorectomy, and represents a transient change. In fact, osteocalcin returns toward premenopausal levels 15–20 years after the menopause. The reasons for this substantial fluctuation pre- vs post-menopause (with eventual return to "normal") are not fully understood.

As indicated above, the major synthetic product of osteoblasts is type I collagen. Hence, in principle, indices of type I collagen synthesis should be ideal bone formation markers. Several such assays have been developed in recent years, directed against either the carboxy- or amino-extension peptides of the procollagen molecule. These extension peptides (carboxyterminal propeptide of type I collagen and aminoterminal propeptide of type I procollagen) guide assembly of the collagen triple helix and are cleaved from the newly formed molecule in a stoichiometric relationship with collagen biosynthesis. However, because type I collagen is not unique to bone, these peptides are also produced by other tissues that synthesize type I collagen, including skin. Thus it is difficult to sort out the bone component from other tissues.

Bone Resorption Markers

In contrast to markers of bone formation, where the non-collagenous proteins produced by osteoblasts seem to be the most useful markers, it is the collagen degradation products, rather than specific osteoclast proteins, that are most useful as markers of bone resorption. As the skeleton is resorbed, the collagen breakdown products are released into the circulation and ultimately cleared by the kidney. A predominant amino acid of type I collagen is hydroxyproline, and assay of its level in the urine has been used for many years to assess bone resorption. This has been a relatively good marker, since the hydroxyproline released during degradation of collagen is not formed (i.e., the proline is not hydroxylated) until the proline is part of the collagen molecule. However, hydroxyproline is not specific to bone collagen, and dietary protein sources can also contribute to urinary hydroxyproline excretion. Because of this, and to enable correct assessment of hydroxyproline, patients had to be on a collagen-free diet for 1–3 days before a 24-h collection for hydroxyproline measurement. Moreover, a major drawback of urinary hydroxyproline measurements is that they require high-pressure liquid chromatographic (HPLC) methods, which are relatively time-consuming and expensive.

Nowadays there are rapid and relatively inexpensive immunoassays for various collagen breakdown products, increasing the clinical use of bone resorption markers. These products are cross-linked N- and C-telopeptides of type I collagen from bone. Collagen is a triple helix, with the amino- and carboxy-terminals of the collagen chains connected to adjacent collagen chains by cross-links. During the process of collagen breakdown, these telopeptides are released into the circulation and cleared by the kidney. When osteoclasts resorb bone, they release a variety of collagen degradation products into the circulation that are metabolized further by the liver and the kidney. Thus urine contains these various telopeptides in specific forms that can be measured as both free and protein-bound moieties.

Finally, the only osteoclast-specific product that has been evaluated to any extent as a bone

resorption marker is tartrate-resistant acid phosphatase (TRAP). Acid phosphatase is a lysosomal enzyme present in a number of tissues, including bone, prostate, platelets, erythrocytes, and the spleen. Osteoclasts contain a TRAP that is released into the circulation. However, plasma TRAP is not entirely specific for osteoclasts, and the enzyme is relatively unstable in frozen samples. Because of these limitations, TRAP has not been used to any significant extent in the clinical assessment of bone resorption, although the recent development of immunoassays using monoclonal antibodies specifically directed against the bone isoenzyme of TRAP may improve its clinical use.

Some of the issues regarding the use of various bone biochemical markers are as follows. First, urinary resorption markers are generally reported after normalization to creatinine excretion. This has certain limitations, including variability in the creatinine measurement that contributes to the overall variability in the measurement of the urinary markers. A second issue is that many of the bone turnover markers have circadian rhythms, so the timing of sampling is of some importance. Peak levels usually occur between 4 and 8 a.m. [119]. Hence, for the urine markers, it is best to obtain either a 24-h urine collection or, if that is inconvenient for the patient, a second morning void sample can be used.

Bone Turnover and Aging

In adults a third consideration regarding bone turnover markers is that most of the markers tend to be positively associated with age [120], with the exception of a significant decline from adolescence to about age 25 years, as the skeletal consolidation is completed [121]. This issue must be kept in mind when normative data for each of the markers are established. A fourth issue regarding bone turnover is the potential for differential changes in the various bone formation or resorption markers in different disease states or in response to different therapies. Thus, for example, bone specific AP tends to show much larger increases than OC in Paget's disease of bone, whereas glucocorticoid therapy is generally associated with larger decrements in OC levels as opposed to bone specific AP levels [122].

Finally, one has to be aware of the potential variability (technical and biological) of the various bone turnover markers. Bone mineral density can be measured by DEXA with an accuracy of greater than 95 % and a precision error for repeat measurements of between 0.5 and 2.5 %. In contrast, the biochemical markers of bone remodeling are subject to intra- and inter-assay variability (technical variability) as well as individual patient biological variability.

Accordingly, bone biochemical markers assess balance between resorption and formation, and although bone turnover markers are generally inversely correlated with bone mineral density, these correlations are not strong enough to have any value in terms of predicting bone mass for a given individual. Thus, these markers cannot and should not be used to diagnose osteoporosis or to predict bone mass; direct measurement of bone mineral density by DEXA is extremely effective at accomplishing that outcome.

There is a growing body of evidence supporting a role for components of the nuclear envelope in the metabolism and regulation of age-related bone loss (for review see [123]). More specifically, Lamin A/C appears to have a critical role in bone metabolism involving cell differentiation, function and survival [124]. Further studies on other nuclear envelope components are necessary to determine any additional regulatory roles for this important cellular entity.

Age-related fractures are the most common manifestation of osteoporosis and are responsible for the greatest proportion of the morbidity and mortality from this disease. Biochemical, biomechanical, and non-skeletal factors contribute to fragility fractures in the elderly. Over a lifespan, women lose approximately 42 % of their spinal and 58 % of their femoral bone mass [125]. Surprisingly, rates of bone loss in the eighth and ninth decades of life may be comparable to or even exceed those found in the immediate peri- and postmenopausal period of some women. This

is because of the uncoupling in the bone remodeling cycle of older individuals, resulting in a marked increase in bone resorption, but no change or even a decrease in bone formation. This uncoupling has facilitated the efforts of the pharmaceutical industry in their search to produce effective therapeutic entities for the treatment of bone loss. Essentially drugs that decrease bone resorption also tend to show decreased bone formation due to the coupling that exists between the two activities. Whereas, the opposite is true of drugs that tend to increase bone formation – they show an eventual increase in bone resorption. Hence, with the uncoupling that takes place in older individuals, pharmaceutical companies have been able to develop drugs that will decrease bone resorption without the concurrent or at least resultant decrease in bone formation.

Role of Bone and Bone Cells in Stem Cell Biology

As indicated earlier, although bone has been classically viewed as providing the structural support for the human body, and bone cells as being involved in maintaining bone and skeletal homeostasis, novel key roles for bone and bone cells in human physiology are being discovered in the area of stem cell biology. Cells of the stromal/osteoblastic lineage play central regulatory roles as part of the hematopoietic stem cell (HSC) niche *in vivo*. They are capable of directing stem cell self-renewal and proliferation, allowing a subsequent differentiation and repopulation of the hematopoietic system through Notch activation and BMP signaling [126, 127]. Interestingly, this novel function of stromal/osteoblastic cells is stimulated by parathyroid hormone (PTH), a key regulator of bone and mineral homeostasis. Activation of PTH1R in a specific population of stromal/osteoblastic cells results in stimulation of Jagged 1 protein production and targeting to the cell surface. There it interacts with Notch on the surface of adjacent HSCs triggering a biological response that results in increased HSC proliferation. Pharmacologic use of PTH increases the number of HSCs mobilized into the peripheral blood for stem cell harvests, protects stem cells from repeated exposure to cytotoxic chemotherapy, and expands stem cells in transplant recipients [128].

All these cellular interactions take place within a specialized microenvironment in the bone marrow, the HSC niche. It is proposed that these niches localize at specific anatomical sites requiring a unique micro-architecture that can only be structurally provided by bone tissue. Some of these structures are found in trabecular bone localized to the endosteal surface of bone [129]. Moreover, activated HSCs migrate out of the stromal/osteoblastic niche in trabecular bone and closer to specialized blood vessels where they actually proliferate and begin to differentiated in close relationship to sinusoid endothelial cells [130]. These data suggest that the stromal/osteoblast niche is a quiescent niche where HSCs undergo self-renewal, while proliferation and subsequent differentiation take place in the vascular niche some distance away from the stromal/osteoblast niche. This concept is consistent with an oxygen gradient and the effect of oxygen tension on stem cell physiology. The stromal/osteoblast niche is an environment with low oxygen tension, anatomically at a distance from blood vessels, while the vascular niche provides a high oxygen tension environment. This agrees with the *in vitro* effects of oxygen observed on HSC differentiation, whereby low oxygen preserves a more developmentally primitive HSC while higher oxygen favors HSC differentiation [131, 132]. This scenario may not only be true for the HSC compartment in bone marrow. MSCs represent a heterogeneous population of cells at different stages of differentiation. Developmentally primitive MSCs with a broad differentiation potential have been identified in human bone marrow [133–135]. Similarly, low oxygen tension favors a more primitive phenotype [136], while inhibiting osteoblastic differentiation [70, 137]. Thus, it is likely that the most primitive MSCs may also localize to a specific niche similar to that of the HSC niche, whereby the unique microenvironment is provide by specialized bone anatomical sites. Alternatively, both MSCs and HSCs may share the same niche, particularly

since a population of human primitive MSCs [135] express PTH1R on their surface and respond to PTH stimulation.

References

1. Olsen BR, Reginato AM, Wang W. Bone development. Annu Rev Cell Dev Biol. 2000;16:191–220.
2. Pechak DG, Kujawa MJ, Caplan AI. Morphological and histochemical events during first bone formation in embryonic chick limbs. Bone. 1986;7:441–58.
3. Shapiro IM, Landis WJ, Risbud MV. Matrix vesicles: are they anchored exosomes? Bone. 2015;79:29–36.
4. Foster JW, Dominguez-Steglich MA, Guioli S, et al. Campomelic dysplasia and autosomal sex reversal caused by mutations in an SRY-related gene. Nature. 1994;372:525–30.
5. Wagner T, Wirth J, Meyer J, et al. Autosomal sex reversal and campomelic dysplasia are caused by mutations in and around the SRY-related gene SOX9. Cell. 1994;79:1111–20.
6. Bi W, Deng JM, Zhang Z, et al. Sox9 is required for cartilage formation. Nat Genet. 1999;22:85–9.
7. Iyama K, Ninomiya Y, Olsen BR, et al. Spatiotemporal pattern of type X collagen gene expression and collagen deposition in embryonic chick vertebrae undergoing endochondral ossification. Anat Rec. 1991;229:462–72.
8. Gerber HP, Vu TH, Ryan AM, et al. VEGF couples hypertrophic cartilage remodeling, ossification and angiogenesis during endochondral bone formation. Nat Med. 1999;5:623–8.
9. Park SR, Oreffo RO, Triffitt JT. Interconversion potential of cloned human marrow adipocytes in vitro. Bone. 1999;24:549–54.
10. Doherty MJ, Ashton BA, Walsh S, et al. Vascular pericytes express osteogenic potential in vitro and in vivo. J Bone Miner Res. 1998;13:828–38.
11. Schiller PC, D'Ippolito G, Brambilla R, et al. Inhibition of gap-junctional communication induces the trans-differentiation of osteoblasts to an adipocytic phenotype in vitro. J Biol Chem. 2001;276:14133–8.
12. Dallas SL, Bonewald LF. Dynamics of the transition from osteoblasts to osteocyte. Ann N Y Acad Sci. 2010;1192:437–43 (mini-review).
13. Compton JT, Lee FY. A review of osteocyte function and the emerging importance of sclerostin. J Bone Joint Surg. 2014;96:1659–68 (review).
14. Holtrop ME. The ultrastructure of bone. Ann Clin Lab Sci. 1975;5:264–71.
15. Parfitt AM. The actions of parathyroid hormone on bone: relation to bone remodeling and turnover, calcium homeostasis, and metabolic bone disease. Part I of IV parts: mechanisms of calcium transfer between blood and bone and their cellular basis: morphological and kinetic approaches to bone turnover. Metabolism. 1976;25:809–44.
16. Zhang D, Weinbaum S, Cowin SC. Electrical signal transmission in a bone cell network: the influence of a discrete gap junction. Ann Biomed Eng. 1998; 26:644–59.
17. Zhang D, Cowin SC, Weinbaum S. Electrical signal transmission and gap junction regulation in a bone cell network: a cable model for an osteon. Ann Biomed Eng. 1997;25:357–74.
18. Schiller PC, Mehta PP, Roos BA, et al. Hormonal regulation of intercellular communication: parathyroid hormone increases connexin 43 gene expression and gap-junctional communication in osteoblastic cells. Mol Endocrinol. 1992;6:1433–40.
19. Schiller PC, D'Ippolito G, Roos BA, et al. Anabolic or catabolic responses of MC3T3-E1 osteoblastic cells to parathyroid hormone depend on time and duration of treatment. J Bone Miner Res. 1999; 14:1504–12.
20. Schiller PC, D'Ippolito G, Balkan W, et al. Gap-junctional communication mediates parathyroid hormone stimulation of mineralization in osteoblastic cultures. Bone. 2001;28:38–44.
21. Schiller PC, D'Ippolito G, Balkan W, et al. Gap-junctional communication is required for the maturation process of osteoblastic cells in culture. Bone. 2001;28:362–9.
22. Civitelli R, Beyer EC, Warlow PM, et al. Connexin43 mediates direct intercellular communication in human osteoblastic cell networks. J Clin Invest. 1993;91:1888–96.
23. Lecanda F, Warlow PM, Sheikh S, et al. Connexin43 deficiency causes delayed ossification, craniofacial abnormalities, and osteoblast dysfunction. J Cell Biol. 2000;151:931–44.
24. Furlan F, Lecanda F, Screen J, et al. Proliferation, differentiation and apoptosis in connexin43-null osteoblasts. Cell Commun Adhes. 2001;8:367–71.
25. Plotkin LI, Manolagas SC, Bellido T. Transduction of cell survival signals by connexin-43 hemichannels. J Biol Chem. 2002;277:8648–57.
26. Noble BS, Stevens H, Loveridge N, et al. Identification of apoptotic changes in osteocytes in normal and pathological human bone. Bone. 1997; 20:273–82.
27. Noble BS, Peet N, Stevens HY, et al. Mechanical loading: biphasic osteocyte survival and targeting of osteoclasts for bone destruction in rat cortical bone. Am J Physiol Cell Physiol. 2003;284:C934–43.
28. Plotkin LI, Aguirre JI, Kousteni S, et al. Bisphosphonates and estrogens inhibit osteocyte apoptosis via distinct molecular mechanisms downstream of extracellular signal-regulated kinase activation. J Biol Chem. 2005;280:7317–25.
29. Plotkin LI, Mathov I, Aguirre JI, et al. Mechanical stimulation prevents osteocyte apoptosis: requirement of integrins, Src kinases, and ERKs. Am J Physiol Cell Physiol. 2005;289:C633–43.
30. Ducy P, Zhang R, Geoffroy V, et al. Osf2/Cbfa1: a transcriptional activator of osteoblast differentiation. Cell. 1997;89:747–54.

31. Otto F, Thornell AP, Crompton T, et al. Cbfa1, a candidate gene for cleidocranial dysplasia syndrome, is essential for osteoblast differentiation and bone development. Cell. 1997;89:765–71.
32. Komori T, Yagi H, Nomura S, et al. Targeted disruption of Cbfa1 results in a complete lack of bone formation owing to maturational arrest of osteoblasts. Cell. 1997;89:755–64.
33. Mundlos S, Otto F, Mundlos C, et al. Mutations involving the transcription factor CBFA1 cause cleidocranial dysplasia. Cell. 1997;89:773–9.
34. Ducy P, Starbuck M, Priemel M, et al. A Cbfa1-dependent genetic pathway controls bone formation beyond embryonic development. Genes Dev. 1999; 13:1025–36.
35. Kim S, Koga T, Isobe M, et al. Stat1 functions as a cytoplasmic attenuator of Runx2 in the transcriptional program of osteoblast differentiation. Genes Dev. 2003;17:1979–91.
36. Lee KS, Hong SH, Bae SC. Both the Smad and p38 MAPK pathways play a crucial role in Runx2 expression following induction by transforming growth factor-beta and bone morphogenetic protein. Oncogene. 2002;21:7156–63.
37. Zhang YW, Yasui N, Ito K, et al. A RUNX2/PEBP2alpha A/CBFA1 mutation displaying impaired transactivation and Smad interaction in cleidocranial dysplasia. Proc Natl Acad Sci U S A. 2000;97:10549–54.
38. Alliston T, Choy L, Ducy P, et al. TGF-beta-induced repression of CBFA1 by Smad3 decreases cbfa1 and osteocalcin expression and inhibits osteoblast differentiation. EMBO J. 2001;20:2254–72.
39. Zamurovic N, Cappellen D, Rohner D, et al. Coordinated activation of notch, Wnt, and transforming growth factor-beta signaling pathways in bone morphogenic protein 2-induced osteogenesis. Notch target gene Hey1 inhibits mineralization and Runx2 transcriptional activity. J Biol Chem. 2004;279:37704–15.
40. Sowa H, Kaji H, Hendy GN, et al. Menin is required for bone morphogenetic protein 2- and transforming growth factor beta-regulated osteoblastic differentiation through interaction with Smads and Runx2. J Biol Chem. 2004;279:40267–75.
41. Sierra J, Villagra A, Paredes R, et al. Regulation of the bone-specific osteocalcin gene by p300 requires Runx2/Cbfa1 and the vitamin D3 receptor but not p300 intrinsic histone acetyltransferase activity. Mol Cell Biol. 2003;23:3339–51.
42. Wang W, Wang YG, Reginato AM, et al. Groucho homologue Grg5 interacts with the transcription factor Runx2-Cbfa1 and modulates its activity during postnatal growth in mice. Dev Biol. 2004; 270:364–81.
43. Bialek P, Kern B, Yang X, et al. A twist code determines the onset of osteoblast differentiation. Dev Cell. 2004;6:423–35.
44. Nakashima K, Zhou X, Kunkel G, et al. The novel zinc finger-containing transcription factor osterix is required for osteoblast differentiation and bone formation. Cell. 2002;108:17–29.
45. Akiyama Ddagger H, Kim Ddagger JE, Nakashima K, et al. Osteo-chondroprogenitor cells are derived from Sox9 expressing precursors. Proc Natl Acad Sci U S A. 2005;102:14665–70.
46. Huang LF, Fukai N, Selby PB, et al. Mouse clavicular development: analysis of wild-type and cleidocranial dysplasia mutant mice. Dev Dyn. 1997;210: 33–40.
47. Inada M, Yasui T, Nomura S, et al. Maturational disturbance of chondrocytes in Cbfa1-deficient mice. Dev Dyn. 1999;214:279–90.
48. Kim IS, Otto F, Zabel B, et al. Regulation of chondrocyte differentiation by Cbfa1. Mech Dev. 1999;80:159–70.
49. Jimenez MJ, Balbin M, Lopez JM, et al. Collagenase 3 is a target of Cbfa1, a transcription factor of the runt gene family involved in bone formation. Mol Cell Biol. 1999;19:4431–42.
50. Porte D, Tuckermann J, Becker M, et al. Both AP-1 and Cbfa1-like factors are required for the induction of interstitial collagenase by parathyroid hormone. Oncogene. 1999;18:667–78.
51. Logan CY, Nusse R. The Wnt signaling pathway in development and disease. Annu Rev Cell Dev Biol. 2004;20:781–810.
52. Church VL, Francis-West P. Wnt signalling during limb development. Int J Dev Biol. 2002;46:927–36.
53. Boyden LM, Mao J, Belsky J, et al. High bone density due to a mutation in LDL-receptor-related protein 5. N Engl J Med. 2002;346:1513–21.
54. Little RD, Recker RR, Johnson ML. High bone density due to a mutation in LDL-receptor-related protein 5. N Engl J Med. 2002;347:943–4; author reply -4.
55. Kato M, Patel MS, Levasseur R, et al. Cbfa1-independent decrease in osteoblast proliferation, osteopenia, and persistent embryonic eye vascularization in mice deficient in Lrp5, a Wnt coreceptor. J Cell Biol. 2002;157:303–14.
56. Holmen SL, Zylstra CR, Mukherjee A, et al. Essential role of beta-catenin in postnatal bone acquisition. J Biol Chem. 2005;280:21162–8.
57. Day TF, Guo X, Garrett-Beal L, et al. Wnt/beta-catenin signaling in mesenchymal progenitors controls osteoblast and chondrocyte differentiation during vertebrate skeletogenesis. Dev Cell. 2005; 8:739–50.
58. Hill TP, Spater D, Taketo MM, et al. Canonical Wnt/beta-catenin signaling prevents osteoblasts from differentiating into chondrocytes. Dev Cell. 2005; 8:727–38.
59. Hu H, Hilton MJ, Tu X, et al. Sequential roles of Hedgehog and Wnt signaling in osteoblast development. Development. 2005;132:49–60.
60. Canalis E. Wnt signaling in osteoporosis: mechanisms and novel therapeutic approaches. Nat Rev Endocrinol. 2013;9:575–83.
61. Mannstadt M, Juppner H, Gardella TJ. Receptors for PTH and PTHrP: their biological importance and

functional properties. Am J Physiol. 1999;277: F665–75.
62. Swarthout JT, D'Alonzo RC, Selvamurugan N, et al. Parathyroid hormone-dependent signaling pathways regulating genes in bone cells. Gene. 2002;282:1–17.
63. Qin L, Qiu P, Wang L, et al. Gene expression profiles and transcription factors involved in parathyroid hormone signaling in osteoblasts revealed by microarray and bioinformatics. J Biol Chem. 2003;278:19723–31.
64. Wang BL, Dai CL, Quan JX, et al. Parathyroid hormone regulates osterix and Runx2 mRNA expression predominantly through protein kinase A signaling in osteoblast-like cells. J Endocrinol Invest. 2006;29:101–8.
65. Locklin RM, Khosla S, Turner RT, et al. Mediators of the biphasic responses of bone to intermittent and continuously administered parathyroid hormone. J Cell Biochem. 2003;89:180–90.
66. Mikuni-Takagaki Y, Naruse K, Azuma Y, et al. The role of calcium channels in osteocyte function. J Musculoskelet Neuronal Interact. 2002;2:252–5.
67. Sekiya H, Mikuni-Takagaki Y, Kondoh T, et al. Synergistic effect of PTH on the mechanical responses of human alveolar osteocytes. Biochem Biophys Res Commun. 1999;264:719–23.
68. Chen X, Macica CM, Ng KW, et al. Stretch-induced PTH-related protein gene expression in osteoblasts. J Bone Miner Res. 2005;20:1454–61.
69. D'Ippolito G, Schiller PC, Perez-stable C, et al. Cooperative actions of hepatocyte growth factor and 1,25-dihydroxyvitamin D3 in osteoblastic differentiation of human vertebral bone marrow stromal cells. Bone. 2002;31:269–75.
70. D'Ippolito G, Diabira S, Howard GA, et al. Low oxygen tension inhibits osteogenic differentiation and enhances stemness of human MIAMI cells. Bone. 2006;39:513–22.
71. Erben RG, Soegiarto DW, Weber K, et al. Deletion of deoxyribonucleic acid binding domain of the vitamin D receptor abrogates genomic and nongenomic functions of vitamin D. Mol Endocrinol. 2002;16: 1524–37.
72. Paredes R, Arriagada G, Cruzat F, et al. Bone-specific transcription factor Runx2 interacts with the 1alpha,25-dihydroxyvitamin D3 receptor to up-regulate rat osteocalcin gene expression in osteoblastic cells. Mol Cell Biol. 2004;24:8847–61.
73. Haussler MR, Whitfield GK, Kaneko I, et al. Molecular mechanisms of vitamin D action. Calcif Tissue Int. 2013;92:77–98 (review).
74. Jones G. Vitamin D, analogs. Endocrinol Metab Clin North Am. 2010;39:447–72 (review).
75. Curtis KM, Aenlle KK, Roos BA, Howard GA. 24R,25-dihydroxyvitamin D_3 promotes the osteoblastic differentiation of human mesenchymal stem cells. Mol Endocrinol. 2014;28:644–58.
76. Ucer S, Iyer S, Bartell SM, et al. The effects of androgens on murine cortical bone do not require AR or ERα signaling in osteoblasts and osteoclasts. J Bone Miner Res. 2015;30:1138–49.
77. Pan W, Quarles LD, Song LH, et al. Genistein stimulates the osteoblastic differentiation via NO/cGMP in bone marrow culture. J Cell Biochem. 2005;94:307–16.
78. Zallone A. Direct and indirect estrogen actions on osteoblasts and osteoclasts. Ann N Y Acad Sci. 2006;1068:173–9.
79. Seeman E. Estrogen, androgen, and the pathogenesis of bone fragility in women and men. Curr Osteoporos Rep. 2004;2:90–6.
80. Jessop HL, Sjoberg M, Cheng MZ, et al. Mechanical strain and estrogen activate estrogen receptor alpha in bone cells. J Bone Miner Res. 2001;16: 1045–55.
81. Zaman G, Jessop HL, Muzylak M, et al. Osteocytes use estrogen receptor alpha to respond to strain but their ERalpha content is regulated by estrogen. J Bone Miner Res. 2006;21:1297–306.
82. Melville KM, Kelly NH, Surita G, et al. Effects of deletion of ERα in osteoblast-lineage cells on bone mass and adaptation to mechanical loading differ in female and male mice. J Bone Miner Res. 2015;30: 1468–80.
83. Li X, Cao X. BMP signaling and skeletogenesis. Ann N Y Acad Sci. 2006;1068:26–40.
84. Zaidi SK, Sullivan AJ, van Wijnen AJ, et al. Integration of Runx and Smad regulatory signals at transcriptionally active subnuclear sites. Proc Natl Acad Sci U S A. 2002;99:8048–53.
85. Afzal F, Pratap J, Ito K, et al. Smad function and intranuclear targeting share a Runx2 motif required for osteogenic lineage induction and BMP2 responsive transcription. J Cell Physiol. 2005;204:63–72.
86. Lee MH, Kim YJ, Kim HJ, et al. BMP-2-induced Runx2 expression is mediated by Dlx5, and TGF-beta 1 opposes the BMP-2-induced osteoblast differentiation by suppression of Dlx5 expression. J Biol Chem. 2003;278:34387–94.
87. Ryoo HM, Lee MH, Kim YJ. Critical molecular switches involved in BMP-2-induced osteogenic differentiation of mesenchymal cells. Gene. 2006;366:51–7.
88. Li T, Surendran K, Zawaideh MA, et al. Bone morphogenetic protein 7: a novel treatment for chronic renal and bone disease. Curr Opin Nephrol Hypertens. 2004;13:417–22.
89. Spencer EM, Liu CC, Si ECC, Howard GA. In vivo actions of insulin-like growth factor-I (IGF-I) on bone formation and resorption in Rats. Bone. 1991; 12:21–6.
90. Green ED, Maffei M, Braden VV, et al. The human obese (OB) gene: RNA expression pattern and mapping on the physical, cytogenetic, and genetic maps of chromosome 7. Genome Res. 1995;5:5–12.
91. Maffei M, Halaas J, Ravussin E, et al. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nat Med. 1995;1:1155–61.
92. Wolf G. Leptin: the weight-reducing plasma protein encoded by the obese gene. Nutr Rev. 1996;54: 91–3.

93. Steppan CM, Crawford DT, Chidsey-Frink KL, et al. Leptin is a potent stimulator of bone growth in ob/ob mice. Regul Pept. 2000;92:73–8.
94. Ducy P, Amling M, Takeda S, et al. Leptin inhibits bone formation through a hypothalamic relay: a central control of bone mass. Cell. 2000;100:197–207.
95. Shi Y, Yadav VK, Suda N, et al. Dissociation of the neuronal regulation of bone mass and energy metabolism by leptin in vivo. Proc Natl Acad Sci U S A. 2008;105:20529–33.
96. Hess R, Pino AM, Rios S, et al. High affinity leptin receptors are present in human mesenchymal stem cells (MSCs) derived from control and osteoporotic donors. J Cell Biochem. 2005;94:50–7.
97. Zheng B, Jiang J, Luo K, et al. Increased osteogenesis in osteoporotic bone marrow stromal cells by overexpression of leptin. Cell Tissue Res. 2015. doi:10.1007/s00441-01502167-y.
98. Canalis E. Mechanisms of glucocorticoid action in bone. Curr Osteoporos Rep. 2005;3:98–102.
99. Ohnaka K, Taniguchi H, Kawate H, et al. Glucocorticoid enhances the expression of dickkopf-1 in human osteoblasts: novel mechanism of glucocorticoid-induced osteoporosis. Biochem Biophys Res Commun. 2004; 318:259–64.
100. Ohnaka K, Tanabe M, Kawate H, et al. Glucocorticoid suppresses the canonical Wnt signal in cultured human osteoblasts. Biochem Biophys Res Commun. 2005;329:177–81.
101. Bassett JH, Williams GR. The molecular actions of thyroid hormone in bone. Trends Endocrinol Metab. 2003;14:356–64.
102. Stevens DA, Hasserjian RP, Robson H, et al. Thyroid hormones regulate hypertrophic chondrocyte differentiation and expression of parathyroid hormone-related peptide and its receptor during endochondral bone formation. J Bone Miner Res. 2000;15: 2431–42.
103. Robson H, Siebler T, Stevens DA, et al. Thyroid hormone acts directly on growth plate chondrocytes to promote hypertrophic differentiation and inhibit clonal expansion and cell proliferation. Endocrinology. 2000;141:3887–97.
104. Gruber R, Czerwenka K, Wolf F, et al. Expression of the vitamin D receptor, of estrogen and thyroid hormone receptor alpha- and beta-isoforms, and of the androgen receptor in cultures of native mouse bone marrow and of stromal/osteoblastic cells. Bone. 1999;24:465–73.
105. Salto C, Kindblom JM, Johansson C, et al. Ablation of TRalpha2 and a concomitant overexpression of alpha1 yields a mixed hypo- and hyperthyroid phenotype in mice. Mol Endocrinol. 2001;15:2115–28.
106. Pereira RC, Jorgetti V, Canalis E. Triiodothyronine induces collagenase-3 and gelatinase B expression in murine osteoblasts. Am J Physiol. 1999;277: E496–504.
107. Fang S, Deng Y, Gu P, Fan X. MicroRNAs regulate bone development and regeneration. Int J Mol Sci. 2015;16:8227–53 (review).
108. Engsig MT, Chen QJ, Vu TH, et al. Matrix metalloproteinase 9 and vascular endothelial growth factor are essential for osteoclast recruitment into developing long bones. J Cell Biol. 2000;151:879–89.
109. Tondravi MM, McKercher SR, Anderson K, et al. Osteopetrosis in mice lacking haematopoietic transcription factor PU.1. Nature. 1997;386:81–4.
110. DeKoter RP, Singh H. Regulation of B lymphocyte and macrophage development by graded expression of PU.1. Science. 2000;288:1439–41.
111. Luchin A, Suchting S, Merson T, et al. Genetic and physical interactions between Microphthalmia transcription factor and PU.1 are necessary for osteoclast gene expression and differentiation. J Biol Chem. 2001;276:36703–10.
112. Simonet WS, Lacey DL, Dunstan CR, et al. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. Cell. 1997;89:309–19.
113. Dai XM, Ryan GR, Hapel AJ, et al. Targeted disruption of the mouse colony-stimulating factor 1 receptor gene results in osteopetrosis, mononuclear phagocyte deficiency, increased primitive progenitor cell frequencies, and reproductive defects. Blood. 2002;99:111–20.
114. Blair HC, Zaidi M. Osteoclastic differentiation and function regulated by old and new pathways. Rev Endocr Metab Disord. 2006;7:23–32.
115. Choi SJ, Han JH, Roodman GD. ADAM8: a novel osteoclast stimulating factor. J Bone Miner Res. 2001;16:814–22.
116. Rao H, Lu G, Kajiya H, et al. Alpha9beta1: a novel osteoclast integrin that regulates osteoclast formation and function. J Bone Miner Res. 2006;21: 1657–65.
117. Kobayashi Y, Uehara S, Koide M, Takahaski N. The regulation of osteoclasts differentiation by Wnt signals. BonKEy Rep. 2015;4, Article number:713 (review).
118. Whyte MP. Hypophosphatasia and the role of alkaline phosphatase in skeletal mineralization. Endocr Rev. 1994;15:439–61.
119. McKane WR, Khosla S, Egan KS, et al. Role of calcium intake in modulating age-related increases in parathyroid function and bone resorption. J Clin Endocrinol Metab. 1996;81:1699–703.
120. Khosla S, Melton 3rd LJ, Atkinson EJ, et al. Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. J Clin Endocrinol Metab. 1998;83:2266–74.
121. Eastell R, Simmons PS, Colwell A, et al. Nyctohemeral changes in bone turnover assessed by serum bone Gla-protein concentration and urinary deoxypyridinoline excretion: effects of growth and ageing. Clin Sci (Lond). 1992;83:375–82.
122. Duda Jr RJ, O'Brien JF, Katzmann JA, et al. Concurrent assays of circulating bone Gla-protein and bone alkaline phosphatase: effects of sex, age, and metabolic bone disease. J Clin Endocrinol Metab. 1988;66:951–7.

123. Vidal C, Bermeo S, Fatkin D, Duque G. Role of the nuclear envelope in the pathogenesis of age-related bone loss and osteoporosis. BoneKEy Rep. 2012;1, Article number:62 (review).
124. Pacheco LM, Gomez LA, Dias J, et al. Progerin expression disrupts critical adult stem cell functions involved in tissue repair. Aging. 2014;6:1049–63.
125. Riggs BL, Wahner HW, Seeman E, et al. Changes in bone mineral density of the proximal femur and spine with aging. Differences between the postmenopausal and senile osteoporosis syndromes. J Clin Invest. 1982;70:716–23.
126. Calvi LM, Adams GB, Weibrecht KW, et al. Osteoblastic cells regulate the haematopoietic stem cell niche. Nature. 2003;425:841–6.
127. Zhang J, Niu C, Ye L, et al. Identification of the haematopoietic stem cell niche and control of the niche size. Nature. 2003;425:836–41.
128. Adams GB, Martin RP, Alley IR, et al. Therapeutic targeting of a stem cell niche. Nat Biotechnol. 2007;25:238–43.
129. Yin T, Li L. The stem cell niches in bone. J Clin Invest. 2006;116:1195–201.
130. Kiel MJ, Yilmaz OH, Iwashita T, et al. SLAM family receptors distinguish hematopoietic stem and progenitor cells and reveal endothelial niches for stem cells. Cell. 2005;121:1109–21.
131. Cipolleschi MG, Dello Sbarba P, Olivotto M. The role of hypoxia in the maintenance of hematopoietic stem cells. Blood. 1993;82:2031–7.
132. Cipolleschi MG, D'Ippolito G, Bernabei PA, et al. Severe hypoxia enhances the formation of erythroid bursts from human cord blood cells and the maintenance of BFU-E in vitro. Exp Hematol. 1997; 25:1187–94.
133. Reyes M, Lund T, Lenvik T, et al. Purification and ex vivo expansion of postnatal human marrow mesodermal progenitor cells. Blood. 2001;98:2615–25.
134. D'Ippolito G, Howard GA, Roos BA, et al. Isolation and characterization of marrow-isolated adult multilineage inducible (MIAMI) cells. Exp Hematol. 2006;34:1608–10.
135. D'Ippolito G, Diabira S, Howard GA, et al. Marrow-isolated adult multilineage inducible (MIAMI) cells, a unique population of postnatal young and old human cells with extensive expansion and differentiation potential. J Cell Sci. 2004;117:2971–81.
136. Breyer A, Estharabadi N, Oki M, et al. Multipotent adult progenitor cell isolation and culture procedures. Exp Hematol. 2006;34:1596–601.
137. Paquet J, Deschepper M, Moya A, et al. Oxygen tension regulates human mesenchymal stem cell paracrine functions. Stem Cells Transl Med. 2015;4:809–21.

Aging and Bone

2

Jeffrey M. Gimble, Z. Elizabeth Floyd,
Moustapha Kassem, and Mark E. Nuttall

Introduction

This chapter will provide a general overview of the aging process followed by the potential effect that aging may have in bone biology. Three important aspects will be considered: decreased number of osteoblasts, increasing adipogenesis and significant osteoblast/osteocytes apoptosis during the aging process in bone. Other aspects of bone aging have been addressed in recent reviews [1, 2].

J.M. Gimble, MD, PhD (✉)
Center for Stem Cell Research and Regenerative Medicine and Departments of Medicine, Structural and Cellular Biology, and Surgery, Tulane University School of Medicine, New Orleans, LA 70112, USA

LaCell LLC, New Orleans, LA USA
e-mail: jgimble@tulane.edu

Z.E. Floyd, PhD
Ubiquitin Biology Laboratory, Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA 70808, USA
e-mail: Elizabeth.Floyd@pbrc.edu

M. Kassem, PhD
Department of Endocrinology and Metabolism, University Hospital of Odense, Odense, Denmark

Department of Anatomy, Stem Cell Unit, King Saud University, Riyadh, Saudi Arabia
e-mail: mkassem@health.sdu.dk

M.E. Nuttall, PhD
Business Development and Licensing, Department of Neuroscience, Janssen Pharmaceuticals Companies of Johnson & Johnson, Titusville, NJ 08560, USA
e-mail: mnuttall@its.jnj.com

Aging: A Definition

The term "aging" is often qualified by adjectives such as "accelerated", "biological" or "chronological", depending on the context. A number of these definitions of aging have been elegantly summarized in Carrington's review entitled "Aging bone and cartilage: cross-cutting issues" [3]. In the clinical care setting, aging is generally associated with the gradual loss of a wide range of physiological homeostatic processes [3] (Table 2.1). These include decreased fertility [4], decreased resilience in response to environmental stressors such as infections, surgery, or physical attack [5], decreased physical strength and increased risk of mortality. Inevitably, aging is also associated with end of life and death [4, 6].

At the cellular level, several fundamental and inter-connected processes accompany aging *in vitro* and *in vivo* [3] (Table 2.1). Hayflick was the first to discover that mammalian diploid cells cultured in vitro are not immortal but exhibit limited life span; termed as the Hayflick limit and estimated by the number of doublings the cells undergo in vitro. During the limited in vitro life span, cultured cells exhibit progressive genomic and proteomic changes that culminate in growth arrest. These processes have described as the replicative senescence phenotype or the Hayflick phenomenon [7]. These pioneering observations set the framework for much of our understanding of cellular senescence and in vivo physiological aging based upon the Hayflick model for

G. Duque, D.P. Kiel (eds.), *Osteoporosis in Older Persons: Advances in Pathophysiology and Therapeutic Approaches*, DOI 10.1007/978-3-319-25976-5_2

Table 2.1 Macro- and micro- manifestations of aging [3]

Clinical	Cellular
Decreased fertility	Telomere shortening
Decreased physical strength and/or mental acuity	Increased oxidative damage
Decreased resilience and stress response	Altered apoptosis or programmed cell death
Increased mortality	Increased Advanced Glycation End products (AGEs)

With permission from Elsevier

replicative senescence. Furthermore, it has been employed extensively in biogerontology research to unravel mechanisms of age-related cellular defects [8]. Using this model, several investigators have reported an inverse relationship between the donor age and maximal proliferative potential of the cells in vitro [9]. The Kassem laboratory has characterised a Hayflick model for replicative senescence of human osteoblastic cells [10–13]. During continuous culture in vitro, human osteoblasts exhibited typical senescence-associated phenotype including decreased osteoblast marker production (alkaline phosphatase (AP), osteocalcin, collagen type I), decreased mean telomere fragment length and expression of senescence-associated β-galactosidase (SA β-gal) [14, 15].

Contribution of Telomere Shortening to Age-Related Osteoblast Dysfunction

With each progressive mitotic cycle, telomeres located at the ends of chromosomes decrease in length and this has been proposed as a molecular mechanism underlying cellular senescence [16]. It has been postulated that the telomere length acts as a "mitotic clock" and thus once the telomeres reach critical size, cellular senescence phenotype is expressed. On the other hand, overexpression of telomerase, the reverse transcriptase enzyme responsible for maintaining telomere length, leads to cell immortalization [17] and abolishes the in vitro replicative senescence phenotype [18]. Consistent with this hypothesis, recent pre-clinical studies have found that murine strains with defects in telomere associated enzymes (Werner helicase and/or telomerase) display skeletal changes characteristic of human osteoporosis [19] In addition, in a murine model of telomerase deficiency (TERC deficient mice) accelerated aging phenotype with decreased bone mass and impaired skeletal stem cell functions in vitro and in vivo has been described [20].

Other Aspects of Cellular Senescence

The Kassem laboratory has examined the effect of donor age on the maximal proliferative potential of human bone marrow stromal stem cells (BMSC). An age-related decline in the maximal life span from 41 ± 10 population doublings (PD) in young donors to 24 ± 11 PD in old donors was observed [10]. These results thus suggest that human aging is associated with a proliferation defect of hBMSC [10]. Other aspects of cellular senescence include increased rate of somatic cell DNA mutations [3, 6] and changes in DNA methylation and histone acetylation patterns [14, 21], leading to altered gene expression profiles and differentiation functions. Reduced oxidative phosphorylation in the mitochondria of senescent cells leads to reduced energy availability and metabolic functions [22]. In parallel, mitochondrial dysfunction results in elevated levels of free radicals in the form of reactive oxygen species (ROS) and this has long been postulated as a causative factor in cellular senescence and aging [23, 24]. The generation of ROS has been associated with altered signal transduction responses to growth factors [25]. In addition, elevated levels of ROS cause increased expression of pro-apoptotic or programmed cell death regulators within differentiated cell types [26]. These changes cause the cells to be more sensitive to exogenous stress that leads to subsequent apoptosis [27]. An additional biochemical event associated with aging is the formation of Advanced Glycation Endproducts (AGEs), formed through the non-enzymatic interaction of glucose with amino groups, known as the Maillard reaction [28]. Glycated forms of collagen and other proteins accumulate in tissues with low levels of cellular turnover, such as bone [28]. While AGEs have been well established as the target for diagnostic and prognostic clinical testing in diabetes,

they may have an equivalent potential as biomarkers for aging. Likewise, receptors for AGEs, also known as RAGEs, may be responsible for alterations associated with aging and chronic disease [29, 30]. The gene for one of these receptors lies within the major histocompatibility locus and has been associated with the inflammatory response [29]; its activation induces the NFκB transcription factor responsible for regulating the expression of pro-inflammatory cytokines such as IL-6 and TNFα [31]. The accumulated impact of each of these biochemical events results in the cellular changes characterized as "aging".

Aging and Bone Physiology

Bone development is a dynamic process that begins in the embryo and extends throughout the lifetime of the individual (Fig. 2.1). The osteogenic process in the embryo provides a paradigm for our understanding of the physiology of bone in the adult and the consequences of aging. The *condensation* of mesenchyme gives rise to intramembranous and endochondral bone formation in the embryo [32]. In the former case, the progenitor/stem cells differentiate directly into osteoblasts while in the latter, the cells form chondrocytes first which subsequently mineralize their extracellular matrix and become osteoblasts [32]. These events are closely linked with angiogenesis and the secretion of angiogenic factors such as vascular endothelial derived factor (VEGF) in a coordinated and time dependent manner [32]. Bone accumulation reflects a life-long balance or homeostasis between *bone formation* by osteoblasts and *bone resorption* by osteoclasts. As will be discussed further below, multiple hormonal, cytokine, biomechanical, nutritional, and environmental factors influence these events. Shortly after birth, *adipogenesis* or the formation of fat cells occurs within the marrow cavity of the distal phalanges and tarsal bones and advances proximally towards the axial skeleton throughout life. These events are regulated, in part, by the body's hematopoietic demands. In humans, p*eak bone mass* is reached during the third decade of life. After this point, bone mass decreases. In women, the rate of loss is briefly accelerated during the *perimenopausal transition* at much higher rates of 5–10 % per year which puts women at greater risk of *osteoporosis* at a younger age than men. Aging per se is associated with progressive bone loss in both men and women at a comparable rate of 1–2 % per year, and is caused by intrinsic dysfunction of osteoblastic cells leading to impaired bone formation as well as extrinsic factors characteristic of endocrine aging [1, 2]. In this context the senescence microenvironment plays an inhibitory role on osteoblastic cells [33] .

Skeletal Stem Cell (Also Known as Bone Marrow Stromal or Mesenchymal Stem Cells) (BMSC)

The mesodermal cells in the developing embryo give rise to the "anlagen" or condensation that ultimately forms bone. Friedenstein and his colleagues performed pioneering studies in the 1960s and 1970s identifying a population of bone marrow stromal cells with the ability to differentiate along multiple lineage pathways, including adipocyte, chondrocyte, and osteoblast [34]. Over the years, these cells have been identified by many different names, including Fibroblast Stem Cells [35], Mechanocytes [34], Nurse Cells [36], Reticuloendothelial Cells [36, 37], Stromal Cells [38, 39], Stromal Stem Cells [40, 41], and Westin-Bainton Cells [37] and now recognized as skeletal stem cells [42]. It has

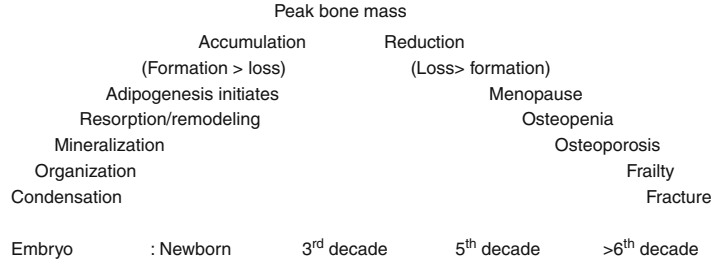


Fig. 2.1 Events in the progression of bone development

been recognized that BMSCs reside in the bone marrow microenvironment throughout life. Studies have documented that cloned BMSCs retain their multipotent differentiation characteristics, consistent with the identification of a true "stem cell" [43–45]. These studies have led to a new appreciation of the existence of "adult" or "somatic" stem cells in multiple tissues of the body, terms that were formerly restricted to the progenitors of the hematopoietic lineages, i.e., hematopoietic stem cells (HSCs). A simple assay used to quantify the number of BMSCs is based on their ability to form colonies when cultured in vitro, known as colony forming unit-fibroblast (CFU-F). Nucleated bone marrow cells are plated at limiting dilutions on a plastic surface and the number of fibroblast "colonies" (defined as groups of cells of more than 50 cells) with fibroblast morphology are determined after a 1–3 week expansion period. Based on this approach, studies have found that the number of murine bone marrow BMSCs decreases with advancing age [46]. Likewise, in man, the number of CFU-F decreases during the first decade of life [47]. In the later decades of life, between the ages of 20–70, the number of CFU-F remains relatively constant [48, 49]. Thus, human studies show that with aging there is maintenance of CFU-F cell population size in the bone marrow and that the observed decline in the number of CFU-F in early adulthood may represent changes in the skeletal dynamics from a modelling mode characteristic of skeletal growth and consolidation to a remodelling dynamic characteristic of the adult skeleton. This may also explain the experimental results of the presence of an age-related decline in the CFU-F number in mice as they continue to grow throughout their lifespan.

The Inverse Relationship Between Adipocytes and Osteoblasts

Clinical epidemiological observations have established that a relationship exists between adipocytes and osteoblast differentiation and functions in the bone marrow microenvironment. Autopsy studies of large number of participants of varying ages demonstrated that the percentage of the marrow cavity occupied by fat increased with advancing age [50–53]. Adipose accumulation was observed in the femur, iliac crest, and vertebral bodies. Work by Meunier et al [54] in the early 1970s extended the initial pathological studies. Using bone marrow biopsies, they reported a correlation between osteoporosis and the degree of adipogenesis in the iliac crest bone marrow cavity in a cohort of 84 subjects [54].

More recent, non-invasive studies using quantitative magnetic resonance imaging (MRI) have further documented the age-dependent increase in marrow fat [55–60]. Quantitative MRI has documented that increased marrow fat correlates directly with reduced cortical bone content in both young and old human subjects [61, 62]. Furthermore, studies have determined that while men within the age range of 20–60 display a greater marrow fat content than their age matched female counterparts, this gender-dependent pattern is reversed with advanced age [63]. Instead, the bone marrow of women of ages >60 contains 10 % greater fat content than that of their age matched male counterparts [63].

Beresford and colleagues performed landmark studies regarding the differentiation of MSCs in the early 1990s that provide a mechanistic understanding to these clinical observations [64]. They observed that cultures of BMSC could select the adipogenic or osteoblastic lineage pathways equally under controlled culture conditions. If, however, they delayed the addition of glucocorticoid or vitamin D3, they were able to promote osteoblast or adipocyte differentiation, respectively [64]. They concluded that the MSC response to nuclear hormone receptor ligands could regulate an inverse relationship between the number of adipocytes and osteoblasts in bone marrow [64]. Other laboratories later confirmed these important findings [65]. It is now recognized that a wide range of exogenous and endogenous factors can regulate MSC adipogenesis and osteogenesis in an inverse or reciprocal manner (Table 2.2). The levels of such factors may change with aging. Recent work by the Kassem laboratory has demonstrated that

Table 2.2 Pathways regulating bone marrow MSC adipogenic and/or osteogenic differentiation [66]

Nuclear hormone receptors	Transmembrane signal transduction pathways	Adipocyte-derived adipokines and factors
Vitamin D3	Bone morphogenetic protein (BMP)	Adiponectin, dlk1(pref-1)
Estrogen/androgen	Insulin	Angiotensin
Glucocorticoids	Parathyroid hormone	Free fatty acids
LXR	Transforming growth factor β (TGF β)	Leptin
PPAR	Wnt signaling	Oxidized LDLs

With permission from John Wiley and Sons

sera from aged females is less able to support osteoblastic function in human MSCs as compared to that from younger females [33]. In contrast, both sera were equally effective in supporting adipocyte differentiation [33].

While the specific serum components responsible for this remain to be determined, recent studies may shed some light. Within serum are found MSC-derived membrane encapsulated exosomes or cytoplasmic-derived microvesicles [67–69]. Global proteomic analyses using mass spectroscopy have begun to systematically identify the most abundant cytokines found within the MSC secretome which include angiogenic, chemokines, immunomodulatory, and proliferative growth factors [67–70]. Additionally, the exosomes are a rich source of micro RNAs (miRNAs) capable of directing expression of downstream mRNA targets involved in both adipogenic and osteogenic differentiation [68, 71–74]. There is increasing interest in the potential use of miRNAs as pharmaceutical targets to manipulate MSC differentiation and function in vivo (for review see: [75]).

Biochemical Signaling Pathways, Genetic and Pharmaceutical Targets in Aging

Nuclear hormone receptors are a large family of transcription factors that control a broad range of physiological and metabolic responses. These proteins respond to small lipophilic ligands that move easily across cell membranes as well as between cells and organs and range from fatty acids to steroids, making the nuclear hormone receptors important targets for therapeutic intervention in metabolic disorders [76, 77].

The peroxisome proliferator-activated receptor gamma (PPARγ) is activated by fatty acids derived from dietary and metabolic sources and is the target of the anti-diabetic thiazolidinedione class of insulin sensitizing drugs such as rosiglitazone and pioglitazone [78]. PPARγ is essential for the development of adipose cells, including the adipose depots of the bone marrow [78–80]. In vitro studies using bone marrow-derived mesenchymal stem cells find that PPARγ-mediated induction of adipogenesis inhibits osteoblastic bone formation [64, 65]. The reciprocal relationship between PPARγ activity and osteogenesis is particularly evident with increased age [81, 82]. Recent evidence indicates that the use of thiazolidinediones in older diabetic adults may be associated with bone loss in women [83]. These studies indicate that therapeutic approaches to the treatment of diabetes that target PPARγ may lead to enhanced bone loss in women at risk for osteoporosis.

The glucocorticoid receptor is another nuclear hormone receptor whose activation has important therapeutic implications. Glucocorticoids are widely used due to their anti-inflammatory effects (reviewed in [84]). The side effects associated with long-term use of glucocorticoids include increased fat accumulation and osteoporosis. *In vitro* studies show that dexamethasone treatment of BMSCs leads to increased expression of genes required for adipogenesis [85]. These changes are associated with decreased expression of genes that regulate osteoblast formation, suggesting glucocorticoids stimulate production of bone marrow-derived adipocytes at the expense of bone formation. The effects of glucocorticoid receptor activation are particularly problematic in the aging population, which is associated with decreased osteoblast formation [86].

Nuclear hormone receptors are closely linked with transmembrane signaling via the Wnt/β-catenin signaling pathway. Wnt pathways are important regulators of developmental and endocrine functions. Interaction between nuclear receptor and the Wnt pathway plays a prominent role in bone and adipocyte development. Activation of Wnt signaling blocks the formation of adipocytes by inhibiting the expression of PPARγ and C/EBPα [87, 88]. Human studies of mutant forms of the Wnt co receptor, the low density lipoprotein related protein 5 (LRP5), demonstrate the importance of Wnt signaling in bone formation. Loss of LRP5 function is associated with decreased bone mass [89] while gain-of-function mutations in LRP5 lead to increased bone mass [90]. In vitro studies of MSC have shown that Wnt activation enhances osteoblastic and inhibits adipocytic differentiation [91, 92]. Other in vitro studies have attributed Wnt-dependent stimulation of osteogenesis to Wnt10b [93], a Wnt signaling protein found in stromal vascular cells, but not adipocytes [88].

The bone morphogenetic proteins (BMP) belong to the transforming growth factor beta (TGF-β) family and are important determinants of bone and fat formation. Recent studies of human bone marrow mesenchymal cells indicate BMP and Wnt signaling cooperate in regulating inhibition of adipocyte development [94]. In particular, BMP signaling regulates expression of Wnt10b and LRP5, both components of the Wnt pathway involved in inhibiting adipocyte formation.

Adipocytes secrete a number of proteins ("adipokines") that function as hormones through an endocrine pathway. Leptin is a 16 kDa peptide hormone that binds to the leptin receptor, a member of the cytokine receptor signaling pathway [95]. Originally identified as a satiety factor, leptin's role has expanded to include a range of effects, including the regulation of bone formation. Murine studies indicate that age-related loss of bone strength is accompanied by decreased serum leptin levels [96]. Studies of elderly men show that leptin exerts a modest effect on bone strength independent of fat mass [97]. Further studies demonstrate that MSC exhibit high affinity leptin binding when undergoing either adipogenesis or osteogenesis [98]. Leptin binding was decreased in mesenchymal cells derived from post-menopausal osteoporotic donors, supporting a role for leptin in determining bone strength in an elderly population.

Adiponectin is another adipocyte-secreted protein that links body weight with regulation of bone mass. Adiponectin is well-described as being secreted by white adipose tissue and having a positive effect on insulin sensitivity. Recent studies show that bone marrow-derived mesenchymal cells contain adiponectin receptors and also produce adiponectin [99, 100]. The *in vitro* evidence suggests a complex role for adiponectin in regulating bone density. Adiponectin may act directly on bone via endocrine or autocrine pathways and indirectly via improvement of insulin sensitivity. Another recent study shows bone marrow adipose tissue itself may be the primary source of adiponectin under certain clinically relevant conditions such as caloric restriction. Adiponectin secretion from the bone marrow fat affected skeletal muscle responses to caloric restriction, suggesting bone marrow tissue functions in an endocrine manner [101].

Dlk1/Pref-1 (Delta-like 1 or pre-adipocyte factor 1) is a secreted factor by adipocytic cells that belongs to the Delta/Notch/Serrate family. A number of recent studies have reported a regulatory role of Dlk1/Pref-1 in MSC biology and their differentiation to osteoblastic or adipocytic cells (For review pls see: [102]). Dlk1/Pref-1 inhibits newly formed bone in ex vivo neonatal calvaria origin cultures while transgenic (Tg) mice that over-expressed Dlk1/Pref-1 under the collagen type I 3.6 Kb promoter exhibited decreases in both trabecular bone mass and bone formation rate [103]. Interestingly, histomorphometry and in vitro whole bone marrow culture assays for osteoclast differentiation, revealed marked stimulation of bone resorption in Dlk1-Tg mice and the effects on osteoclastic cells were mediated via osteoblast-dependent mechanism(s) through activation of the NF-kB signaling and increased osteoblastic production of a number of pro-inflammatory, osteoclast-stimulating cytokines . Serum levels of Dlk1/pref-1 are increased in a cohort of postmenopausal estrogen-deficient

women and were positively correlated with serum levels of the bone resorption marker, CTx-I (C-terminal of type I collagen). Estrogen replacement therapy in postmenopausal women led to reduction of serum Dlk1/pref-1 to the premenopausal range and was associated with normalization of bone turnover markers [104]. Finally, some recent studies have reported the presence of an inverse relationship between serum Dlk1/pref-1 and BMD in Estrogen deficient patients with anorexia nervosa [105].

Resistin, another adipokine associated with insulin resistance [106], is also expressed in bone marrow-derived mesenchymal cells [107]. Resistin levels are inversely related to bone density [108] in aging men, suggesting a role for resistin in determining bone formation. Although the mechanism of action of these adipokines is not well understood, the relationship between bone and fat formation make these proteins an important target for therapeutic intervention.

In pre-clinical rodent models, deficiencies in the nuclear envelope protein, Lamin A/C, have been found to cause increased adiposity within bone and muscle [109]. This correlated with increased expression of the adipogenic transcription factors C/EBP and PPARγ and decreased expression of β-catenin and Wnt10b in both bone and muscle [109]. Consistent with these observations, mutations in the human lamin A/C gene have been associated with lipodystrophy, muscular dystrophy, and skeletal abnormalities [109]. It remains to be determined if this nuclear envelop structural protein encoding gene is involved in age-dependent osteoporosis and sarcopenia.

A recent clinical trial has examined the impact of a bisphosphonate on marrow adipogenesis in post-menopausal women [110]. Following 3 years of treatment, women receiving risedronate displayed reduced marrow adipose volume and adipocyte numbers relative to placebo controls based on histology [110]. This was paralleled by decreased expression of PPARγ [110]. Since bisphosphonates can inhibit osteoclast activity, cause osteoclast apoptosis, and induce osteoblast differentiation, any or all of these activities may account for the drug's mechanism of action [110].

Why Fat?

The role of adipocytes in the bone marrow cavity remains an area of active investigation and speculation [79]. A number of teleological hypotheses have been posed:

(a) That adipocytes fill up space in the marrow cavity that is not required for hematopoiesis. The marrow cavity occupies a greater volume of the adult organism relative to that of a newborn or child. Consequently, less than 100 % of the volume may be required at any given time for blood cell production (Passive Role).
(b) That adipocytes in the marrow contribute to the overall synthesis, processing, and storage of lipids and triglycerides (Active Role).
(c) That adipocytes in the marrow serve as an energy reserve for local or systemic events requiring a rapid metabolic response (Active Role).
(d) That adipocytes retain functions associated with other MSC lineages, such as hematopoietic stem cell support, through the release of regulatory cytokines and the surface expression of HSC adhesion factors, and/or osteogenesis and mineralization (Active Role).
(e) That adipocytes provide bone with mechanical advantages to withstand stresses associated with physical activity (Active Role).

Which Fat?

The bone marrow is just one of many adipose depots in the body (Table 2.3). Each serves a different function and has greatest importance at specific human developmental stages. Brown adipose tissue (BAT) acts as a non-shivering heat source and is located around vital organs such as the heart, carotid arteries, kidneys, and gonads. During the critical period following birth, BAT provides neonatal humans with a survival advantage, allowing them to maintain their core body temperature with a minimum expenditure of energy. Later in life, human BAT stores disappear; however, this is not the case in small rodents or hibernating mammals. Changes in ambient

Table 2.3 Adipose tissue depots in man [111]

Type of adipose tissue depot	Function
Brown	Non-shivering thermogenesis
Bone marrow	Multiple – hematopoietic, energy and lipid metabolism, other?
Mammary	Lactation support
Mechanical	Weight bearing stress protection
White	Energy reservoir

With Permission

temperature and daylight cycles signal the BAT stores in these animals to increase in size and activity. The BAT provides the necessary energy and heat to allow these animals to survive the winter without significant loss of body mass or function. Brown adipocytes express transcriptional regulators (Myf5, Pax7, PRDM16) linking their origins more closely to the skeletal muscle lineage rather than white adipocytes [112, 113]. These cis-acting factors drive the downstream expression of uncoupling protein 1 (UCP1), a thermogenic protein within the mitochondria which historically has been employed as the quintessential BAT biomarker [114]. Bone marrow adipose tissue displays some features in common with BAT. The Nobel Laureate, Charles Huggins, correlated the degree of bone marrow adiposity with the core temperature of the marrow cavity. He found that the femur and ulna (lower core temperatures) contained more marrow fat than the vertebra and ribs (higher core temperatures) [115–117]. Further independent studies have confirmed these initial findings [118, 119]. In the armadillo, which has bony plates exposed close to the skin's surface, the marrow cavity transitions between a red (hematopoietic) and yellow (fatty) phenotype in accordance with the season and ambient temperature [119]. Comparable manipulation of the marrow fat can be achieved using hematopoietic stressors or stimuli. Under conditions of anemia, due to exposure to phenylhydrazine, prolonged hypoxia, or in response to sickle cell disease, adiposity within the marrow cavity is reduced [120–125]. Under conditions of artificial polycythemia (hypertransfusion), in contrast, marrow adiposity is increased [126]. Recent molecular studies have detected expression of PRDM16 and UCP1 in murine bone marrow adipocytes, consistent with a brown adipocyte phenotype [127]. Furthermore, these biomarkers were reduced in 24 month old mice as compared to younger controls [127]. Brown adipocyte markers have been detected in murine models of heterotopic ossification and in bone-like formations in human atherosclerotic vessels and valves [128–131]. While these studies are suggestive, there remains a need for definitive studies identifying brown adipocyte markers in human marrow adipose specimens.

Nevertheless, bone marrow adipose tissue displays some features in common with white adipose tissue (WAT). In some species, such as rabbit, bone marrow fat plays an active role in clearing chylomicrons and triglycerides from the circulation [132, 133]. Under conditions of extreme starvation in animal models, bone marrow adipose depots are depleted to an extent equivalent to WAT [134]. However, in human subjects, anorexia is paradoxically associated with increased levels of marrow adiposity [135]. Pre-clinical studies in murine models confirm that severe caloric restriction results in increased adipogenesis within the bone marrow at the expense of bone formation [136]. Thus, the marrow adipocytes do not exclusively exhibit the behavior of extramedullary white adipocytes under all conditions.

A third adipocyte sub-type merits consideration in the context of the bone marrow microenvironment. Recent investigations have identified a novel class of Beige or Brite (BRown/whITE) adipocytes [137, 138]. Like white adipocytes, beige cells are not directly related to the skeletal muscle lineage and lack expression of *Pax7* or *Myf5* [137, 138]; however, unlike white adipocytes, beige cells can express *PRDM16*, thereby inducing the downstream thermogenic protein, UCP1 [137, 138]. Classically, adipose biologists thought that adult humans lacked functional brown adipose tissue. This concept was challenged by PET scan findings identifying thermogenic adipose depots in adult human subjects and these have been attributed, in part, to the differentiation of beige adipocytes within white adipose tissue depots [139–141]. Recent pre-clinical murine studies have linked the induction of beige

adipocytes to increased bone mass and it is postulated that paracrine factors derived from the beige adipocytes are responsible [142]. Further studies will be needed to determine if beige adipocytes contribute to human bone metabolism.

What Makes It Bone vs. Fat?

Genetic factors exert considerable influence over the physiology and pathology of MSC differentiation and bone formation or loss. Specific genes have been identified that are associated with exceptionally strong or weak bone phenotypes. An example is that of LDL-receptor Related Protein 5 (LRP5), which functions as a receptor for the Wnt signal transduction pathway. In families with a dominant negative mutation in LRP5, inheritance of the gene leads to a condition known as osteoporosis-psuedoglioma associated with defective bone formation [64]. Likewise, in families with a constitutively active mutation in LRP5, inheritance gives subjects a bone phenotype that appears to be impervious to fracture [90, 143]. These clinical findings are consistent with *in vitro* and *in vivo* murine studies. Activation of Wnt signaling transduction inhibits the adipogenic pathway in cell models [87, 88]. When transgenic mice over-express Wnt10b under the control of an adipocyte-specific promoter, their bone marrow lacks adipocytes and displays increased evidence of osteoblast activity [93]. At a broader level, genetic factors associated with ***ethnicity*** influence bone physiology. For example, the risk of osteoporosis is greater in Caucasian and Asian women as compared to those of African-American origins; however, the genetic basis for this remains an area of active investigation. Nevertheless, there is little evidence that this phenomenon is due to bone instead of fat formation.

Epigenetic factors exert a level of influence comparable to genetic factors. ***Physical activity*** has a direct relationship to bone mass and bone health. In industrialized societies, even "healthy" individuals spend less time each day in physical activity as they enter the work force. An individual's level of high impact exercise correlates with increased bone formation and bone strength. Weight bearing activities, such as gymnastics and high impact exercise, enhance bone metabolism and remodeling. In contrast, enforced bed rest is associated with a reduction in bone mass and bone strength. Patients with chronic illness who are bed-ridden, a condition more frequently observed in aged populations, are therefore at increased risk of osteoporotic changes. With prolonged space flight, physicians and investigators have determined that weightlessness is detrimental to osteogenesis. The net bone loss may reflect both osteoblastic bone formation and/or enhanced osteoclastic bone resorption. A recent study in mice demonstrated that exercise can reverse the effect of a high fat diet on bone marrow fat accumulation. High fat-fed mice that were given access to a running wheel had limited bone marrow fat accumulation and enhanced bone formation [144], providing further support for the role of exercise in preserving bone mass and limiting the amount of bone marrow fat with aging.

The ***physical environment*** also determines an individual's sun exposure and, consequently, the biosynthesis of vitamin D and its active metabolites. These nuclear hormone receptor ligands play a critical role in regulating calcium metabolism in the bone, intestine, and kidney, with subsequent consequences on parathyroid hormone action. Whether an individual works indoors or outdoors will have a direct bearing on vitamin D pathways. In many elderly, the hours spent outdoors decrease as fitness declines, resulting in low or inadequate levels of vitamin D receptor ligands.

Nutrition has been a target to offset the risk of vitamin D deficiency. We now fortify milk products with vitamin D3 to insure that individuals receive a minimum daily level; however, since many elderly reduce their intake of dairy products for reasons of taste or lactose intolerance, this strategy is not always effective. Nutrition exerts other effects on bone and fat metabolism. Dietary components such as flavinoids and antioxidants have been linked to osteoblast differentiation and longevity (see apoptosis). Conjugated linoleic acid (CLA), a component of animal fats,

has been found to reduce adipose tissue depots in animal models [145]. Independent studies indicate that CLA can increase bone mass [146] and this appears to be mediated through effects inhibiting the formation and activation of osteoclasts via the RANKL signaling pathway [147]. In a similar manner, diets containing fish oil (rich in omega-3 fatty acids) protected vertebral bone mass in wild type aging mice relative to diets containing safflower oil (rich in omega-6 fatty acids) [148]. Furthermore, PPARγ mediated the omega 3 fatty acid effect since mice with a constitutively active PPARγ genotype lacked a differential response between the fish and safflower oil diets [148]. These pre-clinical findings suggest that similar genotypic polymorphisms in nuclear hormone or other receptors may account for patient-to-patient variation in bone response to dietary interventions [148].

When dietary nutrition leads to a state where net energy consumption exceeds energy demands, it often results in ***obesity***. While obesity manifests as an abundance of extramedullary white adipose tissue, it correlates with enhanced bone mass [149]. Several factors may account for this. First, with increased weight, an individual's skeleton is forced to bear greater loads. Biomechanical stimuli may enhance bone formation relative to bone resorption. Second, obesity alters circulating hormone levels, directly or indirectly. Adipocytes express aromatase, allowing these cells to generate estrogenic-like compounds [149]. Adipocytes secrete insulin-like growth factors and obesity is associated with hyperinsulinemia secondary to insulin resistance, both of which can lead to bone protection; clinical analyses support this hypothesis [149]. Obesity has also been associated with elevated levels of parathyroid hormone [150]. Third, adipokines such as leptin have been associated with positive effects on osteoblast differentiation and mineralization in murine *in vitro* and *in vivo* models while inhibiting adipogenesis [151, 152]. These leptin effects seem to be mediated through peripheral mechanisms acting locally within the marrow microenvironment. Independent studies suggest that leptin administered by intra-ventricular injection causes bone loss through centrally mediated mechanisms involving the hypothalamus [153, 154]. The development of leptin resistance and the activity of the blood brain barrier may account for the apparent discrepancy in these data. Another adipokine, adiponectin, has been associated with BMSCs differentiation and altered bone mineral density. Unlike other adipokines, adiponectin decreases with obesity [155]. When added to murine bone marrow stromal cells, adiponectin inhibited adipocyte differentiation through a COX2 mediated pathway [156]. Transgenic mice over-expressing adiponectin displayed increased bone mass due to enhanced osteoblast activity and suppressed osteoclast function [157]. Both adiponectin and its receptors have been detected in human BMSCs [99] and adiponectin levels have been inversely correlated to bone mineral density in clinical studies [155, 158]. As with leptin, the mechanism of adiponectin actions will require further investigation.

Although obesity correlates with increased bone mass, accumulating evidence challenges the perception that obesity-related increases in bone mass protect against fractures in aging individuals. Epidemiologic studies find an increased risk of fracture in obese men and women [159], but the effect of obesity on the risk of fractures depends on several factors, including upper versus lower extremity fracture sites, sex, age and ethnicity (reviewed in [160]). There is emerging evidence in murine models of obesity that bone quality is not enhanced by the higher bone mass [161] and other studies indicate that the production of pro-inflammatory factors from adipose tissue may contribute to a negative effect of obesity on bone health [162].

Murine models have also established that bone remodeling is linked to insulin-mediated responses in osteoblasts and that bone resorption affects systemic insulin sensitivity [163, 164]. Insulin stimulates bone remodeling in a complex series of steps that initiate in osteoblasts and favor differentiation of bone resorbing osteoclasts. The insulin resistance associated with high fat diet-induced obesity also occurs in bone and leads to increased bone mass, primarily due to decreased numbers of osteoclasts [165]. Likewise, there is evidence that commonly used

treatments for osteoporosis may increase fasting glucose levels [166]. Together, these findings raise important questions about the relationship between bone health and insulin sensitivity in the obese aging population.

Menopause is associated with a rapid decline in circulating estrogen and as a consequence there is trabecular bone loss, which results in a loss of bone strength. Paradoxically there are increases in bone size (medullary bone and periosteal diameter) after menopause. The increase in size is caused by increased periosteal apposition, which partially preserves strength [167]. Loss of bone mass that follows the loss of ovarian function is associated with an increase in the rates of bone resorption and bone formation, with the former exceeding the latter, and an increase in the number of osteoclasts in trabecular bone. Postmenopausal bone loss is associated with excessive osteoclast activity. In addition to these marrow changes, menopause is associated with a gain in fat mass and a loss of lean body mass, but these changes in body composition are not prevented by hormone replacement therapy [168]. It is clear that the loss of ovarian function causes dramatic changes to bone marrow cell activity as well as extramedullary cell activity. In addition, menopause results in quite dramatic changes in susceptibility to certain diseases such as cardiovascular disease. It is complex to tease out what drives these changes because of the complexity of the cell systems involved and the interplay between different cell types. In terms of bone turnover there appears to be effects on the development and activity of both osteoblasts and osteoclasts.

Data indicate that changes in estrogen status in vivo are associated with the secretion of mononuclear cell immune factors in vitro and suggest that alterations in the local production of bone-acting cytokines may underlie changes in bone turnover caused by surgically induced menopause and estrogen replacement [169]. There is now a large body of evidence suggesting that the decline in ovarian function with menopause is associated with spontaneous increases in pro-inflammatory cytokines. The cytokines that have obtained the most attention are IL-1, IL-6, GM-CSF, and TNF-. The exact mechanisms by which estrogen interferes with cytokine activity are still incompletely known but may potentially include interactions of the estrogen receptor with other transcription factors, modulation of nitric oxide activity, antioxidative effects, plasma membrane actions, and changes in immune cell function. Experimental and clinical studies strongly support a link between the increased state of pro-inflammatory cytokine activity and postmenopausal bone loss [170]

The production of interleukin-6 by stromal–osteoblastic cells, as well as the responsiveness of bone marrow cells to cytokines such as interleukin-6 and interleukin-11, is regulated by sex steroids. When gonadal function is lost, the formation of osteoclasts as well as osteoblasts increases in the marrow, both changes apparently mediated by an increase in the production of interleukin-6 and perhaps by an increase in the responsiveness of bone marrow progenitor cells not only to interleukin-6 but also to other cytokines with osteoclastogenic and osteoblastogenic properties. This is supported by both in vitro and ex-vivo experimental data. Osteoclast formation in response to either interleukin-6 in combination with the soluble interleukin-6 receptor or interleukin-11 is significantly greater in cultures of bone marrow from ovariectomized mice than in cultures from mice that have undergone sham operations, even when the cultures have the same number of osteoblastic support cells and an interleukin-6 signal of the same magnitude. These findings indicate that not only the production of the osteoclast precursors but also their responsiveness to interleukin-6 (and to interleukin-11) is enhanced in a state of estrogen deficiency.

Studies of the effect of ovariectomy on the formation of osteoblast progenitors in cultures of bone marrow suggest that loss of ovarian function increased osteoblastic activity. The number of fibroblast CFU (colony forming units) is increased several-fold in ovariectomized mice. At this stage there is no mechanistic explanation for the observation that the formation of osteoclasts and the formation of osteoblast progenitors in the marrow increase simultaneously after the loss of ovarian function. It has been hypothesized that changes in levels of systemic hormones alters

the sensitivity of osteoblast and osteoclast precursors to several cytokine signals by modulating glycoprotein 130 [171]. It is clear that there is still considerable work to be done before we fully understand the control of marrow cell development and activity under normal physiological condition and after menopause. It will be interesting to understand whether sex steroids themselves positively drive activity and/or development of osteoclast and osteoblast progenitors and menopause results in the removal of this activity or, paradoxically, whether indeed gonadal steroids inhibit/control bone formation and resorption and menopause results in the relief of this repression.

Apoptosis and the Aging Bone

Apoptosis, or programmed cell death, has been postulated to act as a cellular mechanism accounting for the effects of aging on bone [3] (Table 2.4). Apoptosis is initiated by the activation of a proteolytic enzyme cascade leading to cellular self-destruction. Unlike cell death due to necrosis, apoptotic cells death is characterized by cell shrinkage and disintegration without damage to the neighboring cells. Pioneering studies by Jilka and colleagues demonstrated that cytokines such as TNF induced apoptosis in MSC-like cell lines *in vitro* [172]. To further address the mechanism, Weinstein, Jilka, and colleagues used an *in vivo* murine model to examine the potential apoptotic effects of glucocorticoids [173]. Chronic treatment with glucocorticoids activated apoptotic pathways in osteoblasts and osteocytes of the intact bone while reducing osteoblastogenesis [173]. Additional causes of osteoblast and osteocyte apoptosis have been identified. Thiazolidinedione compounds, known ligands for the peroxisome proliferator activated receptor γ adipogenic transcription factor, stimulated osteoblast and osteocyte apoptotic events when administered to mice [174]. In rodents maintained under conditions simulating weightlessness, there was a rapid increase in the number of apoptotic osteoblasts within the bone; this was followed by increased numbers of osteoclasts and bone resorption [175]. The addition of AGEs to cultures of human MSCs led to increased numbers of apoptotic cells and this correlated with a reduced capacity for differentiation [176].

A number of agents antagonize apoptosis in osteoblasts and osteocytes. Endocrine factors such as parathyroid hormone and calcitonin increased bone formation by protecting osteoblasts from apoptosis in rodent models [177, 178]. Similar actions are displayed by the active form of vitamin D ($1,25(OH)_2D_3$) [179] and cytokines including TGFβ and those acting through the gp130 receptor pathway, such as IL-6 and oncostatin M [172]. Pharmaceutical agents such as the bisphosphonates exert anti-apoptotic effects on osteoblasts through mechanisms involving the extracellular signal-regulated kinases (ERKs) and the connexin43 channel [179]. Likewise, lipids such as α-linoleic acid blocked apoptosis in human bone marrow-derived MSCs exposed to TNFα or hydrogen peroxide [180]. It appeared that the α-linoleic acid prevented

Table 2.4 Cellular apoptosis in the marrow microenvironment

Cell type	Agonists	Antagonists
Osteoblast/osteocyte	Glucocorticoids & thiazolidinediones	Bisphosphonates, $1,25(OH)_2D_3$, calcitonin
	AGE	α-Linoleic acid
	TNF	CD40 Ligand
	Weightlessness	TGFβ, IL-6, PTH
Osteoclasts	Bisphosphonates	
	β3 integrin	
Adipocytes	CLA	Glucocorticoids
	TNF	
	Retinoic acid	

the generation of reactive oxygen species and subsequent activation of the NFκB and c-jun N-terminal kinase pathways [180]. Finally, since osteoblasts express the TNF receptor-related surface protein CD40, interaction with the CD40 ligand serves to protect them from apoptosis initiated by a variety of agents, including glucocorticoids, TNFα, and proteasomal activators [181].

Despite these findings, without apoptosis, bone formation may be impaired. Studies of mice deficient in the enzyme caspase-3, critical to the apoptotic cascade, found that they displayed reduced bone formation *in vivo* and reduced bone marrow-derived MSC differentiation *in vitro* [182]. These findings could be mimicked using a caspase 3 inhibitor in wild type mice [182]. Biochemical studies implicated the TGFβ/Smad signal transduction pathway as the underlying mechanism [182]. Independent studies created a transgenic mouse over-expressing the bcl2 anti-apoptotic protein under an osteoblast-selective promoter [183]. While the osteoblasts isolated from the transgenic bone were resistant to glucocorticoid-induced apoptosis, the cells displayed reduced mineralization. The transgenic mice were smaller than their wild-type littermates [183]. Thus, osteoblastic apoptosis is a complex phenomenon that may have both positive and negative effects on bone formation.

Apoptotic events influence the activity of other cell types within the bone marrow microenvironment. Osteoclasts undergo apoptosis in response to bisphosphonates or in the absence vitronectin, the natural ligand for α3β1 integrin [184, 185]. Bisphosphonates are the accepted standard of care for the treatment of osteoporosis in the elderly. While few, if any, studies have been performed on bone marrow-derived adipocytes, evidence from extramedullary adipocytes indicates that they are relatively resistant to apoptotic stimuli due to induced levels of bcl2 [186]. Nevertheless, adipocytes undergo apoptosis in response to TNFα [187], although this occurs in a depot specific pattern; adipocytes from omental fat were more susceptible than those from subcutaneous fat [188]. The relative apoptotic sensitivity of bone marrow adipocytes has not been reported. Additional agents exert apoptotic actions on adipocytes, including CLA, retinoic acid, botanical extracts, and cytokines acting through the gp130 receptor [145, 189, 190]. Some investigators postulate that pharmaceutical agents and/or functional foods targeting the adipocyte apoptotic pathway will have the combined benefit of reducing obesity while improving bone growth by reducing bone marrow adipogenesis and enhancing osteoblast function [190].

References

1. Kassem M, Marie PJ. Senescence-associated intrinsic mechanisms of osteoblast dysfunctions. Aging Cell. 2011;10:191–7.
2. Marie PJ, Kassem M. Extrinsic mechanisms involved in age-related defective bone formation. J Clin Endocrinol Metab. 2011;96:600–9.
3. Carrington JL. Aging bone and cartilage: cross-cutting issues. Biochem Biophys Res Commun. 2005;328:700–8.
4. Kirkwood TB, Austad SN. Why do we age? Nature. 2000;408:233–8.
5. Miller RA. When will the biology of aging become useful? future landmarks in biomedical gerontology. J Am Geriatr Soc. 1997;45:1258–67.
6. Busuttil RA, Dolle M, Campisi J, Vijga J. Genomic instability, aging, and cellular senescence. Ann N Y Acad Sci. 2004;1019:245–55.
7. Hayflick L. The limited in vitro lifetime of human diploid cell strains. Exp Cell Res. 1965;37:614–36.
8. Campisi J. From cells to organisms: can we learn about aging from cells in culture? Exp Gerontol. 2001;36:607–18.
9. Cristofalo VJ, Allen RG, Pignolo RJ, Martin BG, Beck JC. Relationship between donor age and the replicative lifespan of human cells in culture: a reevaluation. Proc Natl Acad Sci U S A. 1998;95:10614–9.
10. Kassem M, Ankersen L, Eriksen EF, Clark BF, Rattan SI. Demonstration of cellular aging and senescence in serially passaged long-term cultures of human trabecular osteoblasts. Osteoporos Int. 1997;7:514–24.
11. Kveiborg M, Rattan SI, Clark BF, Eriksen EF, Kassem M. Treatment with 1,25-dihydroxyvitamin D3 reduces impairment of human osteoblast functions during cellular aging in culture. J Cell Physiol. 2001;186:298–306.
12. Stenderup K, Justesen J, Clausen C, Kassem M. Aging is associated with decreased maximal life span and accelerated senescence of bone marrow stromal cells. Bone. 2003;33:919–26.
13. Stenderup K, Rosada C, Justesen J, Al-Soubky T, Dagnaes-Hansen F, Kassem M. Aged human bone

marrow stromal cells maintaining bone forming capacity in vivo evaluated using an improved method of visualization. Biogerontology. 2004;5:107–18.
14. Dimri GP, Lee X, Basile G, Acosta M, Scott G, Roskelley C, Medrano EE, Linskens M, Rubelj I, Pereira-Smith O, et al. A biomarker that identifies senescent human cells in culture and in aging skin in vivo. Proc Natl Acad Sci U S A. 1995;92: 9363–7.
15. Allsopp RC, Chang E, Kashefi-Aazam M, Rogaev EI, Piatyszek MA, Shay JW, Harley CB. Telomere shortening is associated with cell division in vitro and in vivo. Exp Cell Res. 1995;220:194–200.
16. Harley CB, Futcher AB, Greider CW. Telomeres shorten during ageing of human fibroblasts. Nature. 1990;345:458–60.
17. Harley CB. Telomere loss: mitotic clock or genetic time bomb? Mutat Res. 1991;256:271–82.
18. Simonsen JL, Rosada C, Serakinci N, Justesen J, Stenderup K, Rattan SI, Jensen TG, Kassem M. Telomerase expression extends the proliferative life-span and maintains the osteogenic potential of human bone marrow stromal cells. Nat Biotechnol. 2002;20:592–6.
19. Brennan TA, Egan KP, Lindborg CM, Chen Q, Sweetwyne MT, Hankenson KD, Xie SX, Johnson FB, Pignolo RJ. Mouse models of telomere dysfunction phenocopy skeletal changes found in human age-related osteoporosis. Dis Model Mech. 2014; 7:583–92.
20. Saeed H, Abdallah BM, Ditzel N, Catala-Lehnen P, Qiu W, Amling M, Kassem M. Telomerase-deficient mice exhibit bone loss owing to defects in osteoblasts and increased osteoclastogenesis by inflammatory microenvironment. J Bone Miner Res Off J Am Soc Bone Miner Res. 2011;26: 1494–505.
21. Bandyopadhyay D, Medrano EE. The emerging role of epigenetics in cellular and organismal aging. Exp Gerontol. 2003;38:1299–307.
22. Lesnefsky EJ, Hoppel CL. Oxidative phosphorylation and aging. Ageing Res Rev. 2006;5:402–33.
23. Harman D. Aging: a theory based on free radical and radiation chemistry. J Gerontol. 1956;11:298–300.
24. Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. Nature. 2000;408:239–47.
25. Li J, Holbrook NJ. Common mechanisms for declines in oxidative stress tolerance and proliferation with aging. Free Radic Biol Med. 2003; 35:292–9.
26. Ikeyama S, Wang XT, Li J, Podlutsky A, Martindale JL, Kokkonen G, van Huizen R, Gorospe M, Holbrook NJ. Expression of the pro-apoptotic gene gadd153/chop is elevated in liver with aging and sensitizes cells to oxidant injury. J Biol Chem. 2003; 278:16726–31.
27. Li J, Holbrook NJ. Elevated gadd153/chop expression and enhanced c-Jun N-terminal protein kinase activation sensitizes aged cells to ER stress. Exp Gerontol. 2004;39:735–44.
28. DeGroot J. The AGE, of the matrix: chemistry, consequence and cure. Curr Opin Pharmacol. 2004; 4:301–5.
29. Schmidt AM, Stern DM. Receptor for age (RAGE) is a gene within the major histocompatibility class III region: implications for host response mechanisms in homeostasis and chronic disease. Front Biosci J Virtual Library. 2001;6:D1151–60.
30. Pricci F, Leto G, Amadio L, Iacobini C, Romeo G, Cordone S, Gradini R, Barsotti P, Liu FT, Di Mario U, Pugliese G. Role of galectin-3 as a receptor for advanced glycosylation end products. Kidney Int Suppl. 2000;77:S31–9.
31. Yan SD, Schmidt AM, Anderson GM, Zhang J, Brett J, Zou YS, Pinsky D, Stern D. Enhanced cellular oxidant stress by the interaction of advanced glycation end products with their receptors/binding proteins. J Biol Chem.1994;269: 9889–97.
32. Olson BR. Bone embryology. In: Favus MJ, editor. Primer on the metabolic bone diseases and disorders of mineral metabolism. Washington, DC: American society for bone and mineral research; 2006. p. 2–6.
33. Abdallah BM, Haack-Sorensen M, Fink T, Kassem M. Inhibition of osteoblast differentiation but not adipocyte differentiation of mesenchymal stem cells by sera obtained from aged females. Bone. 2006; 39:181–8.
34. Friedenstein AJ. Precursor cells of mechanocytes. Int Rev Cytol. 1976;47:327–59.
35. Friedenstein AJ, Chailakhjan RK, Lalykina KS. The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. Cell Tissue Kinet. 1970;3:393–403.
36. Foy H, Kondi A. Reticulo-endothelial cells as 'nurses' for plasma cells and erythroblasts in baboons. Nature. 1964;204:293.
37. Westen H, Bainton DF. Association of alkaline-phosphatase-positive reticulum cells in bone marrow with granulocytic precursors. J Exp Med. 1979;150: 919–37.
38. Weiss L, Sakai H. The hematopoietic stroma. Am J Anat. 1984;170:447–63.
39. Gimble JM, Pietrangeli C, Henley A, Dorheim MA, Silver J, Namen A, Takeichi M, Goridis C, Kincade PW. Characterization of murine bone marrow and spleen-derived stromal cells: analysis of leukocyte marker and growth factor mRNA transcript levels. Blood. 1989;74:303–11.
40. Owen M. Marrow stromal stem cells. J Cell Sci Suppl. 1988;10:63–76.
41. Owen M, Friedenstein AJ. Stromal stem cells: marrow-derived osteogenic precursors. Ciba Found Symp. 1988;136:42–60.
42. Kassem M, Bianco P. Skeletal stem cells in space and time. Cell. 2015;160:17–9.
43. Grigoriadis AE, Heersche JN, Aubin JE. Differentiation of muscle, fat, cartilage, and bone from progenitor cells present in a bone-derived clonal cell

population: effect of dexamethasone. J Cell Biol. 1988;106:2139–51.
44. Nuttall ME, Patton AJ, Olivera DL, Nadeau DP, Gowen M. Human trabecular bone cells are able to express both osteoblastic and adipocytic phenotype: implications for osteopenic disorders. J Bone Miner Res Off J Am Soc Bone Miner Res. 1998; 13:371–82.
45. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, Moorman MA, Simonetti DW, Craig S, Marshak DR. Multilineage potential of adult human mesenchymal stem cells. Science. 1999;284:143–7.
46. Jiang D, Fei RG, Pendergrass WR, Wolf NS. An age-related reduction in the replicative capacity of two murine hematopoietic stroma cell types. Exp Hematol. 1992;20:1216–22.
47. D'Ippolito G, Schiller PC, Ricordi C, Roos BA, Howard GA. Age-related osteogenic potential of mesenchymal stromal stem cells from human vertebral bone marrow. J Bone Miner Res Off J Am Soc Bone Miner Res. 1999;14:1115–22.
48. Stenderup K, Justesen J, Eriksen EF, Rattan SI, Kassem M. Number and proliferative capacity of osteogenic stem cells are maintained during aging and in patients with osteoporosis. J Bone Miner Res Off J Am Soc Bone Miner Res. 2001;16: 1120–9.
49. Justesen J, Stenderup K, Eriksen EF, Kassem M. Maintenance of osteoblastic and adipocytic differentiation potential with age and osteoporosis in human marrow stromal cell cultures. Calcif Tissue Int. 2002;71:36–44.
50. Custer RP. Studies on the structure and function of bone marrow. II. Variations in cellularity of various bones with advancing years of life and their relative response to stimuli. J Lab Clin Med. 1932;17: 960–2.
51. Hartsock RJ, Smith EB, Petty CS. Normal variations with aging of the amount of hematopoietic tissue in bone marrow from the anterior iliac crest. A study made from 177 cases of sudden death examined by necropsy. Am J Clin Pathol. 1965;43:326–31.
52. Vost A. Osteoporosis: a necropsy study of vertebrae and iliac crests. Am J Pathol. 1963;43:143–51.
53. Hudson G. Bone-marrow volume in the human foetus and newborn. Br J Haematol. 1965;11:446–52.
54. Meunier P, Aaron J, Edouard C, Vignon G. Osteoporosis and the replacement of cell populations of the marrow by adipose tissue. A quantitative study of 84 iliac bone biopsies. Clin Orthop Relat Res. 1971;80:147–54.
55. Babyn PS, Ranson M, McCarville ME. Normal bone marrow: signal characteristics and fatty conversion. Magn Reson Imaging Clin N Am. 1998;6:473–95.
56. Sheu Y, Cauley JA. The role of bone marrow and visceral fat on bone metabolism. Curr Osteoporos Rep. 2011;9:67–75.
57. Roldan-Valadez E, Pina-Jimenez C, Favila R, Rios C. Gender and age groups interactions in the quantification of bone marrow fat content in lumbar spine using 3 T MR spectroscopy: a multivariate analysis of covariance (Mancova). Eur J Radiol. 2013;82:e697–702.
58. Breault SR, Heye T, Bashir MR, Dale BM, Merkle EM, Reiner CS, Faridi KF, Gupta RT. Quantitative dynamic contrast-enhanced MRI of pelvic and lumbar bone marrow: effect of age and marrow fat content on pharmacokinetic parameter values. AJR Am J Roentgenol. 2013;200:W297–303.
59. Hardouin P, Pansini V, Cortet B. Bone marrow fat. Joint Bone Spine. 2014;81:313–9.
60. Pansini V, Monnet A, Salleron J, Hardouin P, Cortet B, Cotten A. 3 Tesla (1) H MR spectroscopy of hip bone marrow in a healthy population, assessment of normal fat content values and influence of age and sex. J Magn Reson Imaging JMRI. 2014;39:369–76.
61. Wren TA, Chung SA, Dorey FJ, Bluml S, Adams GB, Gilsanz V. Bone marrow fat is inversely related to cortical bone in young and old subjects. J Clin Endocrinol Metab. 2011;96:782–6.
62. Di Iorgi N, Mo AO, Grimm K, Wren TA, Dorey F, Gilsanz V. Bone acquisition in healthy young females is reciprocally related to marrow adiposity. J Clin Endocrinol Metab. 2010;95:2977–82.
63. Griffith JF, Yeung DK, Ma HT, Leung JC, Kwok TC, Leung PC. Bone marrow fat content in the elderly: a reversal of sex difference seen in younger subjects. J Magn Reson Imaging JMRI. 2012;36:225–30.
64. Beresford JN, Bennett JH, Devlin C, Leboy PS, Owen ME. Evidence for an inverse relationship between the differentiation of adipocytic and osteogenic cells in rat marrow stromal cell cultures. J Cell Sci. 1992;102(Pt 2):341–51.
65. Dorheim MA, Sullivan M, Dandapani V, Wu X, Hudson J, Segarini PR, Rosen DM, Aulthouse AL, Gimble JM. Osteoblastic gene expression during adipogenesis in hematopoietic supporting murine bone marrow stromal cells. J Cell Physiol. 1993; 154:317–28.
66. Gimble JM, Zvonic S, Floyd ZE, Kassem M, Nuttall ME. Playing with bone and fat. J Cell Biochem. 2006;98:251–66.
67. Lavoie JR, Rosu-Myles M. Uncovering the secretes of mesenchymal stem cells. Biochimie. 2013;95: 2212–21.
68. Maumus M, Jorgensen C, Noel D. Mesenchymal stem cells in regenerative medicine applied to rheumatic diseases: role of secretome and exosomes. Biochimie. 2013;95:2229–34.
69. Kupcova SH. Proteomic techniques for characterisation of mesenchymal stem cell secretome. Biochimie. 2013;95:2196–211.
70. Kristensen LP, Chen L, Nielsen MO, Qanie DW, Kratchmarova I, Kassem M, Andersen JS. Temporal profiling and pulsed SILAC labeling identify novel secreted proteins during ex vivo osteoblast differentiation of human stromal stem cells. Mol Cell Proteomics MCP. 2012;11:989–1007.

71. Wei J, Li H, Wang S, Li T, Fan J, Liang X, Li J, Han Q, Zhu L, Fan L, Zhao RC. let-7 enhances osteogenesis and bone formation while repressing adipogenesis of human stromal/mesenchymal stem cells by regulating HMGA2. Stem Cells Dev. 2014;23:1452–63.
72. Clark EA, Kalomoiris S, Nolta JA, Fierro FA. Concise review: MicroRNA function in multipotent mesenchymal stromal cells. Stem Cells. 2014;32:1074–82.
73. Eskildsen T, Taipaleenmaki H, Stenvang J, Abdallah BM, Ditzel N, Nossent AY, Bak M, Kauppinen S, Kassem M. MicroRNA-138 regulates osteogenic differentiation of human stromal (mesenchymal) stem cells in vivo. Proc Natl Acad Sci U S A. 2011;108:6139–44.
74. Chen L, Holmstrom K, Qiu W, Ditzel N, Shi K, Hokland L, Kassem M. MicroRNA-34a inhibits osteoblast differentiation and in vivo bone formation of human stromal stem cells. Stem Cells. 2014; 32:902–12.
75. Taipaleenmaki H, Bjerre Hokland L, Chen L, Kauppinen S, Kassem M. Mechanisms in endocrinology: micro-RNAs: targets for enhancing osteoblast differentiation and bone formation. Eur J Endocrinol Eur Fed Endocrine Soc. 2012;166:359–71.
76. Takada I, Suzawa M, Kato S. Nuclear receptors as targets for drug development: crosstalk between peroxisome proliferator-activated receptor gamma and cytokines in bone marrow-derived mesenchymal stem cells. J Pharmacol Sci. 2005;97:184–9.
77. Nettles KW, Greene GL. Ligand control of coregulator recruitment to nuclear receptors. Annu Rev Physiol. 2005;67:309–33.
78. Sadie-Van Gijsen H, Hough FS, Ferris WF. Determinants of bone marrow adiposity: the modulation of peroxisome proliferator-activated receptor-gamma2 activity as a central mechanism. Bone. 2013;56:255–65.
79. Gimble JM, Robinson CE, Wu X, Kelly KA. The function of adipocytes in the bone marrow stroma: an update. Bone. 1996;19:421–8.
80. Gimble JM, Robinson CE, Wu X, Kelly KA, Rodriguez BR, Kliewer SA, Lehmann JM, Morris DC. Peroxisome proliferator-activated receptor-gamma activation by thiazolidinediones induces adipogenesis in bone marrow stromal cells. Mol Pharmacol. 1996;50:1087–94.
81. Akune T, Ohba S, Kamekura S, Yamaguchi M, Chung UI, Kubota N, Terauchi Y, Harada Y, Azuma Y, Nakamura K, Kadowaki T, Kawaguchi H. PPARgamma insufficiency enhances osteogenesis through osteoblast formation from bone marrow progenitors. J Clin Invest. 2004;113:846–55.
82. Kawaguchi H, Akune T, Yamaguchi M, Ohba S, Ogata N, Chung UI, Kubota N, Terauchi Y, Kadowaki T, Nakamura K. Distinct effects of PPARgamma insufficiency on bone marrow cells, osteoblasts, and osteoclastic cells. J Bone Miner Metab. 2005;23:275–9.
83. Schwartz AV, Sellmeyer DE, Vittinghoff E, Palermo L, Lecka-Czernik B, Feingold KR, Strotmeyer ES, Resnick HE, Carbone L, Beamer BA, Park SW, Lane NE, Harris TB, Cummings SR. Thiazolidinedione use and bone loss in older diabetic adults. J Clin Endocrinol Metab. 2006;91:3349–54.
84. Rosen J, Miner JN. The search for safer glucocorticoid receptor ligands. Endocr Rev. 2005;26:452–64.
85. Li X, Jin L, Cui Q, Wang GJ, Balian G. Steroid effects on osteogenesis through mesenchymal cell gene expression. Osteoporos Int. 2005;16:101–8.
86. Srouji S, Livne E. Bone marrow stem cells and biological scaffold for bone repair in aging and disease. Mech Ageing Dev. 2005;126:281–7.
87. Bennett CN, Ross SE, Longo KA, Bajnok L, Hemati N, Johnson KW, Harrison SD, MacDougald OA. Regulation of Wnt signaling during adipogenesis. J Biol Chem. 2002;277:30998–1004.
88. Ross SE, Hemati N, Longo KA, Bennett CN, Lucas PC, Erickson RL, MacDougald OA. Inhibition of adipogenesis by Wnt signaling. Science. 2000;289: 950–3.
89. Gong Y, Slee RB, Fukai N, Rawadi G, Roman-Roman S, Reginato AM, Wang H, Cundy T, Glorieux FH, Lev D, Zacharin M, Oexle K, Marcelino J, Suwairi W, Heeger S, Sabatakos G, Apte S, Adkins WN, Allgrove J, Arslan-Kirchner M, Batch JA, Beighton P, Black GC, Boles RG, Boon LM, Borrone C, Brunner HG, Carle GF, Dallapiccola B, De Paepe A, Floege B, Halfhide ML, Hall B, Hennekam RC, Hirose T, Jans A, Juppner H, Kim CA, Keppler-Noreuil K, Kohlschuetter A, LaCombe D, Lambert M, Lemyre E, Letteboer T, Peltonen L, Ramesar RS, Romanengo M, Somer H, Steichen-Gersdorf E, Steinmann B, Sullivan B, Superti-Furga A, Swoboda W, van den Boogaard MJ, Van Hul W, Vikkula M, Votruba M, Zabel B, Garcia T, Baron R, Olsen BR, Warman ML, Osteoporosis-Pseudoglioma Syndrome Collaborative G. LDL receptor-related protein 5 (LRP5) affects bone accrual and eye development. Cell. 2001;107:513–23.
90. Boyden LM, Mao J, Belsky J, Mitzner L, Farhi A, Mitnick MA, Wu D, Insogna K, Lifton RP. High bone density due to a mutation in LDL-receptor-related protein 5. N Engl J Med. 2002;346:1513–21.
91. Taipaleenmaki H, Abdallah BM, AlDahmash A, Saamanen AM, Kassem M. Wnt signalling mediates the cross-talk between bone marrow derived pre-adipocytic and pre-osteoblastic cell populations. Exp Cell Res. 2011;317:745–56.
92. Qiu W, Andersen TE, Bollerslev J, Mandrup S, Abdallah BM, Kassem M. Patients with high bone mass phenotype exhibit enhanced osteoblast differentiation and inhibition of adipogenesis of human mesenchymal stem cells. J Bone Miner Res Off J Am Soc Bone Miner Res. 2007;22:1720–31.
93. Bennett CN, Longo KA, Wright WS, Suva LJ, Lane TF, Hankenson KD, MacDougald OA. Regulation of osteoblastogenesis and bone mass by Wnt10b. Proc Natl Acad Sci U S A. 2005;102:3324–9.

94. Zhou S, Eid K, Glowacki J. Cooperation between TGF-beta and Wnt pathways during chondrocyte and adipocyte differentiation of human marrow stromal cells. J Bone Miner Res Off J Am Soc Bone Miner Res. 2004;19:463–70.
95. Tartaglia LA, Dembski M, Weng X, Deng N, Culpepper J, Devos R, Richards GJ, Campfield LA, Clark FT, Deeds J, Muir C, Sanker S, Moriarty A, Moore KJ, Smutko JS, Mays GG, Wool EA, Monroe CA, Tepper RI. Identification and expression cloning of a leptin receptor, OB-R. Cell. 1995;83:1263–71.
96. Hamrick MW, Ding KH, Pennington C, Chao YJ, Wu YD, Howard B, Immel D, Borlongan C, McNeil PL, Bollag WB, Curl WW, Yu J, Isales CM. Age-related loss of muscle mass and bone strength in mice is associated with a decline in physical activity and serum leptin. Bone. 2006;39:845–53.
97. Crabbe P, Goemaere S, Zmierczak H, Van Pottelbergh I, De Bacquer D, Kaufman JM. Are serum leptin and the Gln223Arg polymorphism of the leptin receptor determinants of bone homeostasis in elderly men? Eur J Endocrinol Eur Fed Endocrine Soc. 2006;154:707–14.
98. Hess R, Pino AM, Rios S, Fernandez M, Rodriguez JP. High affinity leptin receptors are present in human mesenchymal stem cells (MSCs) derived from control and osteoporotic donors. J Cell Biochem. 2005;94:50–7.
99. Berner HS, Lyngstadaas SP, Spahr A, Monjo M, Thommesen L, Drevon CA, Syversen U, Reseland JE. Adiponectin and its receptors are expressed in bone-forming cells. Bone. 2004;35:842–9.
100. Shinoda Y, Yamaguchi M, Ogata N, Akune T, Kubota N, Yamauchi T, Terauchi Y, Kadowaki T, Takeuchi Y, Fukumoto S, Ikeda T, Hoshi K, Chung UI, Nakamura K, Kawaguchi H. Regulation of bone formation by adiponectin through autocrine/paracrine and endocrine pathways. J Cell Biochem. 2006;99:196–208.
101. Cawthorn WP, Scheller EL, Learman BS, Parlee SD, Simon BR, Mori H, Ning X, Bree AJ, Schell B, Broome DT, Soliman SS, DelProposto JL, Lumeng CN, Mitra A, Pandit SV, Gallagher KA, Miller JD, Krishnan V, Hui SK, Bredella MA, Fazeli PK, Klibanski A, Horowitz MC, Rosen CJ, MacDougald OA. Bone marrow adipose tissue is an endocrine organ that contributes to increased circulating adiponectin during caloric restriction. Cell Metab. 2014;20:368–75.
102. Abdallah BM, Jafari A, Zaher W, Qiu W, Kassem M. Skeletal (stromal) stem cells: an update on intracellular signaling pathways controlling osteoblast differentiation. Bone. 2015;70:28–36.
103. Abdallah BM, Ditzel N, Mahmood A, Isa A, Traustadottir GA, Schilling AF, Ruiz-Hidalgo MJ, Laborda J, Amling M, Kassem M. DLK1 is a novel regulator of bone mass that mediates estrogen deficiency-induced bone loss in mice. J Bone Miner Res Off J Am Soc Bone Miner Res. 2011; 26:1457–71.
104. Abdallah BM, Bay-Jensen AC, Srinivasan B, Tabassi NC, Garnero P, Delaisse JM, Khosla S, Kassem M. Estrogen inhibits Dlk1/FA1 production: a potential mechanism for estrogen effects on bone turnover. J Bone Miner Res Off J Am Soc Bone Miner Res. 2011;26:2548–51.
105. Bredella MA, Fazeli PK, Freedman LM, Calder G, Lee H, Rosen CJ, Klibanski A. Young women with cold-activated brown adipose tissue have higher bone mineral density and lower Pref-1 than women without brown adipose tissue: a study in women with anorexia nervosa, women recovered from anorexia nervosa, and normal-weight women. J Clin Endocrinol Metab. 2012;97:E584–90.
106. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA. The hormone resistin links obesity to diabetes. Nature. 2001;409:307–12.
107. Thommesen L, Stunes AK, Monjo M, Grosvik K, Tamburstuen MV, Kjobli E, Lyngstadaas SP, Reseland JE, Syversen U. Expression and regulation of resistin in osteoblasts and osteoclasts indicate a role in bone metabolism. J Cell Biochem. 2006; 99:824–34.
108. Oh KW, Lee WY, Rhee EJ, Baek KH, Yoon KH, Kang MI, Yun EJ, Park CY, Ihm SH, Choi MG, Yoo HJ, Park SW. The relationship between serum resistin, leptin, adiponectin, ghrelin levels and bone mineral density in middle-aged men. Clin Endocrinol (Oxf). 2005;63:131–8.
109. Tong J, Li W, Vidal C, Yeo LS, Fatkin D, Duque G. Lamin A/C deficiency is associated with fat infiltration of muscle and bone. Mech Ageing Dev. 2011;132:552–9.
110. Duque G, Li W, Adams M, Xu S, Phipps R. Effects of risedronate on bone marrow adipocytes in postmenopausal women. Osteoporos Int. 2011;22: 1547–53.
111. Gimble JM, Nuttall ME. Bone and fat: old questions, new insights. Endocrine. 2004;23:183–8.
112. Kajimura S, Seale P, Kubota K, Lunsford E, Frangioni JV, Gygi SP, Spiegelman BM. Initiation of myoblast to brown fat switch by a PRDM16-C/EBP-beta transcriptional complex. Nature. 2009;460:1154–8.
113. Seale P, Kajimura S, Yang W, Chin S, Rohas LM, Uldry M, Tavernier G, Langin D, Spiegelman BM. Transcriptional control of brown fat determination by PRDM16. Cell Metab. 2007;6:38–54.
114. Jacobsson A, Stadler U, Glotzer MA, Kozak LP. Mitochondrial uncoupling protein from mouse brown fat. Molecular cloning, genetic mapping, and mRNA expression. J Biol Chem. 1985;260:16250–4.
115. Huggins C, Blocksom BH. Changes in outlying bone marrow accompanying a local increase of temperature within physiological limits. J Exp Med. 1936;64:253–74.
116. Huggins C, Noonan WJ. An increase in reticuloendothelial cells in outlying bone marrow consequent upon a local increase in temperature. J Exp Med. 1936;64:275–80.

117. Huggins C, Blocksom BH, Noonan WJ. Temperature conditions in bone marrow of rabbit, pigeon, and albino rat. Am J Physiol. 1936;115:253–74.
118. Petrakis NL. Some physiological and developmental considerations of the temperature-gradient hypothesis of bone marrow distribution. Am J Phys Anthropol. 1966;25:119–29.
119. Weiss LP, Wislocki GB. Seasonal variations in hematopoiesis in the dermal bones of the nine-banded armadillo. Anat Rec. 1956;126:143–63.
120. Tavassoli M. Marrow adipose cells and hemopoiesis: an interpretative review. Exp Hematol. 1984;12:139–46.
121. Tavassoli M, Crosby WH. Bone marrow histogenesis: a comparison of fatty and red marrow. Science. 1970;169:291–3.
122. Tavassoli M, Maniatis A, Crosby WH. Induction of sustained hemopoiesis in fatty marrow. Blood. 1974;43:33–8.
123. Tavassoli M, Maniatis A, Crosby WH. The effects of phenylhydrazine-induced haemolysis on the behaviour of regenerating marrow stroma. Br J Haematol. 1972;23:707–11.
124. Maniatis A, Tavassoli M, Crosby WH. Factors affecting the conversion of yellow to red marrow. Blood. 1971;37:581–6.
125. Bathija A, Davis S, Trubowitz S. Marrow adipose tissue: response to erythropoiesis. Am J Hematol. 1978;5:315–21.
126. Brookoff D, Weiss L. Adipocyte development and the loss of erythropoietic capacity in the bone marrow of mice after sustained hypertransfusion. Blood. 1982;60:1337–44.
127. Krings A, Rahman S, Huang S, Lu Y, Czernik PJ, Lecka-Czernik B. Bone marrow fat has brown adipose tissue characteristics, which are attenuated with aging and diabetes. Bone. 2012;50:546–52.
128. Olmsted-Davis E, Gannon FH, Ozen M, Ittmann MM, Gugala Z, Hipp JA, Moran KM, Fouletier-Dilling CM, Schumara-Martin S, Lindsey RW, Heggeness MH, Brenner MK, Davis AR. Hypoxic adipocytes pattern early heterotopic bone formation. Am J Pathol. 2007;170:620–32.
129. Salisbury E, Hipp J, Olmsted-Davis EA, Davis AR, Heggeness MH, Gannon FH. Histologic identification of brown adipose and peripheral nerve involvement in human atherosclerotic vessels. Hum Pathol. 2012;43:2213–22.
130. Salisbury EA, Lazard ZW, Ubogu EE, Davis AR, Olmsted-Davis EA. Transient brown adipocyte-like cells derive from peripheral nerve progenitors in response to bone morphogenetic protein 2. Stem Cells Transl Med. 2012;1:874–85.
131. Stephens EH, Saltarrelli Jr JG, Balaoing LR, Baggett LS, Nandi I, Anderson KM, Morrisett JD, Reardon MJ, Simpson MA, Weigel PH, Olmsted-Davis EA, Davis AR, Grande-Allen KJ. Hyaluronan turnover and hypoxic brown adipocytic differentiation are co-localized with ossification in calcified human aortic valves. Pathol Res Pract. 2012;208:642–50.
132. Hussain MM, Mahley RW, Boyles JK, Fainaru M, Brecht WJ, Lindquist PA. Chylomicron-chylomicron remnant clearance by liver and bone marrow in rabbits. Factors that modify tissue-specific uptake. J Biol Chem. 1989;264:9571–82.
133. Hussain MM, Mahley RW, Boyles JK, Lindquist PA, Brecht WJ, Innerarity TL. Chylomicron metabolism. Chylomicron uptake by bone marrow in different animal species. J Biol Chem. 1989;264:17931–8.
134. Tavassoli M, Eastlund DT, Yam LT, Neiman RS, Finkel H. Gelatinous transformation of bone marrow in prolonged self-induced starvation. Scand J Haematol. 1976;16:311–9.
135. Bredella MA, Fazeli PK, Miller KK, Misra M, Torriani M, Thomas BJ, Ghomi RH, Rosen CJ, Klibanski A. Increased bone marrow fat in anorexia nervosa. J Clin Endocrinol Metab. 2009;94:2129–36.
136. Devlin MJ, Cloutier AM, Thomas NA, Panus DA, Lotinun S, Pinz I, Baron R, Rosen CJ, Bouxsein ML. Caloric restriction leads to high marrow adiposity and low bone mass in growing mice. J Bone Miner Res Off J Am Soc Bone Miner Res. 2010;25:2078–88.
137. Wu J, Cohen P, Spiegelman BM. Adaptive thermogenesis in adipocytes: is beige the new brown? Genes Dev. 2013;27:234–50.
138. Harms M, Seale P. Brown and beige fat: development, function and therapeutic potential. Nat Med. 2013;19:1252–63.
139. Virtanen KA, Lidell ME, Orava J, Heglind M, Westergren R, Niemi T, Taittonen M, Laine J, Savisto NJ, Enerback S, Nuutila P. Functional brown adipose tissue in healthy adults. N Engl J Med. 2009;360:1518–25.
140. van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM, Drossaerts JM, Kemerink GJ, Bouvy ND, Schrauwen P, Teule GJ. Cold-activated brown adipose tissue in healthy men. N Engl J Med. 2009;360:1500–8.
141. Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, Kuo FC, Palmer EL, Tseng YH, Doria A, Kolodny GM, Kahn CR. Identification and importance of brown adipose tissue in adult humans. N Engl J Med. 2009;360:1509–17.
142. Rahman S, Lu Y, Czernik PJ, Rosen CJ, Enerback S, Lecka-Czernik B. Inducible brown adipose tissue, or beige fat, is anabolic for the skeleton. Endocrinology. 2013;154:2687–701.
143. Little RD, Carulli JP, Del Mastro RG, Dupuis J, Osborne M, Folz C, Manning SP, Swain PM, Zhao SC, Eustace B, Lappe MM, Spitzer L, Zweier S, Braunschweiger K, Benchekroun Y, Hu X, Adair R, Chee L, FitzGerald MG, Tulig C, Caruso A, Tzellas N, Bawa A, Franklin B, McGuire S, Nogues X, Gong G, Allen KM, Anisowicz A, Morales AJ, Lomedico PT, Recker SM, Van Eerdewegh P, Recker RR, Johnson ML. A mutation in the LDL receptor-related protein 5 gene results in the autosomal dominant high-bone-mass trait. Am J Hum Genet. 2002;70:11–9.

144. Styner M, Thompson WR, Galior K, Uzer G, Wu X, Kadari S, Case N, Xie Z, Sen B, Romaine A, Pagnotti GM, Rubin CT, Styner MA, Horowitz MC, Rubin J. Bone marrow fat accumulation accelerated by high fat diet is suppressed by exercise. Bone. 2014;64:39–46.
145. Hargrave KM, Li C, Meyer BJ, Kachman SD, Hartzell DL, Della-Fera MA, Miner JL, Baile CA. Adipose depletion and apoptosis induced by trans-10, cis-12 conjugated linoleic acid in mice. Obes Res. 2002;10:1284–90.
146. Park Y, Albright KJ, Liu W, Storkson JM, Cook ME, Pariza MW. Effect of conjugated linoleic acid on body composition in mice. Lipids. 1997;32:853–8.
147. Rahman MM, Bhattacharya A, Fernandes G. Conjugated linoleic acid inhibits osteoclast differentiation of RAW264.7 cells by modulating RANKL signaling. J Lipid Res. 2006;47:1739–48.
148. Bonnet N, Somm E, Rosen CJ. Diet and gene interactions influence the skeletal response to polyunsaturated fatty acids. Bone. 2014;68:100–7.
149. Reid IR. Relationships among body mass, its components, and bone. Bone. 2002;31:547–55.
150. Bolland MJ, Grey AB, Ames RW, Horne AM, Gamble GD, Reid IR. Fat mass is an important predictor of parathyroid hormone levels in postmenopausal women. Bone. 2006;38:317–21.
151. Hamrick MW, Della-Fera MA, Choi YH, Pennington C, Hartzell D, Baile CA. Leptin treatment induces loss of bone marrow adipocytes and increases bone formation in leptin-deficient ob/ob mice. J Bone Miner Res Off J Am Soc Bone Miner Res. 2005;20:994–1001.
152. Thomas T, Gori F, Khosla S, Jensen MD, Burguera B, Riggs BL. Leptin acts on human marrow stromal cells to enhance differentiation to osteoblasts and to inhibit differentiation to adipocytes. Endocrinology. 1999;140:1630–8.
153. Takeda S, Elefteriou F, Levasseur R, Liu X, Zhao L, Parker KL, Armstrong D, Ducy P, Karsenty G. Leptin regulates bone formation via the sympathetic nervous system. Cell. 2002;111:305–17.
154. Ducy P, Amling M, Takeda S, Priemel M, Schilling AF, Beil FT, Shen J, Vinson C, Rueger JM, Karsenty G. Leptin inhibits bone formation through a hypothalamic relay: a central control of bone mass. Cell. 2000;100:197–207.
155. Lenchik L, Register TC, Hsu FC, Lohman K, Nicklas BJ, Freedman BI, Langefeld CD, Carr JJ, Bowden DW. Adiponectin as a novel determinant of bone mineral density and visceral fat. Bone. 2003;33:646–51.
156. Yokota T, Meka CS, Medina KL, Igarashi H, Comp PC, Takahashi M, Nishida M, Oritani K, Miyagawa J, Funahashi T, Tomiyama Y, Matsuzawa Y, Kincade PW. Paracrine regulation of fat cell formation in bone marrow cultures via adiponectin and prostaglandins. J Clin Invest. 2002;109:1303–10.
157. Oshima K, Nampei A, Matsuda M, Iwaki M, Fukuhara A, Hashimoto J, Yoshikawa H, Shimomura I. Adiponectin increases bone mass by suppressing osteoclast and activating osteoblast. Biochem Biophys Res Commun. 2005;331:520–6.
158. Jurimae J, Rembel K, Jurimae T, Rehand M. Adiponectin is associated with bone mineral density in perimenopausal women. Horm Metab Res. 2005;37:297–302.
159. Nielson CM, Srikanth P, Orwoll ES. Obesity and fracture in men and women: an epidemiologic perspective. J Bone Miner Res Off J Am Soc Bone Miner Res. 2012;27:1–10.
160. Caffarelli C, Alessi C, Nuti R, Gonnelli S. Divergent effects of obesity on fragility fractures. Clin Interv Aging. 2014;9:1629–36.
161. Lecka-Czernik B, Stechschulte LA, Czernik PJ, Dowling AR. High bone mass in adult mice with diet-induced obesity results from a combination of initial increase in bone mass followed by attenuation in bone formation; implications for high bone mass and decreased bone quality in obesity. Mol Cell Endocrinol. 2015;410:35–41.
162. Cao JJ. Effects of obesity on bone metabolism. J Orthop Surg Res. 2011;6:30.
163. Ferron M, Wei J, Yoshizawa T, Del Fattore A, DePinho RA, Teti A, Ducy P, Karsenty G. Insulin signaling in osteoblasts integrates bone remodeling and energy metabolism. Cell. 2010;142:296–308.
164. Fulzele K, Riddle RC, DiGirolamo DJ, Cao X, Wan C, Chen D, Faugere MC, Aja S, Hussain MA, Bruning JC, Clemens TL. Insulin receptor signaling in osteoblasts regulates postnatal bone acquisition and body composition. Cell. 2010;142:309–19.
165. Wei J, Ferron M, Clarke CJ, Hannun YA, Jiang H, Blaner WS, Karsenty G. Bone-specific insulin resistance disrupts whole-body glucose homeostasis via decreased osteocalcin activation. J Clin Invest. 2014;124:1–13.
166. Kaji H, Hisa I, Inoue Y, Naito J, Sugimoto T, Kasuga M. Analysis of factors affecting increase in bone mineral density at lumbar spine by bisphosphonate treatment in postmenopausal osteoporosis. J Bone Miner Metab. 2009;27:76–82.
167. Ahlborg HG, Johnell O, Turner CH, Rannevik G, Karlsson MK. Bone loss and bone size after menopause. N Engl J Med. 2003;349:327–34.
168. Aloia JF, Vaswani A, Russo L, Sheehan M, Flaster E. The influence of menopause and hormonal replacement therapy on body cell mass and body fat mass. Am J Obstet Gynecol. 1995;172:896–900.
169. Pacifici R, Brown C, Puscheck E, Friedrich E, Slatopolsky E, Maggio D, McCracken R, Avioli LV. Effect of surgical menopause and estrogen replacement on cytokine release from human blood mononuclear cells. Proc Natl Acad Sci U S A. 1991;88:5134–8.
170. Pfeilschifter J, Koditz R, Pfohl M, Schatz H. Changes in proinflammatory cytokine activity after menopause. Endocr Rev. 2002;23:90–119.
171. Manolagas SC, Jilka RL. Bone marrow, cytokines, and bone remodeling. Emerging insights into the

pathophysiology of osteoporosis. N Engl J Med. 1995;332:305–11.
172. Jilka RL, Weinstein RS, Bellido T, Parfitt AM, Manolagas SC. Osteoblast programmed cell death (apoptosis): modulation by growth factors and cytokines. J Bone Miner Res Off J Am Soc Bone Miner Res. 1998;13:793–802.
173. Weinstein RS, Jilka RL, Parfitt AM, Manolagas SC. Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. Potential mechanisms of their deleterious effects on bone. J Clin Invest. 1998; 102:274–82.
174. Soroceanu MA, Miao D, Bai XY, Su H, Goltzman D, Karaplis AC. Rosiglitazone impacts negatively on bone by promoting osteoblast/osteocyte apoptosis. J Endocrinol. 2004;183:203–16.
175. Aguirre JI, Plotkin LI, Stewart SA, Weinstein RS, Parfitt AM, Manolagas SC, Bellido T. Osteocyte apoptosis is induced by weightlessness in mice and precedes osteoclast recruitment and bone loss. J Bone Miner Res Off J Am Soc Bone Miner Res. 2006;21:605–15.
176. Kume S, Kato S, Yamagishi S, Inagaki Y, Ueda S, Arima N, Okawa T, Kojiro M, Nagata K. Advanced glycation end-products attenuate human mesenchymal stem cells and prevent cognate differentiation into adipose tissue, cartilage, and bone. J Bone Miner Res Off J Am Soc Bone Miner Res. 2005;20:1647–58.
177. Jilka RL, Weinstein RS, Bellido T, Roberson P, Parfitt AM, Manolagas SC. Increased bone formation by prevention of osteoblast apoptosis with parathyroid hormone. J Clin Invest. 1999;104:439–46.
178. Plotkin LI, Weinstein RS, Parfitt AM, Roberson PK, Manolagas SC, Bellido T. Prevention of osteocyte and osteoblast apoptosis by bisphosphonates and calcitonin. J Clin Invest. 1999;104:1363–74.
179. Duque G, El Abdaimi K, Henderson JE, Lomri A, Kremer R. Vitamin D inhibits Fas ligand-induced apoptosis in human osteoblasts by regulating components of both the mitochondrial and Fas-related pathways. Bone. 2004;35:57–64.
180. Byun CH, Koh JM, Kim DK, Park SI, Lee KU, Kim GS. Alpha-lipoic acid inhibits TNF-alpha-induced apoptosis in human bone marrow stromal cells. J Bone Miner Res Off J Am Soc Bone Miner Res. 2005;20:1125–35.
181. Ahuja SS, Zhao S, Bellido T, Plotkin LI, Jimenez F, Bonewald LF. CD40 ligand blocks apoptosis induced by tumor necrosis factor alpha, glucocorticoids, and etoposide in osteoblasts and the osteocyte-like cell line murine long bone osteocyte-Y4. Endocrinology. 2003;144:1761–9.
182. Miura M, Chen XD, Allen MR, Bi Y, Gronthos S, Seo BM, Lakhani S, Flavell RA, Feng XH, Robey PG, Young M, Shi S. A crucial role of caspase-3 in osteogenic differentiation of bone marrow stromal stem cells. J Clin Invest. 2004;114:1704–13.
183. Pantschenko AG, Zhang W, Nahounou M, McCarthy MB, Stover ML, Lichtler AC, Clark SH, Gronowicz GA. Effect of osteoblast-targeted expression of bcl-2 in bone: differential response in male and female mice. J Bone Miner Res Off J Am Soc Bone Miner Res. 2005;20:1414–29.
184. Plotkin LI, Manolagas SC, Bellido T. Dissociation of the pro-apoptotic effects of bisphosphonates on osteoclasts from their anti-apoptotic effects on osteoblasts/osteocytes with novel analogs. Bone. 2006;39:443–52.
185. Zhao H, Ross FP, Teitelbaum SL. Unoccupied alpha(v)beta3 integrin regulates osteoclast apoptosis by transmitting a positive death signal. Mol Endocrinol. 2005;19:771–80.
186. Sorisky A, Magun R, Gagnon AM. Adipose cell apoptosis: death in the energy depot. Int J Obes Relat Metab Disord J Int Assoc Study Obes. 2000;24 Suppl 4:S3–7.
187. Prins JB, Niesler CU, Winterford CM, Bright NA, Siddle K, O'Rahilly S, Walker NI, Cameron DP. Tumor necrosis factor-alpha induces apoptosis of human adipose cells. Diabetes. 1997;46:1939–44.
188. Niesler CU, Siddle K, Prins JB. Human preadipocytes display a depot-specific susceptibility to apoptosis. Diabetes. 1998;47:1365–8.
189. Kim HS, Hausman DB, Compton MM, Dean RG, Martin RJ, Hausman GJ, Hartzell DL, Baile CA. Induction of apoptosis by all-trans-retinoic acid and C2-ceramide treatment in rat stromal-vascular cultures. Biochem Biophys Res Commun. 2000; 270:76–80.
190. Nelson-Dooley C, Della-Fera MA, Hamrick M, Baile CA. Novel treatments for obesity and osteoporosis: targeting apoptotic pathways in adipocytes. Curr Med Chem. 2005;12:2215–25.

Calciotropic Hormones

3

E. Paul Cherniack and Bruce R. Troen

The calcium – vitamin D – parathyroid hormone system plays a critical role in both health and disease. Despite longstanding acceptance of its importance in maintaining the skeleton, recent and accumulating data have significantly enhanced our understanding of the pathophysiology of calciotropic hormones in the setting of osteoporosis. Herein we review this information and make recommendations based upon these studies.

Calcium

Calcium is one of the most abundant inorganic elements in the human body. The physiologic roles of calcium in the body are twofold. Firstly, calcium provides structural integrity to the skeleton. In addition, in the extracellular fluids and in the cytosol, the calcium concentration is critical to many biochemical processes, and these include hormone and enzyme secretion, neurotransmission, muscle contraction, blood clotting, and gene expression [1]. Therefore calcium concentrations are tightly regulated.

Calcium is absorbed from the small intestine and kidney via both vitamin D dependent and independent pathways (Fig. 3.1). When calcium is abundant, vitamin D independent mechanisms are predominant. When calcium is scarce, vitamin D-dependent pathways are primarily utilized [1, 2]. There is an age-related decrement in calcium absorption, and this appears in part to be due to widespread vitamin D insufficiency and frank deficiency [3]. However, calcium absorption also declines in post-menopausal women independent of 25-hydroxycholecalciferol (25(OH) vitamin D) and parathyroid hormone (PTH) levels [4].

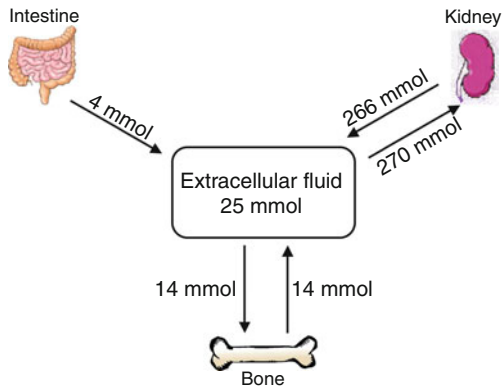


Fig. 3.1 Calcium homeostasis (From Ramasamy [1])

E.P. Cherniack, MD (✉)
Division of Gerontology and Geriatrics, Department of Medicine, Geriatric Research Education and Clinical Center, Miami Veterans Affairs Medical Center, Miller School of Medicine, University of Miami, Miami, FL 33125, USA
e-mail: evan.cherniack@va.gov

B.R. Troen, MD
Division of Geriatrics and Palliative Medicine, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo – SUNY, Research Service – Western New York Veterans Affairs Healthcare System, Buffalo, NY 14203, USA
e-mail: troen@buffalo.edu

G. Duque, D.P. Kiel (eds.), *Osteoporosis in Older Persons: Advances in Pathophysiology and Therapeutic Approaches*, DOI 10.1007/978-3-319-25976-5_3

Vitamin D

Vitamin D is an important multi-purpose steroid hormone that plays an essential role in humans in the maintenance of bone, muscle, immunity, metabolic signaling, and protection against cardiovascular disease and neoplasms. The action of vitamin D on bone is complex. Vitamin D regulates osteoblast differentiation and stimulates expression of alkaline phosphatase and bone matrix proteins [1, 2, 5]. Vitamin D also stimulates osteoclast formation via cellular interaction with osteoblasts and osteoclast cell precursors [6]. While vitamin D indirectly stimulates osteoclast formation, it also enhances gastrointestinal calcium absorption, promotes mineralization, and inhibits PTH induced bone resorption [1, 2, 5].

In humans sunlight exposure is necessary for the precursor of vitamin D, 7-dehydrocholesterol, which is obtained from the diet, to be converted into previtamin D3, which is quickly isomerized into vitamin D3 (cholecalciferol) (Fig. 3.2). Cholecalciferol is subsequently hydroxylated in the liver to 25-hydroxycholecalciferol (25(OH) vitamin D) by the mitochondrial enzyme CYP27A1 and again in the kidney to 1,25-dihydroxycholecalciferol (calcitriol) by the 1-α hydroxylase, CYP27B1 [1, 7]. Calcitriol is the activated form of vitamin D and exerts its effects by directly binding to the vitamin D receptor [3]. Low calcium stimulates the 1-α hydroxylation of 25-hydroxycholecalciferol by CYP27B1. Abundant calcium stimulates the enzymatic conversion of 25-hydroxycholecalciferol to 24,25-$(OH)_2D_3$ and 1,25-dihydroxycholecalciferol to 1,24,25-$(OH)_3D_3$ by CYP24. Conversely, increases in 1,25-dihydroxycholecalciferol inhibit and upregulate the action of CYP27B1 and CYP24, respectively. Therefore calcium and calcitriol work in opposition to regulate both the increased production of calcitriol and its metabolic degradation [3, 8] (Fig. 3.3).

The amount of sunlight capable of causing a mild sunburn stimulates the production and release into the circulation of 10,000–20,000 IU of vitamin D in the following 24 h [9]. But this requires exposure of large parts of the body such as the thorax and legs, not just smaller surface areas such as the face, neck, and arms [10]. Since the production of vitamin D depends upon the extent of ultraviolet exposure, people with darker skin require longer exposure than do those with lighter skin [11, 12]. Furthermore, the skin of older individuals (age 77–82) produces less than half of the cholecalciferol precursor, 7-dehydrocholesterol, than does the skin of younger individuals (age 8–18) [13]. Many elderly individuals consume suboptimal amounts of vitamin D and calcium [14, 15]. There are relatively few dietary sources of vitamin D, and they include fortified milk and orange juice, and salmon and other fatty fish. Vitamin D is well absorbed from the small intestine through a bile-dependent mechanism. However, deficient consumption of dairy products, and high intake of high-protein, low calcium-containing foods has been implicated as

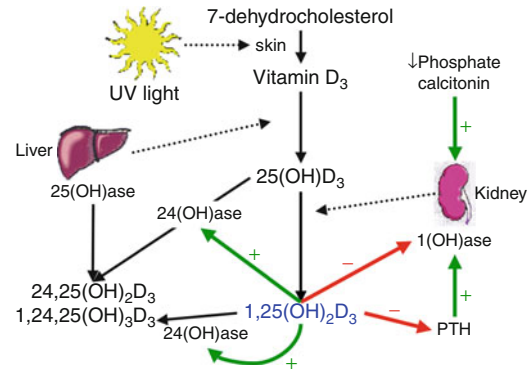


Fig. 3.2 Vitamin D metabolism (Adapted from Ramasamy [1])

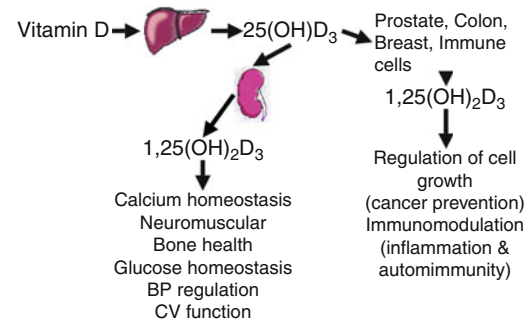


Fig. 3.3 Biologic functions of vitamin D (From Holick [3])

factor for lack of calcium intake [16, 17]. Lactose intolerance and low socioeconomic status also appears to contribute to poor calcium intake [18, 19]. Therefore, decreased vitamin D production and consumption act in concert to predispose to hypovitaminosis D.

A surprisingly large percentage of the population has inadequate vitamin D levels [20]. Frank deficiency is below 10 ng/ml, but levels of 25(OH) vitamin D below 30 ng/ml are now considered to be insufficient [21]. As many as 40–90 % of the elderly have 25(OH) vitamin D levels below 30 ng/ml [22–27]. The level of 25(OH) vitamin D can vary as much as 40 % between the summer and winter seasons, most likely due to the seasonal changes in sun and ultraviolet exposure [28]. There is widespread vitamin D insufficiency even in climates with ample amounts of sunlight; however cultural norms dictate clothing coverage, thereby diminishing ultraviolet radiation induced production of vitamin D [29–32]. In one study, there was no difference between veiled and unveiled women [33]. However, approximately 80 % in both groups had 25(OH) vitamin D levels below 16 ng/ml.

Lower vitamin D levels are more common among blacks, and blacks have lower bone mineral densities for given vitamin D levels than whites [34–36]. In the NHANES III, 53–76 % of non-Hispanic blacks were found to have 25(OH) vitamin D levels <20 ng/ml versus 8–33 % of non-Hispanic whites. Many African-Americans do not achieve 25(OH) vitamin D levels ≥ 30 ng/ml at any time of the year. Median vitamin D intakes are 6–31 % lower than other racial groups, and there is decreased consumption of dairy products and fortified cereals. Supplementation with cholecalciferol of up to 2000 IU daily in which African American women did not improve their bone mineral densities, although their mean 25(OH) vitamin D levels increased from 18.76 to 28.32 ng/ml [37].

The spectrum of vitamin D deficiency disease in the skeleton extends ranges from rickets, at the lowest vitamin D levels, to more insidiously developing disease, such as osteoporosis, at higher but still suboptimal levels. The entire range of pathology caused by hypovitaminosis D has been termed “hypovitaminosis D osteopathy (HVO)” [38, 39]. Initially described by Michael Parfitt, there are three progressive stages [38]. In the least severe, lack of vitamin D results in calcium malabsorption, elevation of parathryoid hormone (PTH) level occurs to increase calcium absorption, and osteoporosis occurs, with bone remodeling and loss of osteoporosis. In a second more severe stage, continued lack of calcium and bone remodeling create the histologic changes of osteomalacia. In the most extreme state of deficiency, bone remodeling ceases and the clinical manifestations of rickets are present [39].

For over a decade, studies have reported that supplementation with vitamin D and calcium reduce fracture risk, falls, and improve balance [40–42]. Vitamin D is well known to play a role in maintaining skeletal integrity, regulating calcium entry via receptors in bone and small intestine [43–45]. In several studies in which vitamin D in community-dwelling elderly was supplemented, a 10–30 percent reduction in non-vertebral fracture incidence was noted over several years [46, 47]. A study of 389 ambulatory elderly individuals supplemented daily with 700 IU of vitamin D and 500 mg of calcium observed an approximately 68% lower non-vertebral fracture risk after 3 years [46]. More than 3000 healthy older persons (mean age 84) who received 800 IU of cholecalciferol and 1.2 g of calcium for a year and a half experienced a 43% lower incidence of hip fracture and a 32 percent lower incidence of non-vertebral fractures [48]. These benefits were confirmed in a separate 2-year study of 583 ambulatory institutionalized women showing that the same doses of calcium and vitamin D reduced hip fracture by 40 % [49]. However, when 800 IU of cholecalciferol was provided to more than 8000 older individuals with a previous history of fracture or risk factors for fracture in two trials lasting 2–5 years, fracture incidence was not reduced [50, 51]. However compliance rates were 56 % and 60 %, and in only a small percentage of subjects were 25(OH) vitamin D levels assessed. Possible explanations for varying results include inadequate replacement of vitamin D, different baseline levels of

vitamin D in the populations studied, and differences in the populations studied – particularly with respect to baseline bone mineral density, fall predisposition, and adherence to the regimen. Furthermore, neither studied was powered sufficiently to detect decreases in fracture incidence less than 30 %. A meta-analysis concluded that 700–800 IU of vitamin D per day significantly reduced vertebral, non-vertebral, and hip fractures, whereas 400 IU per day did not [52]. In the recent Women's Health Initiative study, 500 mg calcium and 400 IU of vitamin D per day was shown to reduce hip fracture in community dwelling women (OR – 0.71: confidence interval 0.52–0.97) who took greater than 80 % of the doses [53].

The role of vitamin D in fracture risk extends beyond bone; it appears to enhance physical performance through an effect on extraskeletal tissues [54]. Vitamin D receptors are found in muscle, although their expression decreases with age [43]. Higher serum levels of 25(OH) vitamin D are correlated with better leg function as assessed by a timed walk test and a repeated sit-to-stand test [54]. Vitamin D supplementation reduces falls in subjects who maintain a minimum calcium intake [40, 41]. A meta-analysis of the effect of vitamin D in 1237 subjects revealed a 22 % reduced risk of falls, with a number needed to treat of only 15 [40]. A dose of 700–800 IU vitamin D per day significantly reduced falls, whereas 400 IU per day did not, although a study in community dwelling Danish demonstrated a fall reduction with 1000 mg of calcium carbonate and 400 IU vitamin D per day [41]. In elderly Australians in residential care, 1000 IU ergocalciferol (vitamin D_2) per day significantly reduced falls, with a number needed to treat of only 12 [55]. This benefit was even greater in compliant individuals with a number to treat of only 8. Fracture rates were not reduced, but the intervention was not powered to demonstrate such an outcome.

Vitamin D supplementation also improves balance. When over 100 subjects whose 25(OH) vitamin D levels were found to be less than 12 ng/ml were supplemented with a single dose of 600,000 IU of ergocalciferol, postural sway improved [56]. Furthermore, 242 disease-free elderly Germans who were supplemented with 800 IU vitamin D and 1000 mg calcium daily for a year exhibited less body sway than those who received calcium alone [57]. The subjects who received vitamin D also had greater quadriceps strength. In a survey of 4100 ambulatory individuals age 60 and above, 25(OH) vitamin D levels below 24 were correlated with reduced walking speed and increased time to stand from a seated position [54]. Vitamin D levels were also positively correlated with neuromuscular performance tasks in a longitudinal survey of 1300 elderly individuals [58]. However, the effect of vitamin D supplementation on parameters of physical performance is not unequivocal. One thousand units of cholecalciferol per day failed to improve upper and lower extremity strength and power in older men [59], and a systematic review found no improvement in muscle strength with vitamin D supplementation using a variety of preparations and doses [60]. No reduction in falls or fractures was observed in nursing home residents given 100,000 IU of ergocalciferol orally every 3 months [61]. However, the serum 25(OH) vitamin D levels of half of the ergocalciferol recipients remained below approximately 30–32 ng/ml . Again, possible explanations for the lack of effect of vitamin D in some investigations include inadequate dose of vitamin D used, variation in baseline vitamin D level, differences in medication compliance, and (in the case of measurements of muscle strength) inadequate choice of assessment parameters [62].

A majority of calciotropic hormone investigators maintains that 32 ng/ml remains the lower limit for an optimal human serum level of 25(OH) vitamin D [9, 63–67], representing the concentration above which most studies imply the maximal bone density and suppression of PTH occurs, and above which calcium absorption is raised [9, 67, 68]. Although PTH serum levels diminish as vitamin D increases, particularly in the elderly, the exact relationship between the two hormones is rather intricate [69, 70]. Some individuals, after sustaining a fracture of the hip, exhibit both low 25(OH) vitamin D and PTH concentrations [71]. Others, particularly post-menopausal women,

retain normal PTH levels in the face of low 25(OH) vitamin D levels [72, 73]. As many as 74 % of those surveyed had normal serum PTH concentrations (8–73 pg/ml) despite 25(OH) vitamin D levels below 20 ng/ml. Other individuals, often female or elderly, termed "vitamin D resistant", maintain high PTH levels despite sufficient vitamin D levels [74–78]. Markers of bone turnover, N-telopeptides, reach their nadir when serum vitamin D concentrations rise above 20 ng/ml, while PTH achieves its lowest concentration when 25(OH) vitamin D concentrations rise above 50 ng/ml [79]. Post-fracture patients with a high vitamin D/PTH ratio achieve better functional outcomes [80]. Racial variation can also occur; caucasians have higher vitamin D/PTH ratios than do blacks [81]. Increased adiposity and worse mobility correlate with a lower ratio [72, 73, 82], and greater intake of vitamin D augments the vitamin D/PTH ratio, particularly in the elderly [83].

While few studies have investigated the relationship between vitamin D and calcium, maximum calcium absorption occurs when vitamin D serum concentrations exceed 32/ng/ml [67]. One study concluded that there was no relationship with calcium absorption and 25(OH) vitamin D levels, but the absorption did correlate with serum 1,25 dihydoxy-vitamin D (calcitriol) concentration [84].

Based on this evidence, and the results of patient investigations in which vitamin D reduced the probability of fractures, falls, improved balance, and epidemiologic investigations about the association between vitamin D and multiple health problems, both an Endocrine Society task force and a panel of international vitamin D experts recommended that people should maintain target vitamin D concentrations of at least 30 ng/ml [63, 85].

The Institute of Medicine published has recommended target serum concentrations of 25(OH) vitamin D of at least 20 ng/ml, but not more [86] because they chose to limit the evidence upon which they based their conclusion to those randomized, prospective controlled trials of vitamin D which utilized supplementation to reduce the incidences of falls and fractures. However, 25(OH) vitamin D levels as high as 36 ng/ml correlated with increased bone mineral densities in older persons [87]. Furthermore, a survey of autopsy-derived bone biopsies noted impaired mineralization of the bone in cadavers at vitamin D levels below 30 ng/ml [88].

Regardless of the precise serum concentration constitutes, inadequate vitamin D status appears to be a serious problem worldwide. Significant numbers of individuals of all age groups (5–93 %) remain vitamin D insufficient even by the Institute of Medicine criterion [89]. An important correlate of the widespread nature of vitamin D insufficiency is its direct relationship to mortality. Several investigations demonstrate that lower mortality occurs in populations with higher serum vitamin D concentrations. A meta-analysis of 57,311 concluded that the risk of death declined with vitamin D supplementation (O.R. 0.93 [95 % C.I. 0.87–0.99]) [90]. A second meta-analysis of 32,142 people reported a reduced mortality risk for an 8 ng/ml higher vitamin D concentration of 0.92 (95 % C.I. 0.89–0.95) [91]. A Cochrane systematic review of studies of 94,148 subjects further noted that vitamin D supplementation reduced mortality (relative risk 0.97 95 % [0.94–1.00]) [92].

Furthermore, a direct relationship exists between vitamin D and mortality in very old individuals. Among 12,203 Australian men at least age 65 who took part in a screening trial for almost 10 years, vitamin D insufficiency correlated with total mortality (O.R. 1.20, 95 % CI 1.02–1.42) [93]. Interestingly, both the lowest and highest quartiles of vitamin D concentration in 775 English women were associated with greater mortality [94].

An important question regarding this relationship is whether lack of vitamin D is a cause of greater mortality, or, alternatively that a higher burden of medical comorbidities ultimately leading to death results in a lower serum vitamin D concentration, perhaps as a manifestation of reduced ingestion or a lack of sunlight exposure. Some investigators interpret the failure of vitamin D supplementation to prevent certain chronic diseases together with the aforementioned inverse relationship between vitamin D levels and

mortality to imply the latter [95, 96]. Other studies suggest that whether supplementation prevents a given disease should not be taken as biologic evidence of repletion of a micronutrient at the cellular level [97], that the doses of vitamin D utilized in such trials may have been too low [98], that the methodology of the trials insufficient to draw the conclusion [99], and that studies are of too short duration to conclude that vitamin D impacted the development of chronic diseases [98, 100].

Vitamin D may improve physical performance and prevent frailty. In 860 individuals all above age 55, increasing serum 25(OH) vitamin D concentrations correlated with better Short Physical Performance Battery Scores (0.61 units, 95 % C.I., $p<0.001$ 0.35–0.61) [101]. A daily supplement of 4000 IU in 21 older individuals over age 65 for 120 days increased intramyonuclear VDR concentration by 30 % and augmented muscle fiber size by 10 % [102]. In a study of vitamin D and mortality, men with lower vitamin D serum concentrations were more likely to be frail at the start of the study (odds ratio, 1.96; 95 % confidence interval [CI], 1.52–2.52), and more likely to develop frailty if none existed at baseline (O.R. 1.56, 95 % CI 1.07–2.27) [93]. Very importantly, irrespective of frailty, low vitamin D levels were predictive of all-cause mortality (hazard ratio, 1.20; 95 % CI, 1.02–1.42).

Supplementation in individuals with insufficient or deficient 25(OH) vitamin D serum concentrations might ultimately prevent or treat individual pathologic conditions. But given the complex pathophysiology of all of these conditions, supplementation may need to be offered closer to the onset of the process rather than years after the process has started. Furthermore, it may be unreasonable to expect this steroid hormone to eradicate intricate and longstanding pathology.

In order to measure the impact of vitamin D on health, using the correct technique and target is an important consideration. The effect of vitamin D binding protein (VDBP) may influence serum vitamin D concentrations. Most serum 25(OH) vitamin D is bound to VDBP. Although VDBP levels generally do not vary among individuals in good health, disease, ethnicity, and genetic factors influence VDBP concentrations and binding capacity [103, 104]. For example, blacks have both lower mean serum 25(OH) vitamin D and VDBP concentrations than whites [105]. VDBP may also impact local cellular hydroxylation of 25(OH) vitamin D to its active form [106]. Johnsen et al. found that serum free and bio-available 25(OH) vitamin D exhibited a better correlation with bone mineral density in 265 post-menopausal women than did total 25(OH) vitamin D [107]. On the other hand, in 2073 "healthy" adults ranging in age from 16 to 98 years (mean 65.7), serum PTH appeared to be independent of VDBP [108]. Of note the mean 25(OH) vitamin D concentration was 27.58 ± 9.88 ng/ml, and "healthy" was not defined. Consequently more studies are needed to refine the relationships between 25(OH) vitamin D, PTY, and VDBP – particularly in various populations.

Given the potential of vitamin D to preserve health, in the face of remaining uncertainties regarding the effect of supplementation on individual morbidities, the evidence about supplementation inspires much debate. The potential advantages to supplementation continue to be numerous. Firstly, vitamin D prevents fractures. One decade ago, a meta-analysis of trials involving 5572 participants established that supplementation of as little as 700–800 IU daily reduced the incidence of fractures by 26 % [52]. In addition, as has been mentioned, there is at least evidence of an association between higher serum vitamin D concentrations and mortality. Furthermore, several studies have suggested that higher vitamin D levels may be protective against colon cancer, metabolic syndrome, and possibly prostate cancer and diabetes [109–113].

Others have interpreted the evidence differently. One meta-analysis concluded that, for multiple individual health outcomes, only the combination of vitamin D and calcium supplementation in prospective trials for the prevention of multiple individual health outcomes reached the 15 % improvement threshold the authors set for significance and only to avert fractures in institutionalized patients [96]. Some experts have criticized the methodology of the meta-analysis,

noting that it incorporated trials of low medication adherence, blinded and unblinded subjects, short duration, and that the 15 % threshold was too stringent [98, 99].

They further suggest that, given supplementation is inexpensive, has a high threshold for toxicity, and the outcomes reflect a long-term complex pathophysiology, the correct interpretation of the results of the trials is not that supplementation in unnecessary, but ought to be initiated earlier in life and maintained for a long duration to prevent important adverse health outcomes [98, 99, 114].

If one would assume that treating insufficiency is warranted, an important related issue is whether one should screen populations for insufficiency. A recent systematic review by the US Preventative Task Force maintained that there is not enough evidence yet to determine whether asymptomatic people should be screened, based on the lack of studies comparing both screened and unscreened populations, and, more controversially, on its conclusion that treatment has only proven benefit in institutionalized patients in preventing falls [115, 116]. This analysis has been criticized for its reliance on studies with low doses of vitamin D supplementation [97]. Another potential rationale against screening that might be made by advocates for vitamin D repletion is that it might be more cost-effective just to treat rather than screen. Although, as has been mentioned, there are no published trials comparing populations to determine whether treatment without screening is more cost effective, cost-benefit analyses might be performed to suggest which alternative would be optimal.

Several current trials may confirm the benefit of supplementation of higher doses of vitamin D on human health. In the VITAL-Bone health trial, the effect of 2000 IU over 25,000 elderly participants receive a combination of vitamin D and omega A-3 fatty acids, and their impact on fractures will be analyzed [117] In addition, the VIVA study is exploring the effect of 4000 IU a day on the physical performance of elderly veterans, as measured by the Short Physical Performance Battery [118]. Finally, the VDOP study will ascertain the impact of three different doses of vitamin D (12,000 IU, 24,000 IU. and 48,000 IU monthly) on 375 individuals at least age 70 for 1 year on bone mineral density (the impact of vitamin D on which has thus far yielded positive but controversial results) [119–121], serum 25(OH) vitamin D, PTH, falls, and fractures [122].

Parathyroid Hormone

PTH is an eighty-four amino acid polypeptide that maintains normal extracellular calcium through its action on the bone, kidney and the intestines (Fig. 3.4). PTH is released from the parathyroid gland in response to insufficient calcium and estrogens, and its release is suppressed by vitamin D and phosphate loss [1]. Its action on bone is complex. PTH acts on osteoblasts to modulate the expression of a variety of growth factors, including IGF-1, TGF-ß1 and TGF-ß2, as well as IL-6 [123, 124]. Persistent elevation of PTH stimulates osteoclast formation, in part via enhancing the expression of RANK ligand by osteoblasts, which plays a critical role in the differentiation and activation of osteoclasts [125]. This, in turn, leads to osteoclastic bone resorption, and the release of calcium from the skeleton [126]. Historically, parathyroid hormone has long been conceived of as a catabolic agent that contributes to bone destruction and loss of bone mineral density. However, the normal physiologic role of PTH depends upon its intermittent secretion and subsequent action as an anabolic agent [126]. As long ago as 1980, Reeve et al. reported that intermittent injection of exogenous PTH in humans stimulated significant new bone formation [127]. Daily subcutaneous injection of PTH increases lumbar spinal and femoral bone mineral density both in postmenopausal women and in men with osteoporosis [128, 129]. PTH reduces vertebral and nonvertebral fractures in post-menopausal women [128]. PTH treatment can also reverse the loss of bone in glucocorticoid-induced osteoporosis in postmenopausal women [130]. Unlike anti-resorptive therapies such as estrogen, raloxifene, bisphosphonates, and calcitonin that inhibit bone resorption, PTH

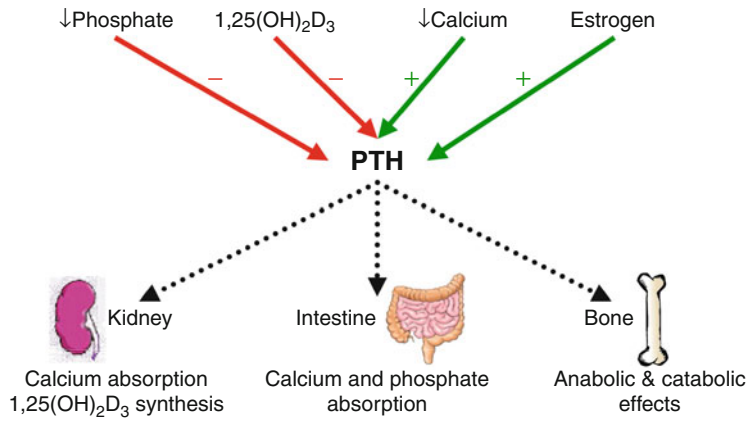


Fig. 3.4 Parathyroid hormone (Adapted from Ramasamy [1])

stimulates new bone formation. PTH enhances bone quality and bone strength by increasing trabecular connectivity [131] and the cross sectional area of the bone [132]. Furthermore, PTH stimulates deposition of bone in appropriate locations in the skeleton, on those surfaces that are subject to mechanical forces [133]. Therefore, new bone is formed where it is needed. PTH has multiple actions on the kidney. It causes retention of calcium by the cortical thick ascending limbs, distal convoluted collecting and connecting tubules. PTH also stimulates the 1α hydroxylation of vitamin D, and excretion of phosphate [1]. In addition, PTH stimulates DNA synthesis in intestinal enterocytes and increases the influx of calcium.

The relationship between PTH and vitamin D is important in the pathogenesis of HVO, but complex. Numerous studies imply that individuals who have lower vitamin D levels have higher PTH levels [20, 23, 78, 134, 135]. With progressive increase in 25(OH) vitamin D levels, there appears to be a plateau in the suppression of PTH that occurs at approximately 30–36 ng/ml 25(OH) vitamin D [20, 23, 135–137]. This suggests that vitamin D is physiologically replete at these levels and above. However Vieth et al. observed no plateau as 25(OH) vitamin D levels increased [78]. Kudlacek et al. found that 25(OH) vitamin D levels were inversely correlated with PTH levels and that PTH levels exhibited a significant age-related increase [27]. For any given level of 25(OH) vitamin D, older subjects exhibit greater levels of PTH [76]. Older adults require 25(OH) vitamin D levels of greater than 40 ng/ml to suppress PTH to the same degree observed in younger subjects with 25(OH) vitamin D levels near 28 ng/ml [78]. Other causes of secondary hyperparathyroidism include declining renal function, estrogen deficiency, and low calcium intake [138].

Sahota et al. found that only half of hip fracture patients with a 25(OH) vitamin D level < 12 ng/ml exhibited secondary hyperparathyroidism [139]. They characterized the remaining hypovitaminotic D patients with low or normal PTH levels as having "functional hypoparathyroidism", and these individuals had greater hip bone mineral density and fewer extracapsular fractures than did those with elevated PTH levels. In a second group of subjects with established vertebral osteoporosis, Sahota et al. found that of the 39 % with 25(OH) vitamin D levels ≤ 12 ng/ml, that only one-third exhibited secondary hyperparathyroidism [69]. The two-thirds of the vitamin D insufficient/deficient patients who did not have an elevated PTH had a lower mean serum calcium and reduced bone turnover than those with elevated PTH levels. Deplas et al. found that less than one-third of hypovitaminotic D patients exhibited secondary hyperparathyroidism [77], and in two additional investigations less than half the patients who had both fractured their hip and were hypovitaminotic D had an elevated PTH [140, 141]. In these subjects, PTH level did not inversely correlate with vitamin D level. Consequently, the feedback sensitivity of the vitamin D-PTH axis appears to be reduced with aging and/or disease. It is possible

that a concomitant magnesium deficiency plays a role in altering the response of PTH to hypovitaminosis D [142]. It is unclear what the implications are for these two distinct populations of elderly patients with vitamin D deficiency (high and low PTH) are for the pathogenesis of osteoporosis and its treatment.

These data suggest that caution may need to be exercised in using PTH as an indicator of vitamin D status, because the PTH response to hypovitaminosis and possibly even frank vitamin D deficiency may vary. Do these data mean that PTH is not a useful indicator of vitamin D status? No. It is widely accepted that PTH levels are, in general, inversely correlated with 25 OH-vitamin D levels. Instead, it may be prudent to assess the suppression in PTH in response to vitamin D supplementation by measuring both the pre- and post-treatment levels. However, controversy exists on the utility of measuring PTH to determine vitamin D repletion. Heaney strongly asserts that decreasing PTH levels will plateau when 25 (OH) vitamin D levels begin to reach a physiologically optimal value [143], whereas Vieth argues that PTH levels continue to decline as 25 (OH) vitamin D levels increase [144].

Calcium intake also influences the relationship between PTH and vitamin D at lower vitamin D levels. A study 2310 healthy individual from Iceland observed that at very low serum 25(OH) vitamin D levels (<10 ng/ml), persons with lower calcium intakes had higher PTH levels [145]. However at higher vitamin D levels, calcium intake did not significantly influence PTH. The action of PTH may exhibit gender-related differences. Both men and women experience age-related increases in PTH. However there is evidence that the bones of elderly women are more sensitive to resorption caused PTH than younger women. When elderly women receive an infusion of calcium, which suppresses their PTH there is a greater increase in markers of bone turnover (urine n-telopeptide) than in younger women [146]. When calcium infusions are given to men, there is no difference in the response of the bones of younger and older men to the suppression of PTH [147]. These differences may be explained by the difference in sex steroid levels between men and women [147]. Nevertheless, after controlling for age, Blain et al. still found that an increased level of PTH was most important predictor of bone loss in men [148].

Calcitonin

The C cells of the thyroid manufacture and release calcitonin, which has multiple effects on body calcium [1]. Calcitonin is secreted when serum calcium is high, and suppressed when calcium is diminished [149] Calcitonin may have actions on other systems such as the reproductive, central nervous, renal, respiratory, and gastrointestinal system, but not all its actions are known [1, 149]. Calcitonin prevents bone resorption, and can be stimulated by PTH. It inhibits osteoclast action and can cause apoptosis [150]. Half of all thyroidectomized men developed osteopenia in one study, and they exhibited lower serum calcium and higher PTH levels than control subjects [151]. However, the physiologic role of calcitonin is uncertain. There are no known pathologic states in humans that result from surplus or deficient calcitonin [150]. Recent data strongly implicate calcitonin in maintaining bone integrity during excessive resorption during lactation [152]. However, with that exception, calcitonin does not appear to significantly contribute to normal skeletal homeostasis or pathophysiology.

Summary/Conclusion

What is the best marker to assess adequate vitamin D supplementation? Thus far, studies have used 25(OH) vitamin D and PTH. Is there a single marker or should several be assessed? Should vitamin D binding protein concentrations and bioavailable 25(OH) vitamin D be routinely measured? Might other outcomes be needed? Potentially, these might include evaluation of handgrip, hip or leg strength, mobility and balance tests, or quality of life instruments. Further investigation will determine what other markers might prove sensitive, specific, and cost-effective. Many

important questions remain to be answered about the role of vitamin D in the preservation of health for the elderly. What should be optimum recommended daily and maximum recommended vitamin D intake for elderly individuals? Despite the report by the Institute of Medicine, we believe that on average the recommended daily intakes of vitamin D for the elderly are far too low, and that all older individuals should take as much vitamin D as needed to raise levels to between 32 and 40 ng/ml [3, 109, 153, 154]. Moreover, supplementation will be necessary, since diet and sunlight alone are inadequate sources of vitamin D [9].

How much vitamin D (cholecalciferol) should be taken? The present Food and Drug Administration recommended daily intake of vitamin D is 400 IU for those age 51–70 and 600 IU for those over age 70, whereas the National Osteoporosis Foundation recommends between 400 and 800 IU per day. However, increasing evidence supports the necessity for daily doses significantly above these levels to achieve levels of vitamin D of 30 ng/ml and higher [154]. Cholecalciferol 100,000 IU orally every 4 months significantly reduced fractures [47]. A once-yearly intramuscular injection of 600,000 IU of cholecalciferol increased 25(OH) vitamin D levels to greater than 50 nmol/l in all subjects, raised average levels to 73 nmol/l after 12 months, normalized PTH levels in two-thirds of those with secondary hyperparathyroidism, and was well tolerated with only mild hypercalcemia in 4 % of recipients [155]. Cholecalciferol supplementation is generally very safe and without toxicity in the absence of primary hyperparathyroidism, even with as much as 10,000 IU per day [156]. There are no adverse effects with concentrations of 25(OH) vitamin D less than 56 ng/ml [156], and there is evidence that increasing levels of 25 (OH) vitamin D up to 48 ng/ml is correlated with increased bone mineral density in both non-Hispanic whites and in Mexican-Americans [35]. Furthermore, it is possible that vitamin D repletion is necessary for optimal anti-resorptive therapy, as several reports have found poorer responses to bisphosphonates in postmenopausal women with vitamin D insufficiency [157–159], although one study found that vitamin D status did not affect the bone mineral density response to alendronate if administered concurrently with cholecalciferol and calcium [160]. As much as 2600 IU per day of vitamin D may be necessary to insure that the 97% of the population is vitamin D replete [21], and more may be needed in the elderly. Indeed two reports in the frail elderly show that doses of 1500–5000 IU per day of cholecalciferol are needed and can be administered without danger of hypercalcemia [161, 162]. The key in the frail elderly is to monitor the response to supplementation by obtaining 25(OH) vitamin D levels every 3–4 months.

Since the incidence of osteoporosis differs by gender, age, or race, future studies are needed to more clearly establish the best diagnostic and supplementation approaches to hypovitaminosis D for different populations. In the meantime, a heightened awareness of the widely prevalent vitamin D insufficiency will permit us to more actively intervene and to raise and maintain 25(OH) vitamin D levels to a minimum of 30 ng/ml.

References

1. Ramasamy I. Recent advances in physiological calcium homeostasis. Clin Chem Lab Med. 2006;44:237–73.
2. Lips P. Vitamin D physiology. Prog Biophys Mol Biol. 2006;92:4–8.
3. Holick MF. The vitamin d epidemic and its health consequences. J Nutr. 2005;135:2739S–48.
4. Nordin BE, Need AG, Morris HA, O'Loughlin PD, Horowitz M. Effect of age on calcium absorption in postmenopausal women. Am J Clin Nutr. 2004;80:998–1002.
5. Dusso AS, Brown AJ, Slatopolsky E. Vitamin D. Am J Physiol Renal Physiol. 2005;289:F8–28.
6. Troen BR. The role of cathepsin K in normal bone resorption. Drug News Perspect. 2004;17:19–28.
7. Anderson PH, O'Loughlin PD, May BK, Morris HA. Determinants of circulating 1,25-dihydroxyvitamin D3 levels: the role of renal synthesis and catabolism of vitamin D. J Steroid Biochem Mol Biol. 2004;89–90:111–3.
8. Holick MF. Resurrection of vitamin D deficiency and rickets. J Clin Invest. 2006;116:2062–72.
9. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr. 2005;135:317–22.

10. Matsuoka LY, Wortsman J, Hollis BW. Use of topical sunscreen for the evaluation of regional synthesis of vitamin D3. J Am Acad Dermatol. 1990;22:772–5.
11. Clemens TL, Adams JS, Henderson SL, Holick MF. Increased skin pigment reduces the capacity of skin to synthesise vitamin D3. Lancet. 1982;1:74–6.
12. Matsuoka LY, Wortsman J, Haddad JG, Kolm P, Hollis BW. Racial pigmentation and the cutaneous synthesis of vitamin D. Arch Dermatol. 1991;127:536–8.
13. MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D3. J Clin Invest. 1985;76:1536–8.
14. Grieger A, Nowson CA. Nutrient intake and plate waste from an Australian residential care facility. Eur J Clin Nutr. 2006;61:655–63.
15. Dumartheray EW, et al. Energy and nutrient intake of Swiss women aged 75–87 years. J Hum Nutr Diet. 2006;19:431–5.
16. Avioli LV. Postmenopausal osteoporosis: prevention versus cure. Fed Proc. 1981;40:2418–22.
17. Gennari C. Calcium and vitamin D nutrition and bone disease of the elderly. Public Health Nutr. 2001;4:547–59.
18. Shahar D, Shai I, Vardi H, Fraser D. Factors associated with low reported energy intake in the elderly. J Nutr Health Aging. 2005;9:300–4.
19. French MR, Moore K, Vernace-Inserra F, Hawker GA. Factors that influence adherence to calcium recommendations. Can J Diet Pract Res. 2005;66:25–9.
20. Holick MF, Siris ES, Binkley N, Beard MK, Khan A, Katzer JT, et al. Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. J Clin Endocrinol Metab. 2005;90:3215–24.
21. Heaney RP. The vitamin D requirement in health and disease. J Steroid Biochem Mol Biol. 2005;97:13–9.
22. Harinarayan CV. Prevalence of vitamin D insufficiency in postmenopausal south Indian women. Osteoporos Int. 2005;16:397–402.
23. Chapuy MC, Preziosi P, Maamer M, Arnaud S, Galan P, Hercberg S, et al. Prevalence of vitamin D insufficiency in an adult normal population. Osteoporos Int. 1997;7:439–43.
24. Vecino-Vecino C, Gratton M, Kremer R, Rodriguez-Manas L, Duque G. Seasonal variance in serum levels of vitamin d determines a compensatory response by parathyroid hormone: study in an ambulatory elderly population in Quebec. Gerontology. 2006;52:33–9.
25. Nakamura K, Nishiwaki T, Ueno K, Yamamoto M. Serum 25-hydroxyvitamin D levels and activities of daily living in noninstitutionalized elderly Japanese requiring care. J Bone Miner Metab. 2005;23:488–94.
26. Levis S, Gomez A, Jimenez C, Veras L, Ma F, Lai S, et al. Vitamin d deficiency and seasonal variation in an adult South Florida population. J Clin Endocrinol Metab. 2005;90:1557–62.
27. Kudlacek S, Schneider B, Peterlik M, Leb G, Klaushofer K, Weber K, et al. Assessment of vitamin D and calcium status in healthy adult Austrians. Eur J Clin Invest. 2003;33:323–31.
28. Meier C, Woitge HW, Witte K, Lemmer B, Seibel MJ. Supplementation with oral vitamin D3 and calcium during winter prevents seasonal bone loss: a randomized controlled open-label prospective trial. J Bone Miner Res. 2004;19:1221–30.
29. Dawodu A, Absood G, Patel M, Agarwal M, Ezimokhai M, Abdulrazzaq Y, et al. Biosocial factors affecting vitamin D status of women of childbearing age in the United Arab Emirates. J Biosoc Sci. 1998;30:431–7.
30. Dawodu A, Dawson KP, Amirlak I, Kochiyil J, Agarwal M, Badrinath P. Diet, clothing, sunshine exposure and micronutrient status of Arab infants and young children. Ann Trop Paediatr. 2001;21:39–44.
31. Gannage-Yared MH, Chemali R, Yaacoub N, Halaby G. Hypovitaminosis D in a sunny country: relation to lifestyle and bone markers. J Bone Miner Res. 2000;15:1856–62.
32. Guzel R, Kozanoglu E, Guler-Uysal F, Soyupak S, Sarpel T. Vitamin D status and bone mineral density of veiled and unveiled Turkish women. J Womens Health Gend Based Med. 2001;10:765–70.
33. Islam MZ, Akhtaruzzaman M, Lamberg-Allardt C. Hypovitaminosis D is common in both veiled and nonveiled Bangladeshi women. Asia Pac J Clin Nutr. 2006;15:81–7.
34. Harris SS. Vitamin D and African Americans. J Nutr. 2006;136:1126–9.
35. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Dawson-Hughes B. Positive association between 25-hydroxy vitamin D levels and bone mineral density: a population-based study of younger and older adults. Am J Med. 2004;116:634–9.
36. Dawson-Hughes B. Racial/ethnic considerations in making recommendations for vitamin D for adult and elderly men and women. Am J Clin Nutr. 2004;80:1763S–6.
37. Aloia JF, Talwar SA, Pollack S, Yeh J. A randomized controlled trial of vitamin D3 supplementation in African American women. Arch Intern Med. 2005;165:1618–23.
38. Parfitt AM. Osteomalacia and related disorders. In: Avioli LV, Krane SM, editors. Metabolic bone disease and clinical related disorders. 2nd ed. Philadelphia: WB Saunders; 1990. p. 329–96.
39. Heaney RP. Lessons for nutritional science from vitamin D. Am J Clin Nutr. 1999;69:825–6.
40. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, et al. Effect of vitamin D on falls: a meta-analysis. JAMA. 2004;291:1999–2006.
41. Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents severe falls in elderly community-dwelling women: a pragmatic population-based 3-year intervention study. Aging Clin Exp Res. 2005;17:125–32.

42. Wilkins CH, Birge SJ. Prevention of osteoporotic fractures in the elderly. Am J Med. 2005;118:1190–5.
43. Bischoff-Ferrari HA, Borchers M, Gudat F, Durmuller U, Stahelin HB, Dick W. Vitamin D receptor expression in human muscle tissue decreases with age. J Bone Miner Res. 2004;19:265–9.
44. Kitazawa R, Kitazawa S. Vitamin D(3) augments osteoclastogenesis via vitamin D-responsive element of mouse RANKL gene promoter. Biochem Biophys Res Commun. 2002;290:650–5.
45. Liang CT, Barnes J, Imanaka S, DeLuca HF. Alterations in mRNA expression of duodenal 1,25-dihydroxyvitamin D3 receptor and vitamin D-dependent calcium binding protein in aged Wistar rats. Exp Gerontol. 1994;29:179–86.
46. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med. 1997;337:670–6.
47. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ. 2003;326:469.
48. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. N Engl J Med. 1992;327:1637–42.
49. Chapuy MC, Pamphile R, Paris E, Kempf C, Schlichting M, Arnaud S, et al. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. Osteoporos Int. 2002;13:257–64.
50. Porthouse J, Cockayne S, King C, Saxon L, Steele E, Aspray T, et al. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. BMJ. 2005;330:1003.
51. Grant AM, Avenell A, Campbell MK, McDonald AM, MacLennan GS, McPherson GC, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. Lancet. 2005; 365:1621–8.
52. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA. 2005;293:2257–64.
53. Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006;354:669–83.
54. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Hu FB, Zhang Y, Karlson EW, et al. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or =60 y. Am J Clin Nutr. 2004;80:752–8.
55. Flicker L, MacInnis RJ, Stein MS, Scherer SC, Mead KE, Nowson CA, et al. Should older people in residential care receive vitamin D to prevent falls? results of a randomized trial. J Am Geriatr Soc. 2005;53:1881–8.
56. Dhesi JK, Jackson SH, Bearne LM, Moniz C, Hurley MV, Swift CG, et al. Vitamin D supplementation improves neuromuscular function in older people who fall. Age Ageing. 2004;33:589–95.
57. Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. Osteoporosis Int 2009;20(2):315–22.
58. Wickerts IS, van Schoor NM, Boeke AJP, Visser M, Deeg DJ, Smit J, Knol DL, Lips P. Vitamin D status predicts physical performance and its decline in older persons. JCEM. 2007;92(6):2058–65.
59. Kenny AM, Biskup B, Robbins B, Marcella G, Burleson JA. Effects of vitamin D supplementation on strength, physical function, and health perception in older, community-dwelling men. J Am Geriatr Soc. 2003;51:1762–7.
60. Latham NK, Anderson CS, Lee A, Bennett DA, Moseley A, Cameron ID. A randomized, controlled trial of quadriceps resistance exercise and vitamin D in frail older people: the Frailty Interventions Trial in Elderly Subjects (FITNESS). J Am Geriatr Soc. 2003;51:291–9.
61. Law M, Withers H, Morris J, Anderson F. Vitamin D supplementation and the prevention of fractures and falls: results of a randomised trial in elderly people in residential accommodation. Age Ageing. 2006; 35:482–6.
62. Judge JO, Kenny A. Vitamin D and quadriceps exercise--got milk? Got a chair? J Am Geriatr Soc. 2003;51:427–8.
63. Souberbielle JC, Body JJ, Lappe JM, Plebani M, Shoenfeld Y, Wang TJ, et al. Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: recommendations for clinical practice. Autoimmun Rev. 2010;9:709–15.
64. Cherniack EP, Florez H, Roos BA, Troen BR, Levis S. Hypovitaminosis D in the elderly: from bone to brain. J Nutr Health Aging. 2008;12:366–73.
65. Cherniack EP, Levis S, Troen BR. Hypovitaminosis D: a widespread epidemic. Geriatrics. 2008;63:24–30.
66. Bischoff-Ferrari HA. The 25-hydroxyvitamin D threshold for better health. J Steroid Biochem Mol Biol. 2007;103:614–9.
67. Heaney RP. The case for improving vitamin D status. J Steroid Biochem Mol Biol. 2007;103:635–41.
68. Hollis BW, Wagner CL, Drezner MK, Binkley NC. Circulating vitamin D3 and 25-hydroxyvitamin D in humans: an important tool to define adequate nutritional vitamin D status. J Steroid Biochem Mol Biol. 2007;103:631–4.
69. Sahota O, Mundey MK, San P, Godber IM, Lawson N, Hosking DJ. The relationship between vitamin D

and parathyroid hormone: calcium homeostasis, bone turnover, and bone mineral density in postmenopausal women with established osteoporosis. Bone. 2004;35:312–9.
70. Sahota O, Masud T, San P, Hosking DJ. Vitamin D insufficiency increases bone turnover markers and enhances bone loss at the hip in patients with established vertebral osteoporosis. Clin Endocrinol (Oxf). 1999;51:217–21.
71. Fisher A, Goh S, Srikusalanukul W, Davis M. Elevated serum PTH is independently associated with poor outcomes in older patients with hip fracture and vitamin D inadequacy. Calcif Tissue Int. 2009;85:301–9.
72. Snijder MB, van Dam RM, Visser M, Deeg DJ, Dekker JM, Bouter LM, et al. Adiposity in relation to vitamin D status and parathyroid hormone levels: a population-based study in older men and women. J Clin Endocrinol Metab. 2005;90:4119–23.
73. Bjorkman MP, Sorva AJ, Risteli J, Tilvis RS. Low parathyroid hormone levels in bedridden geriatric patients with vitamin D deficiency. J Am Geriatr Soc. 2009;57:1045–50.
74. Souberbielle JC, Maury E, Friedlander G, Cormier C. Vitamin D and primary hyperparathyroidism (PHPT). J Steroid Biochem Mol Biol. 2010;121: 199–203.
75. Birge SJ. Can falls and hip fracture be prevented in frail older adults? J Am Geriatr Soc. 1999;47: 1265–6.
76. Maggio D, Cherubini A, Lauretani F, Russo RC, Bartali B, Pierandrei M, et al. 25(OH)D Serum levels decline with age earlier in women than in men and less efficiently prevent compensatory hyperparathyroidism in older adults. J Gerontol A Biol Sci Med Sci. 2005;60:1414–9.
77. Deplas A, Debiais F, Alcalay M, Bontoux D, Thomas P. Bone density, parathyroid hormone, calcium and vitamin D nutritional status of institutionalized elderly subjects. J Nutr Health Aging. 2004;8: 400–4.
78. Vieth R, Ladak Y, Walfish PG. Age-related changes in the 25-hydroxyvitamin D versus parathyroid hormone relationship suggest a different reason why older adults require more vitamin D. J Clin Endocrinol Metab. 2003;88:185–91.
79. Sai AJ, Walters RW, Fang X, Gallagher JC. Relationship between vitamin D, parathyroid hormone, and bone health. J Clin Endocrinol Metab. 2010;96(3):E436–46.
80. Di Monaco M, Vallero F, Di Monaco R, Tappero R, Cavanna A. 25-hydroxyvitamin D, parathyroid hormone, and functional recovery after hip fracture in elderly patients. J Bone Miner Metab. 2006; 24:42–7.
81. Aloia JF, Chen DG, Chen H. The 25(OH)D/PTH threshold in black women. J Clin Endocrinol Metab. 2010;95:5069–73.
82. Valina-Toth AL, Lai Z, Yoo W, Abou-Samra A, Gadegbeku CA, Flack JM. Relationship of vitamin D and parathyroid hormone with obesity and body composition in African Americans. Clin Endocrinol (Oxf). 2010;72:595–603.
83. Florez HJ, Cherniack EP, Gómez-Marín O, Roos BA, Levis S, Troen BR. Age modifies the impact of vitamin D3 supplementation on the 25-OH vitamin D/ parathyroid hormone ratio. J Bone Miner Res. 2007;22:S208.
84. Sato T, Yamamoto H, Sawada N, Nashiki K, Tsuji M, Nikawa T, et al. Immobilization decreases duodenal calcium absorption through a 1,25-dihydroxyvitamin D-dependent pathway. J Bone Miner Metab. 2006;24:291–9.
85. Holick MF, Binkley NC, Bischoff-Ferrar HA, Gordon CM, Hanley DA, Murad MH, Weaver CM. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011; 96:1911–30.
86. Ross AC, Taylor CL, Yaktine AL, Del Valle HB. Dietary reference intakes for calcium and vitamin D. Washington, DC: Institute of Medicine of the National Academies; 2010.
87. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr. 2006;84:18–28.
88. Priemel M, von Domarus C, Klatte TO, Kessler S, Schlie J, Meier S, et al. Bone mineralization defects and vitamin D deficiency: histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. J Bone Miner Res. 2010;25:305–12.
89. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? J Steroid Biochem Mol Biol. 2014;144(Pt A):138–45.
90. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. Arch Intern Med. 2007;167:1730–7.
91. Schottker B, Ball D, Gellert C, Brenner H. Serum 25-hydroxyvitamin D levels and overall mortality. A systematic review and meta-analysis of prospective cohort studies. Ageing Res Rev. 2012;12:708–18.
92. Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, et al. Vitamin D supplementation for prevention of mortality in adults. Cochrane Database Syst Rev. 2011;(1):CD007470.
93. Wong YY, McCaul KA, Yeap BB, Hankey GJ, Flicker L. Low vitamin D status is an independent predictor of increased frailty and all-cause mortality in older men: the health in men study. J Clin Endocrinol Metab. 2013;98:3821–8.
94. Granic A, Aspray T, Hill T, Davies K, Collerton J, Martin-Ruiz C, et al. 25-hydroxyvitamin D and increased all-cause mortality in very old women: the Newcastle 85+ study. J Intern Med. 2014;277:456–67.
95. Autier P, Boniol M, Pizot C, Mullie P. Vitamin D status and ill health: a systematic review. Lancet Diabetes Endocrinol. 2014;2:76–89.

96. Bolland MJ, Grey A, Gamble GD, Reid IR. The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta-analysis. Lancet Diabetes Endocrinol. 2014;2:307–20.
97. Heaney RP, Armas LA. Screening for vitamin d deficiency: is the goal disease prevention or full nutrient repletion? Ann Intern Med. 2015;162:144–5.
98. Anagnostis P, Karras SN, Athyros VG, Annweiler C, Karagiannis A. The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes. Lancet Diabetes Endocrinol. 2014;2:362–3.
99. Bischoff-Ferrari HA, Orav EJ, Willett WC, Dawson-Hughes B. The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes. Lancet Diabetes Endocrinol. 2014;2:363–4.
100. Giovannucci E. Vitamin D status and ill health. Lancet Diabetes Endocrinol. 2014;2:273.
101. Shardell M, Semba RD, Kalyani RR, Hicks GE, Bandinelli S, Ferrucci L. Serum 25-hydroxyvitamin D, plasma klotho, and lower-extremity physical performance among older adults: findings from the InCHIANTI study. J Gerontol A Biol Sci Med Sci. 2015;70:1156–62.
102. Ceglia L, Niramitmahapanya S, da Silva Morais M, Rivas DA, Harris SS, Bischoff-Ferrari H, et al. A randomized study on the effect of vitamin D(3) supplementation on skeletal muscle morphology and vitamin D receptor concentration in older women. J Clin Endocrinol Metab. 2013;98:E1927–35.
103. Yousefzadeh P, Shapses SA, Wang X. Vitamin D binding protein impact on 25-hydroxyvitamin D levels under different physiologic and pathologic conditions. Int J Endocrinol. 2014;2014:981581.
104. Bhan I. Vitamin d binding protein and bone health. Int J Endocrinol. 2014;2014:561214.
105. Powe CE, Evans MK, Wenger J, Zonderman AB, Berg AH, Nalls M, et al. Vitamin D-binding protein and vitamin D status of black Americans and white Americans. N Engl J Med. 2013;369:1991–2000.
106. Chun RF, Peercy BE, Orwoll ES, Nielson CM, Adams JS, Hewison M. Vitamin D and DBP: the free hormone hypothesis revisited. J Steroid Biochem Mol Biol. 2014;144(Pt A):132–7.
107. Johnsen MS, Grimnes G, Figenschau Y, Torjesen PA, Almas B, Jorde R. Serum free and bio-available 25-hydroxyvitamin D correlate better with bone density than serum total 25-hydroxyvitamin D. Scand J Clin Lab Invest. 2014;74:177–83.
108. Dastani Z, Berger C, Langsetmo L, Fu L, Wong BY, Malik S, et al. In healthy adults, biological activity of vitamin D, as assessed by serum PTH, is largely independent of DBP concentrations. J Bone Miner Res. 2014;29:494–9.
109. Florez HJ, Cherniack EP, Troen BR. Impact of vitamin D on the aging population. Trans Endocrinol Metab. 2011;2:73–108.
110. Grant WB. Relation between prediagnostic serum 25-hydroxyvitamin D level and incidence of breast, colorectal, and other cancers. J Photochem Photobiol B. 2010;101:130–6.
111. Levis S, Cherniack EP, Florez H, Roos BA, Troen BR. Vitamin D supplementation in older persons: benefits and requirements. Aging Health. 2009;9:701–9.
112. Vitezova A, Zillikens MC, van Herpt TT, Sijbrands EJ, Hofman A, Uitterlinden AG, et al. Vitamin D status and metabolic syndrome in the elderly: the Rotterdam Study. Eur J Endocrinol. 2015;172:327–35.
113. Clemente-Postigo M, Munoz-Garach A, Serrano M, Garrido-Sanchez L, Bernal-Lopez MR, Fernandez-Garcia D, et al. Serum 25-hydroxyvitamin D and adipose tissue vitamin D receptor gene expression: relationship with obesity and type 2 diabetes. J Clin Endocrinol Metab. 2015;100:E591–5. p. jc20143016.
114. Boucher B. Vitamin D, obesity, and risk of diabetes. Lancet Diab Endocrinol. 2014;2:361–2.
115. LeBlanc ES, Zakher B, Daeges M, Pappas M, Chou R. Screening for vitamin D deficiency: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2015;162:109–22.
116. LeFevre ML, U. S. P. S. T. Force. Screening for vitamin D deficiency in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2015;162:133–40.
117. LeBoff MS, Yue AY, Copeland T, Cook NR, Buring JE, Manson JE. VITAL-bone health: rationale and design of two ancillary studies evaluating the effects of vitamin D and/or omega-3 fatty acid supplements on incident fractures and bone health outcomes in the VITamin D and OmegA-3 TriaL (VITAL). Contemp Clin Trials. 2015;41:259–68.
118. Lagari VS, Gomez-Marin O, Levis S. Study design and baseline characteristics of participants in the vitamin D in Vulnerable Adults at the VA (the VIVA Study). Contemp Clin Trials. 2014;39:66–73.
119. Reid IR, Bolland MJ, Grey A. Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis. Lancet. 2014;383:146–55.
120. Macdonald HM, Wood AD, Aucott LS, Black AJ, Fraser WD, Mavroeidi A, et al. Hip bone loss is attenuated with 1000 IU but not 400 IU daily vitamin D3: a 1-year double-blind RCT in postmenopausal women. J Bone Miner Res. 2013;28:2202–13.
121. Levis S, Theodore G. Summary of AHRQ's comparative effectiveness review of treatment to prevent fractures in men and women with low bone density or osteoporosis: update of the 2007 report. J Manag Care Pharm. 2012;18:S1–15. discussion S13.
122. Schoenmakers I, Francis RM, McColl E, Chadwick T, Goldberg GR, Harle C, et al. Vitamin D supplementation in older people (VDOP): study protocol for a randomised controlled intervention trial with monthly oral dosing with 12,000 IU, 24,000 IU or 48,000 IU of vitamin D(3). Trials. 2013;14:299.
123. Sanders JL, Stern PH. Protein kinase C involvement in interleukin-6 production by parathyroid hormone and tumor necrosis factor-alpha in UMR-106 osteoblastic cells. J Bone Miner Res. 2000;15:885–93.

124. Wu Y, Kumar R. Parathyroid hormone regulates transforming growth factor beta1 and beta2 synthesis in osteoblasts via divergent signaling pathways. J Bone Miner Res. 2000;15:879–84.
125. Troen BR. Molecular mechanisms underlying osteoclast formation and activation. Exp Gerontol. 2003;38:605–14.
126. Hodsman AB, Bauer DC, Dempster DW, Dian L, Hanley DA, Harris ST, et al. Parathyroid hormone and teriparatide for the treatment of osteoporosis: a review of the evidence and suggested guidelines for its use. Endocr Rev. 2005;26:688–703.
127. Reeve J, Meunier PJ, Parsons JA, Bernat M, Bijvoet OL, Courpron P, et al. Anabolic effect of human parathyroid hormone fragment on trabecular bone in involutional osteoporosis: a multicentre trial. Br Med J. 1980;280:1340–4.
128. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344:1434–41.
129. Orwoll ES, Scheele WH, Paul S, Adami S, Syversen U, Diez-Perez A, et al. The effect of teriparatide [human parathyroid hormone (1–34)] therapy on bone density in men with osteoporosis. J Bone Miner Res. 2003;18:9–17.
130. Lane NE, Sanchez S, Modin GW, Genant HK, Pierini E, Arnaud CD. Parathyroid hormone treatment can reverse corticosteroid-induced osteoporosis. Results of a randomized controlled clinical trial. J Clin Invest. 1998;102:1627–33.
131. Dempster DW, Cosman F, Kurland ES, Zhou H, Nieves J, Woelfert L, et al. Effects of daily treatment with parathyroid hormone on bone microarchitecture and turnover in patients with osteoporosis: a paired biopsy study. J Bone Miner Res. 2001;16:1846–53.
132. Uusi-Rasi K, Semanick LM, Zanchetta JR, Bogado CE, Eriksen EF, Sato M, et al. Effects of teriparatide [rhPTH (1–34)] treatment on structural geometry of the proximal femur in elderly osteoporotic women. Bone. 2005;36:948–58.
133. Hagino H, Okano T, Akhter MP, Enokida M, Teshima R. Effect of parathyroid hormone on cortical bone response to in vivo external loading of the rat tibia. J Bone Miner Metab. 2001;19:244–50.
134. Souberbielle JC, Cormier C, Kindermans C, Gao P, Cantor T, Forette F, et al. Vitamin D status and redefining serum parathyroid hormone reference range in the elderly. J Clin Endocrinol Metab. 2001;86:3086–90.
135. Mosekilde L, Hermann AP, Beck-Nielsen H, Charles P, Nielsen SP, Sorensen OH. The Danish Osteoporosis Prevention Study (DOPS): project design and inclusion of 2000 normal perimenopausal women. Maturitas. 1999;31:207–19.
136. Thomas MK, Lloyd-Jones DM, Thadhani RI, Shaw AC, Deraska DJ, Kitch BT, et al. Hypovitaminosis D in medical inpatients. N Engl J Med. 1998;338:777–83.
137. Tangpricha V, Pearce EN, Chen TC, Holick MF. Vitamin D insufficiency among free-living healthy young adults. Am J Med. 2002;112:659–62.
138. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr Rev. 2001;22:477–501.
139. Sahota O, Gaynor K, Harwood RH, Hosking DJ. Hypovitaminosis D and 'functional hypoparathyroidism'-the NoNoF (Nottingham Neck of Femur) study. Age Ageing. 2001;30:467–72.
140. Sakuma M, Endo N, Oinuma T, Hayami T, Endo E, Yazawa T, et al. Vitamin D and intact PTH status in patients with hip fracture. Osteoporos Int. 2006;17:1608–14.
141. Fisher AA, Davis MW. Calcium-PTH-vitamin D axis in older patients with hip fracture. Osteoporos Int. 2007;18:693–5.
142. Sahota O, Mundey MK, San P, Godber IM, Hosking DJ. Vitamin D insufficiency and the blunted PTH response in established osteoporosis: the role of magnesium deficiency. Osteoporos Int. 2006;17:1013–21.
143. Heaney RP. Serum 25-hydroxyvitamin D and parathyroid hormone exhibit threshold behavior. J Endocrinol Invest. 2005;28:180–2.
144. Vieth R, El-Hajj Fuleihan G. There is no lower threshold level for parathyroid hormone as 25-hydroxyvitamin D concentrations increase. J Endocrinol Invest. 2005;28:183–6.
145. Steingrimsdottir L, Gunnarsson O, Indridason OS, Franzson L, Sigurdsson G. Relationship between serum parathyroid hormone levels, vitamin D sufficiency, and calcium intake. JAMA. 2005;294:2336–41.
146. Ledger GA, Burritt MF, Kao PC, O'Fallon WM, Riggs BL, Khosla S. Role of parathyroid hormone in mediating nocturnal and age-related increases in bone resorption. J Clin Endocrinol Metab. 1995;80:3304–10.
147. Kennel KA, Riggs BL, Achenbach SJ, Oberg AL, Khosla S. Role of parathyroid hormone in mediating age-related changes in bone resorption in men. Osteoporos Int. 2003;14:631–6.
148. Blain H, Vuillemin A, Blain A, Guillemin F, De Talance N, Doucet B, et al. Age-related femoral bone loss in men: evidence for hyperparathyroidism and insulin-like growth factor-1 deficiency. J Gerontol A Biol Sci Med Sci. 2004;59:1285–9.
149. Findlay DM, Sexton PM. Calcitonin. Growth Factors. 2004;22:217–24.
150. Miller S. Calcitonin--guardian of the mammalian skeleton or is it just a fish story? Endocrinology. 2006;147:4007–9.
151. Cappelli C, Cottarelli C, Cumetti D, Agosti B, Gandossi E, Rizzoni D, et al. Bone density and mineral metabolism in calcitonin-deficiency patients. Minerva Endocrinol. 2004;29:1–10.
152. Woodrow JP, Sharpe CJ, Fudge NJ, Hoff AO, Gagel RF, Kovacs CS. Calcitonin plays a critical role in regulating skeletal mineral metabolism during lactation. Endocrinology. 2006;147:4010–21.

153. Grant WB, Gorham ED. Commentary: time for public health action on vitamin D for cancer risk reduction. Int J Epidemiol. 2006;35:224–5.
154. Grant WB, Holick MF. Benefits and requirements of vitamin D for optimal health: a review. Altern Med Rev. 2005;10:94–111.
155. Diamond TH, Ho KW, Rohl PG, Meerkin M. Annual intramuscular injection of a megadose of cholecalciferol for treatment of vitamin D deficiency: efficacy and safety data. Med J Aust. 2005; 183:10–2.
156. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr. 1999;69:842–56.
157. Ishijima M, Sakamoto Y, Yamanaka M, Tokita A, Kitahara K, Kaneko H, et al. Minimum required vitamin D level for optimal increase in bone mineral density with alendronate treatment in osteoporotic women. Calcif Tissue Int. 2009;85:398–404.
158. Peris P, Martinez-Ferrer A, Monegal A, Martinez de Osaba MJ, Muxi A, Guanabens N. 25 hydroxyvitamin D serum levels influence adequate response to bisphosphonate treatment in postmenopausal osteoporosis. Bone. 2012;51:54–8.
159. Barone A, Giusti A, Pioli G, Girasole G, Razzano M, Pizzonia M, et al. Secondary hyperparathyroidism due to hypovitaminosis D affects bone mineral density response to alendronate in elderly women with osteoporosis: a randomized controlled trial. J Am Geriatr Soc. 2007;55:752–7.
160. Antoniucci DM, Vittinghoff E, Palermo L, Black DM, Sellmeyer DE. Vitamin D insufficiency does not affect response of bone mineral density to alendronate. Osteoporos Int. 2009;20:1259–66.
161. Ish-Shalom S, Salganik T, Segal E, Raz B, Bromberg I, Vieth R. Comparison of daily, weekly, and monthly vitamin D3 in ethanol dosing protocols for two months in elderly hip fracture patients. J Clin Endocrinol Metab. 2008;93:3430–5.
162. Mocanu V, Stitt PA, Costan AR, Voroniuc O, Zbranca E, Luca V, et al. Long-term effects of giving nursing home residents bread fortified with 125 microg (5000 IU) vitamin D(3) per daily serving. Am J Clin Nutr. 2009;89:1132–7.

The Muscle-Bone Connection

4

Marco Brotto, Janalee Isaacson,
and Eduardo L. Abreu

Mechanical Coupling of Bones and Muscles

The musculoskeletal system is extremely complex. Contrary to the reductionist view that it is made up of only bones and muscles, the system is actually composed of bones, skeletal muscles, nerves, blood vessels, tendons, ligaments, cartilage, joints, and other connective tissues.

Historically, the association between bones and muscles has been primarily seen as a mechanical coupling where one tissue, skeletal muscle, actively applies the load and another tissue, bone, receives the load and serves as the attachment site. This physiologic association supports the locomotion, protection, and the shape/form of animals. In recent years, we have begun to appreciate that the relationship between muscle and bone goes beyond this mechanical coupling; that these two tissues also function at a higher level through crosstalk signaling that is important for their function.

The tight coupling between skeletal muscle and bone in animals begins during embryonic development with the formation of the paraxial mesoderm, which subsequently gives rise to somites that become muscles, bones, tendons, and other tissues [1]. The development of each of these tissues will be discussed later in the chapter. It is important to mention at the outset that as the skeleton develops, it has been postulated that muscle contraction in the fetus contributes to skeletal growth and development and that skeletal adaptations in early postnatal life are driven by changing mechanical forces [2, 3]. Although exercise across all ages has proven beneficial, clearly peak bone mass accrual during pre-pubertal growth is dramatically affected by exercise, or physical activity, and to a lesser extent thereafter [4]. Peak bone mass is achieved by both men and women by their third decade of life, with men having obtained more bone mass due to hormonal and other influences (i.e. diet, genetics, etc.). Human females begin to lose bone mass with a rapid loss phase occurring 2–3 years before menopause and continuing until 3–4 years after the last

M. Brotto, BSN, MS, PhD (✉)
Muscle Biology Research Group-MUBIG,
School of Nursing & Health Studies and School
of Medicine, University of Missouri-Kansas City
(UMKC), Kansas City, 64108 MO, USA

Bone-Muscle Collaborative Sciences,
College of Nursing & Health Innovation,
University of Texas-Arlington,
Arlington, 76019 TX, USA
e-mail: Marco.brotto@uta.edu

J. Isaacson, PhD, RN
Department of Nursing,
Johnson County Community College,
Overland Park, KS 66210-1299, USA
e-mail: isaacson@jccc.edu

E.L. Abreu, MD, DEng
Muscle Biology Research Group-MUBIG,
School of Nursing and Health Studies,
University of Missouri-Kansas City,
Kansas City, MO, USA
e-mail: abreue@umkc.edu

G. Duque, D.P. Kiel (eds.), *Osteoporosis in Older Persons: Advances in Pathophysiology and Therapeutic Approaches*, DOI 10.1007/978-3-319-25976-5_4

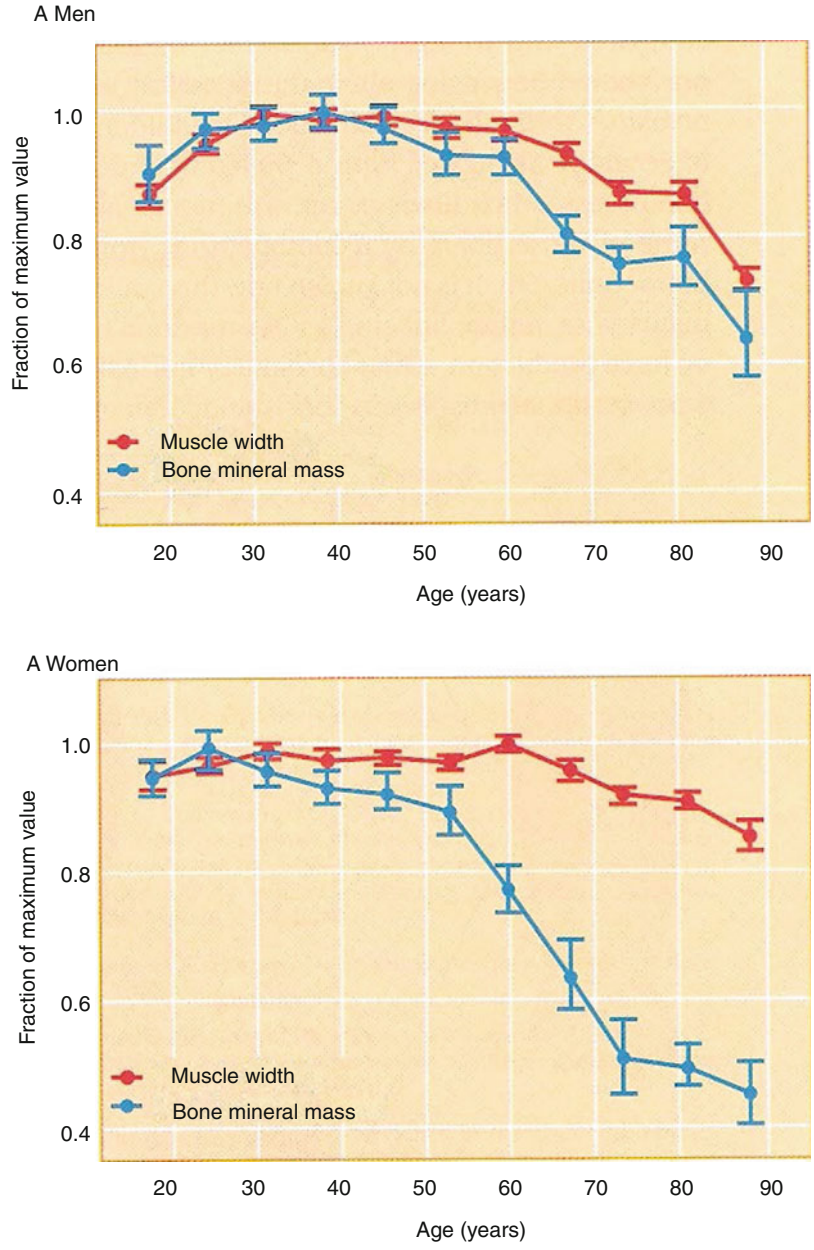


Fig. 4.1 Aging-related changes in bone mineral mass of the radius and muscle width in the forearm in adult men and women (From Novotny et al. [7])

menses [5], then experiencing a more gradual but steady decline. Males do not experience this same dramatic decline, but rather a gradual, steady bone loss beginning in their 50s and 60s [6] (Fig. 4.1). Individuals with reduced bone mass, as seen in osteoporosis, often also develop the reduced muscle mass and function, a condition known as sarcopenia. However, declines in bone mass do not fully explain sarcopenia, nor does muscle atrophy fully explain the totality of osteoporosis. This seeming mystery may be due in part to the use of bone mass and muscle mass as the predominant measures for osteoporosis and sarcopenia. The assessments of bone quality and muscle function might better reflect the physiological basis for these diseases. However, these metrics are not in place to date, especially in the clinical arena.

The mechanical coupling of skeletal muscle and bone is visible. Bone adjusts its mass and architecture to changes in mechanical load and as contraction of skeletal muscle is essential for locomotion, it is obvious that muscle contractions apply load to the bone. This mechanical perspective implies that as muscle function declines, the result would be decreased loading of the skeleton, leading to a reduced bone mass. However, as noted above, the inability to account for totality of the changes in the musculoskeletal system based upon mechanical considerations, while important, is only a part of this major complex problem. For example, it is not possible to explain the development of osteoporosis based solely upon the presence of sarcopenia (and vice-versa). These observations imply that beyond the mechanical coupling there must also be a biochemical coupling.

As we will discuss in this chapter, it is now fully evident that muscle and bone produce factors that circulate and act on distant tissues, thus fulfilling the classical definition of endocrine action. Surprisingly, it has only been recently that the action they have on one another has begun to be under careful investigation. Perhaps this oversight derives from the bias of mechanical coupling and, until recent years, a lack of technology, testing abilities, and bioinformatics techniques. However, understanding this apparent endocrine crosstalk and biochemical coupling is an exciting new avenue of research with tremendous clinical potential.

Beyond Mechanical Coupling: Bone-Muscle Developmental and Genetic Coupling

Considering their common embryonic development while forming from somites originating from the paraxial mesoderm, the intimate relationship and close coupling between the tissues that comprise the musculoskeletal system is therefore unquestionable [3]. Bone and muscle cells share a common mesenchymal precursor and their shared experience of organogenesis occurs through a firmly orchestrated network of genes and proteins during intrauterine development. In fact, some of our own bias to accept a purely mechanical coupling between these two tissues derives from embryology. For example, it is the contraction of muscles in the developing embryo that contributes to the process of skeletal development itself and clearly to the growth of the skeleton, as well as a host of adaptations in early postnatal life that result from the changing mechanical forces [2, 4]. Furthermore, even post-development, the immediate results of muscle load can be discerned on bones, since they adjust their shape and mass to changes in load, and such load can be easily interpreted as coming from muscle contractions. We are obviously not suggesting that contracting forces do not play a major role, but rather, there are a number of additional influences to consider.

While universally accepted that bone and muscle develop embryologically as a unit, the underlying environmental cues that drive skeletal mass and other properties are regulated by a complex set of genetic factors. Heritability studies have estimated that from 40 to 80 % of the major skeletal phenotypes and muscle traits are related to genetics [8–11]. Thus, given the genetic and developmental closeness of these two tissues, it seems highly likely that there would be some degree of shared genetic components underlying some of their phenotypes. The identification of these shared (i.e., pleiotropic) genetic cues are essential to promote the discovery of the molecular/biochemical coupling that exists between muscle and bone, and serve as evidence that bone and muscle interact beyond mechanical.

Genome Wide Association Studies (GWAS)

Over the past decade, GWAS have produced several candidate gene regions that show association with variations in a number of different human bone phenotypes and muscle traits. Even limiting the focus to a small sampling of the bone muscle phenotype GWAS [12–20] and bone phenotype GWAS [21–29] reported in recent years evidence of the powerful genetic coupling between these

tissues. An interesting question that arises is how mechanical forces during development interact with genetic signals. For example, do fetuses that have stronger intrauterine contractions produce genetic signaling that in turn favors the development and formation of stronger bones and muscles and a healthier musculoskeletal system? Or, are there specific genetic signals that lead to bones and muscles of higher mass and strength? Or, is it a combination of both possibilities?

Due to the development of new bioinformatics and statistical models, bivariate GWAS has been used to identify pleiotropic candidate genes/single-nucleotide polymorphisms (SNPs); regions concomitantly associated with traits in both bone and muscle [13, 30–34]. These recent bivariate GWAS based studies, including both bone and muscle phenotypes, have revealed a short list of several novel potentially-pleiotropic candidate genes such as *GLYAT* [13], *HTR1E*, *COL4A2*, *AKAP6*, *SLC2A11*, *RYR3* and *MEF2C* [31], *PRKCH* and *SCNN1B* [30]; *HK2*, *UMOD* and two microRNAs *MIR873* and *MIR876* [34].

The *MEF2C* gene encodes a potent transcription factor (myocyte enhancer factor 2C) that was originally thought to be involved in cardiac and skeletal muscle development and was also used as a marker of myogenic cells in the somites [35]. Intriguing data has recently emerged with the development of the osteocyte specific mouse model of *Mef2C* deletion. These mice display increased bone density through a complex mechanism involving reduced Sost expression and increased osteoprotegerin (OPG) expression resulting in a reduced receptor activator of nuclear factor kB ligand (RANKL)/OPG ratio, and reduced osteoclastogenesis [36]. Therefore, the important roles of MEF2C in cardiac and skeletal muscle development, as well as in adult bone mass regulation, support the concept of shared genetic determinants in bone and muscle and in this case even beyond, since cardiac muscle is also part of this *MEF2C* loop.

Another of the suggestive genes that emerged from the GWAS analyses was *METTL21C*, which is highly expressed in muscle. Interestingly, it has been reported that there may be an association between the METTL21family of proteins and inclusion body myositis with Paget's disease of bone [37–39]. The role of *Mettl21c* in myogenesis was explored using the murine skeletal muscle cell line, C2C12. By silencing the activity of *Mettl21c* through the process of siRNA transfection, we demonstrated a significant decrease in C2C12 myogenesis as evidenced in the reduced fusion index, smaller myotube cell area, and decreased calcium release from the sarcoplasmic reticulum when compared to negative controls (Fig. 4.2).

To study the impact of *Mettl21c* on bone cells, the osteocyte cell line MLO-Y4 was used. We found that a partial knockdown of *Mettl21c* in MLO-Y4 cells led to an increased dexamethasone-induced cell death. These findings further support the concept that bones and muscles share genetic determinants, and that it is through the modulation of specific factors that lead to the phenotypic and functional effects (Fig. 4.3).

Myostatin (*MSTN*), or growth and differentiation factor 8 (*GDF8*), is a member of the TGF-β superfamily and is a muscle-derived factor (myokine) that circulates in the blood, making it an attractive candidate for muscle-bone endocrine signaling [40, 41]. The deletion and/or mutations in myostatin lead to muscle hypertrophy or "double muscling" in animal models [42–47] and in humans [48]. This is a prime example of how a mutation assumed to be restricted to one tissue can lead to altered properties in another (Fig. 4.4). In this case, the loss of myostatin not only leads to muscle doubling, but also leads to a generalized increase in bone density and strength [49]. A question that could lead to major mechanistic insights is how does myostatin exert its effects on bone? Possible explanations include direct effects of mechanical loading of bone due to the increased muscle mass, indirect action by regulating hepatic production of IGF-1 [50], or some other unknown mechanism. While the IGF-1 and GH axis is an important mechanism to be pursued due to its effects on age-related changes in bone and skeletal muscle [51], a tantalizing possibility is that larger volume muscles might release relatively larger amounts of myokines, which in turn reach the bone cells via the canalicular system, exerting anabolic effects on bone.

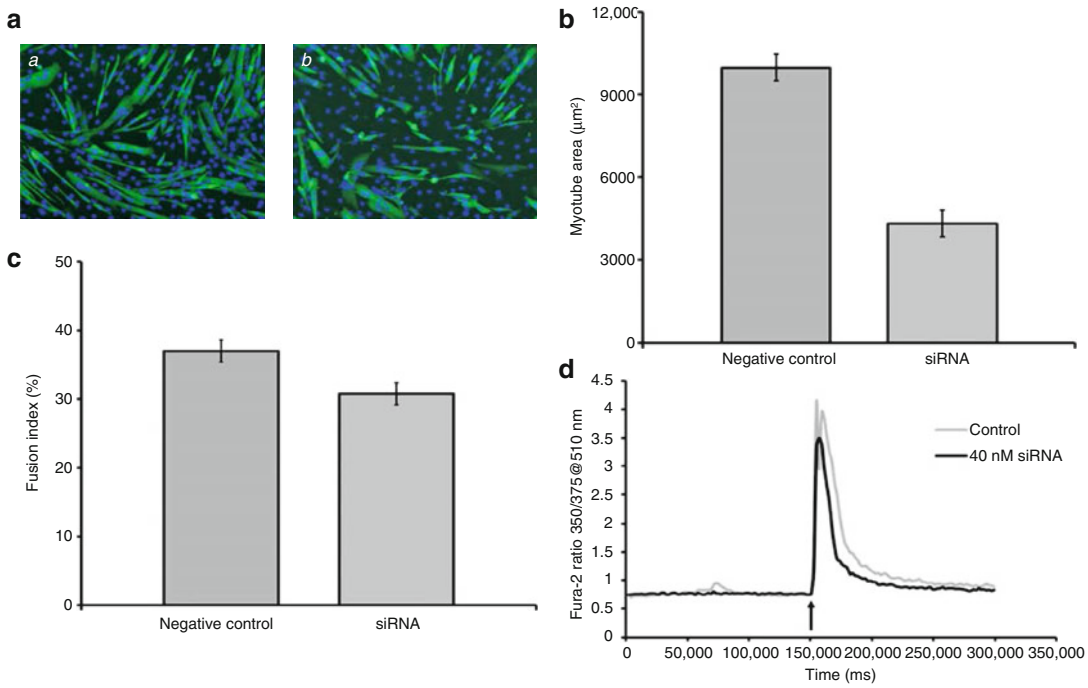


Fig. 4.2 Partial silencing of Mettl21c reduces fusion index, myotubecell area, and calcium release from the sarcoplasmic reticulum. (**a**) Representative fluorescence images of DAPI-stained nuclei (*blue*) and MHC antibody (*green*) of C2C12 at 3 days of differentiation after transfection: (*a*) negative control; and (*b*) Mettl21c-siRNA–treated C2C12 cells. (**b**) Summary data show that the Fusion Index in Mettl21c-siRNA–treated C2C12 cells decreased significantly compared to negative control ($p<0.05$). (**c**) Summary data show that myotubecell area in Mettl21c-siRNA–treated C2C12 cells drastically decreased compared to negative control ($p<0.0001$). (**d**) Representative calcium transients induced by 20 mM caffeine (*arrow*) on C2C12 myotubes loaded with Fura-2/AM. In Mettl21c-siRNA–treated C2C12 myotubes at day 5 of differentiation, compared to negative control, the amplitude peak calcium response to caffeine was significantly decreased and the relaxation phase of the transient was shorter ($p<0.01$). DAPI.4,6-diamidino-2-phenylindole; MHC.myosin heavy chain (From Huang et al. [38])

The possibility of this endocrine-like crosstalk, along with the promise of novel and impactful therapeutic interventions, has motivated research to be conducted in this area.

Disease Conditions with Multiple Tissue Effects

The endocrine interactions that are being discovered through the effects of bone cell secreted factors and myokines go well beyond the musculoskeletal unit. Recent findings have supported the interconnection of bone, muscle, and adipose tissue. The striking rise of chronic diseases such as diabetes, metabolic syndrome, and obesity seem to closely parallel the rise in the prevalence of sarcopenia and osteoporosis, particularly in the elderly population [52]. The musculoskeletal system is the largest organ system of the body. If we embrace the concept that bone, tendon, and muscle all produce and secrete a myriad of factors, and that they influence not only each other but also multiple organs and overall body metabolism, it makes sense that when the musculoskeletal tissues become less effective with aging, organs throughout the body would also be effected. With fewer bone-derived factors (osteokines) and fewer myokines being secreted, it is logical to expect changes in fat metabolism, as well as kidney function, and even testosterone levels; thereby translating into multiple organ effects that are normally interpreted as "aging consequences". This new view not only

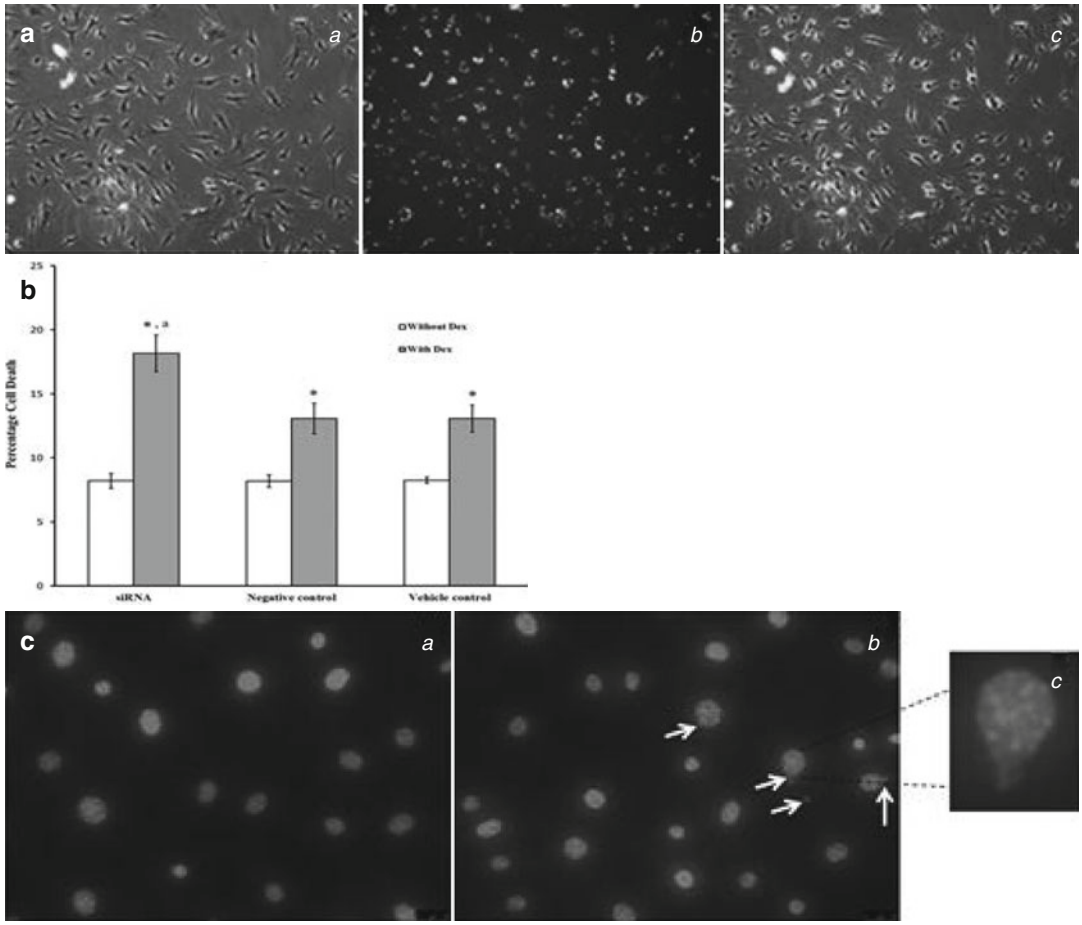


Fig. 4.3 Partial knockdown of Mettl21c in MLO-Y4 osteocytes increased cell death induced by dexamethasone. (**a**) Representative image of MLO-Y4 osteocytes 24 h after transfection of All Star negative control siRNA(200 nM): (*a*) phase contrast image; (*b*) fluorescent image of tagged siRNA; both images were taken from the same area; (*c*) merging of (*a*) and (*b*). (**b**) Summary data of cell death in MLO-Y4 cells transfected with Mettl21C siRNA, with and without Dextreatment. Cell death was detected 48 h after treatment by trypanblue exclusion assay (Dexincreased cell death under all conditions; and Mettl21c knockdown induced cell death levels higher than Dexalone, $p<0.05$). (**c**) The nuclear fragmentation assay shows: (*a*) absence of nuclear blebbingin control MLO-Y4 cells as compared with (*b*) enhanced blebbingin the siRNA-treated MLO-Y4 osteocytes; (*c*) the enlarged image clearly shows the blebbingprocess in siRNA-treated MLO-Y4 osteocytes. Dex. dexamethasone (From Huang et al. [38])

helps to explain some of the multiple organ decline in function, but could also lead to new therapies related to the endocrine function of bone and muscle.

The Unique Case of Fracture Healing

An intriguing and well documented observation that cannot be ignored in the context of bone-muscle interactions is the observation that in open fractures, where muscle injury is also extensive or where muscle atrophy develops, fracture healing is significantly impaired [53–56]. Rodent models of fracture have supported the concept that muscle secretory activity aids in the process of fracture healing. For example, a significant difference (i.e., lesser healing) was found in rats with fractured femurs when their quadriceps muscles had also been paralyzed by botulin injections [57]. In mice with tibial open fracture, Harry et al., reported that when the fracture area

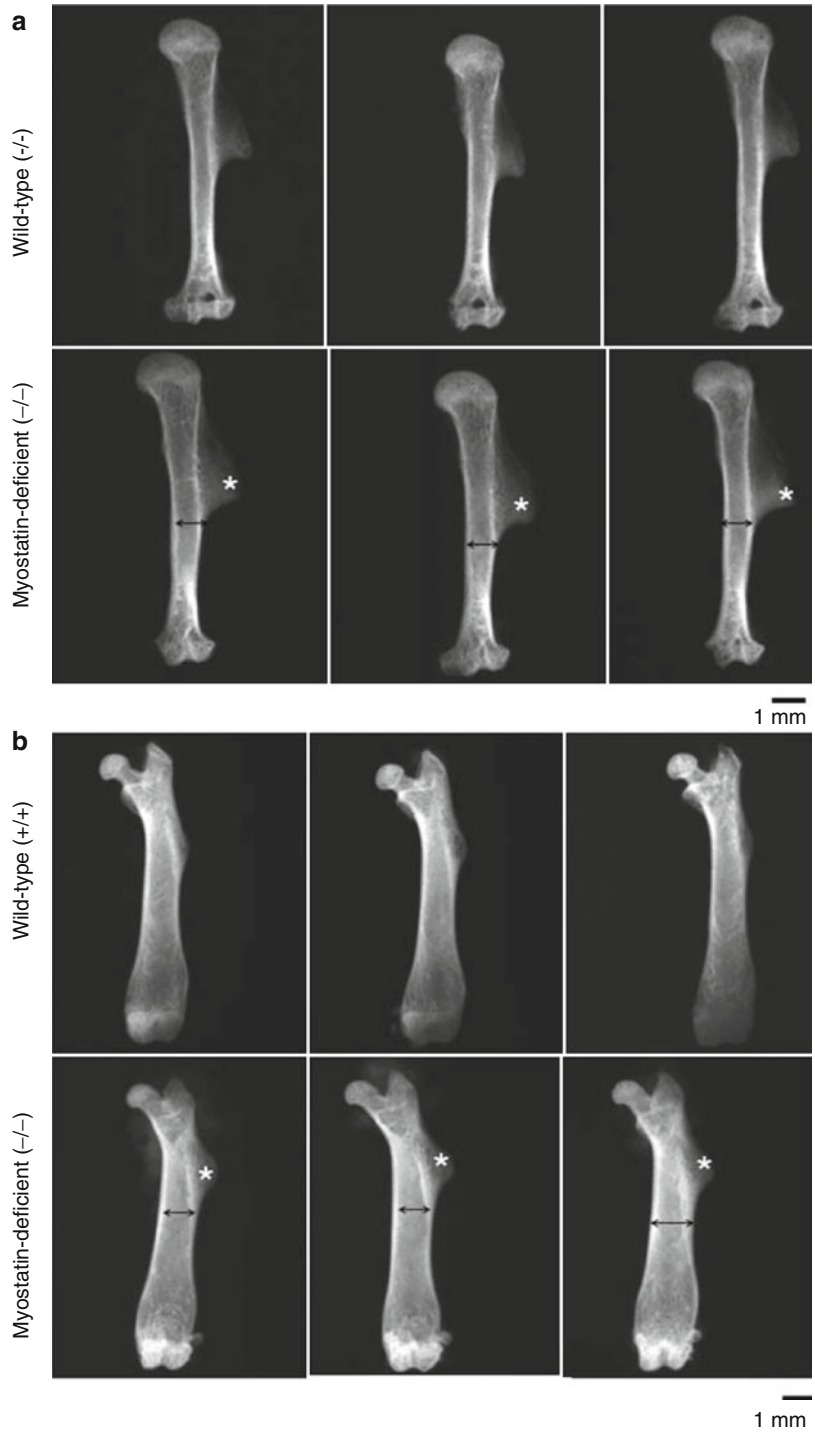


Fig. 4.4 Radiographs demonstrating increased shaft diameter and increased muscle attachment site at the deltoid crest in humerus (**a**), and the third trochanter in femur (**b**) in Myostatin-/-mice compared to wild type. Notice the extension of the articular surface towards the neck of the femur (**b**) (From Elkasrawy and Hamrick [49])

had been covered with muscle flaps, bone repair was significantly improved [58]. The clinical significance of these findings cannot be overstated since these findings have also been reproduced in humans with open tibial fractures [59] (Fig. 4.5 [58]; Table 4.1 [59]).

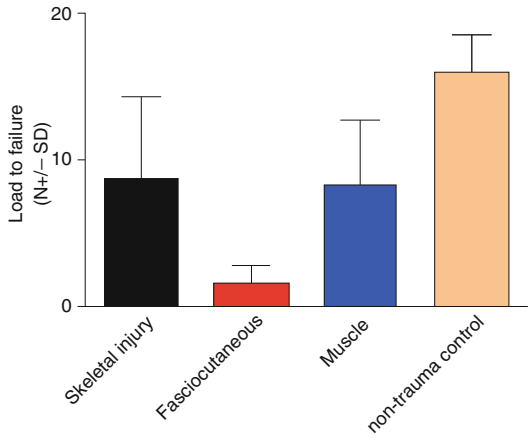


Fig. 4.5 Load at which failure occurred (N), through callus in the fracture groups, and un-fractured cortex in the non-trauma control group, at 28 days post fracture. Bars show standard deviations (SD) (From Hayutin et al. [128])

Table 4.1 Recorded union, delayed union and non-union in-between the study and control groups [58]

	Groups A and B[a] (tribial fracture + compartment) [12, 37, 42, 60–71]	Control group (tibial fracture) [9, 72–75]
No. of cases with available data (%)	238/245, 97.14 %	418/426, 98.12 %
Union (%)	131, 55.04 %	339, 81.10 %
Delayed (union/non union)	107, 44.96 %	79, 18.90 %

[a]Both groups are presented together due to the absence of adequate data of the healing process differentiated per age groups

Taken together, these studies strongly suggest that even under conditions where substantial mechanical forces are not being produced, muscles have the intrinsic biochemical capacity to secrete factors that stimulate growth and repair. It is almost as if muscles could function as a second periosteal layer as recently proposed by Little and colleagues [76, 77]. Yet another line of evidence derives from the documented observation in humans that fracture healing is improved upon the stimulation of the affected bone with pulsed electromagnetic stimulation (PEMS) [78]. Our groups have recently demonstrated that PEMS enhances myogenesis of C2C12 myoblasts [79]. Therefore, it is possible that the improved healing observed with PEMS on bone might be attributable to direct effects on bone cells and to indirect effects of myokines. The idea of circulating factors playing a role in these processes gains further strength in light of the studies conducted by Hamrick and colleagues showing that exogenous myostatin treatment accelerates bone and muscle healing [80].

Bones and Muscles as Endocrine Organs

Anatomic proximity of the musculoskeletal system along with the physiologic roles in mechanical support and body movement has, as mentioned, defined the connection between bones and muscles historically. In fact, so physiologically reasonable is the mechanical relationship between bones and muscles that the consideration of other possible links between the tissues has in some ways been encumbered. In the 1960s, an interdisciplinary group hosted by the University of Utah began to convene annually and compiled an impressive body of evidence in support of the biomechanical relationship between bones and muscles. As a result, a new paradigm emerged that included the mechanostat model, which purported that bone strength and density was largely a function of imposed mechanical forces [81]. That model, together with the Utah paradigm continued to influence for decades research conducted on bone and muscle physiology.

However, a key aspect to the model remained nearly dormant until recent years. Even the staunchest supporters of the model admitted to the likelihood of non-mechanical agents locally and systemically affecting the skeletal architecture [81]. Nevertheless, the vast majority of investigative efforts related to the bone-muscle unit focused on the impact of mechanical loads. Basic research has experienced in recent years an explosion of technical advancements. These new techniques, equipment, cell lines and transgenic animal models provide now increased opportunities to learn more about both the mechanical and

the biochemical relationship between bones and muscles. Additional experimental approaches include the study of specially created cell lines and the development of transgenic animal models. To expand the body of knowledge related to factors secreted by bones and muscles, researchers look for evidence of the impact such factors have throughout the body.

Perchance the easiest way to see the endocrine nature of skeletal muscles is to look to one of its major functions; which is to sequester glucose from the blood stream. Skeletal muscles are essential for the maintenance of body glucose homeostasis as demonstrated by the fact that by having a larger volume of muscles and/or being more active physically a person can help prevent diabetes type II [82–84]. While literally working as an organismal sink for glucose, skeletal muscles can simultaneously undergo catabolic reactions that lead to the release of amino acids, which travel via the blood stream to find in the liver the proper conditions for gluconeogenesis. Under certain conditions, lipids can serve as another source of energy for skeletal muscles. Lipids are also emerging as important signaling molecules; a significant point that will be discussed later in this chapter.

Bone as an Endocrine Organ

A century ago, the predominant understanding of bone physiology was that there were primarily two types of bone cells: osteoblasts and osteoclasts. At the time, it was widely accepted that skeletal homeostasis relied on the function of these two bone cells; bone formation for osteoblasts, and bone resorption for osteoclasts. The primary influences on these two bone effector cells were believed to come from hormones and dietary calcium. Although osteocytes were identified and even recognized to be the most abundant type of bone cell, they were believed to be inert, serving primarily as structural components of the bone matrix. Since then, the dynamic and crucial role of osteocytes has become known. It was in the early 1990s that support for the endocrine function of this important bone cell began to gain momentum. Osteocytes are connected to one another via gap junctions, and it was a focus on this area that provided researchers with insight into the biochemical nature of bone cells. In 1992, Marotti and his team of researchers at the University of Modena, Italy, published their findings and working hypothesis on the metabolic activity of osteocytes. Using transmission electron microscopy (TEM), they demonstrated changes in the skeletal microstructure that occur with aging, as well as evidence of osteocyte modulation of osteoblast activity [85]. Three decades earlier, Dr. Marshall Urist had demonstrated the osteogenic properties of bone by implanting a decalcified and lyophilized sample of bone into host tissue [86]. His experiments revealed that factors present in the sample of bone cells led to neovascularization and bone deposition into the host tissue. It was with the advent of technical advancements that the factors could begin to be identified and studied. Urist recommended the name Bone Morphogenic Protein (BMP) for the factor responsible for new bone formation in his trailblazing experiments. Since then, BMP has come to refer to a group of growth factors implicated in the morphogenesis of tissues throughout the body.

Klein-Nulend and her team observed that bone cells secreted prostaglandins in response to mechanical stress induced in pulsating fluid flow experiments [87]. Research findings continue to support the significant role of prostaglandins in bone homeostasis, particularly the E and F series of prostaglandins [60, 88–91].

Research performed in the early part of this century provided evidence that in addition to their function as a sensory and responsive cell, osteocytes also serve to help regulate bone density through the secretion of sclerostin, a protein that inhibits bone formation [92]. Their work tested the hypothesis that the dysregulation in bone formation resulted from phenotypes observed in osteosclerosis patients. This hypothesis was further supported through genetic testing and the development of transgenic mice with increased sclerostin production and low bone mass. Since these explorations into the biochemical nature of bone cells, continued research by a number of biomedical scientists including Bonewald,

Johnson, Dallas, Karsenty, and Yamashita continue to provide evidence in support of osteoblast/osteocyte-secreted factors that impact not only bone homeostasis but also distant tissues such as the brain, heart, kidney, prostate, and muscle.

Fibroblast growth factor 23, or FGF23, is a bone-derived protein that has been identified as integral to vitamin D metabolism and the regulation of systemic phosphate levels [93]. In their 2012 review, Bonewald and Wacker discussed FGF23 expression in osteocytes and its role in cardiovascular health [94]. This has found additional support from research performed on transgenic mice phenotypes. Although the exact pathways are not fully understood, it appears that osteocyte expression of FGF23 is under the influence of molecules such as DMP1, PHEX, and MEPE [95]. Osteocalcin, which is also known as bone gamma-carboxyglutamic acid-containing protein (BGLAP) is a protein found, as the name implies, in bone and dentin. Osteocalcin helps to provide structure and has been shown to also play a part in energy metabolism, calcium ion homeostasis, and male fertility [96]. It was postulated more than 20 years ago, that bone cells are the primary source of osteocalcin [97], and recent advances in genetic engineering have helped support that idea [75, 96, 98, 99]. Osteocalcin, along with other hormone-like substances secreted by bone cells, are now thought to interact with substances from the liver and adipose tissue in a way that may predispose individuals to obesity, diabetes, non-alcoholic fatty liver disease, and osteoporosis.

The impressive list of bone derived factors continues to grow, and includes: ATP, calcium, DKK1, DMP1, FGF23, MEPE, Nitric Oxide, OPG, osteocalcin, prostaglandins (particularly PGE_2), RANKl, sclerostin, and SOST. These factors represent a myriad of biochemical structures ranging from simple organic molecules to complex proteins, all of which help illustrate the diversity and far-reaching impact of bone as an endocrine organ.

Muscle as an Endocrine Organ

Skeletal muscle represents the majority of muscle tissue in the body and is so named for its functional connection and vicinity to the skeletal system. Also called striated muscle because of its appearance, skeletal muscle is under the control of the somatic nervous system and is responsible for voluntary movement, facial expressions, postural support, and respiratory expansion. Skeletal muscle develops from myogenic precursor cells and myoblasts. Myoblasts are small, mononucleated cells capable of either entering the cell cycle and proliferating, or fusing with other myoblasts to form myotubes. As myoblasts fuse and begin to form myotubes, they enlarge and take on an elongated shape (Fig. 4.6). Muscle cell proliferation and differentiation occur in the embryonic and early stages of development, and continue throughout the lifespan. Skeletal muscle is a dynamic tissue, whose cells undergo myogenesis repeatedly as muscles regenerate in response to injury [100, 101].

The process that leads to muscle contraction begins when acetylcholine (ACh) is released by a motor neuron across the synapse at the neuromuscular junction. Motor neurons originate in the central nervous system and the cell bodies of these neurons are located in the spinal cord. The neuronal fiber (axon) projects outside the spinal cord to directly or indirectly control muscles. At the muscle level, nerve-ending terminals spread and innervate each muscle fiber within a given skeletal muscle. A membrane called the sarcolemma covers each muscle fiber, and within each muscle fiber are thousands of sarcomeres, which are the functional units of contraction. The sarcomere is composed of thick myofilaments called myosin, and thin myofilaments called actin. The neuromuscular junction is a synapse with the terminal end of the motor neuron on one side and the motor end plate of a skeletal muscle fiber on the other. Release of ACh from the motor neuron causes stimulation of a muscle fiber through the exchange of sodium and potassium ions. This leads to the generation of an action potential that spreads along the sarcolemma and is transmitted into the interior of the muscle fiber by structures called transverse tubules, or T-tubules. T-tubules are juxtaposed to the calcium ion storage units, the sarcoplasmic reticulum (SR). As the action potential travels along the T-tubule, it causes the voltage-sensitive receptor named

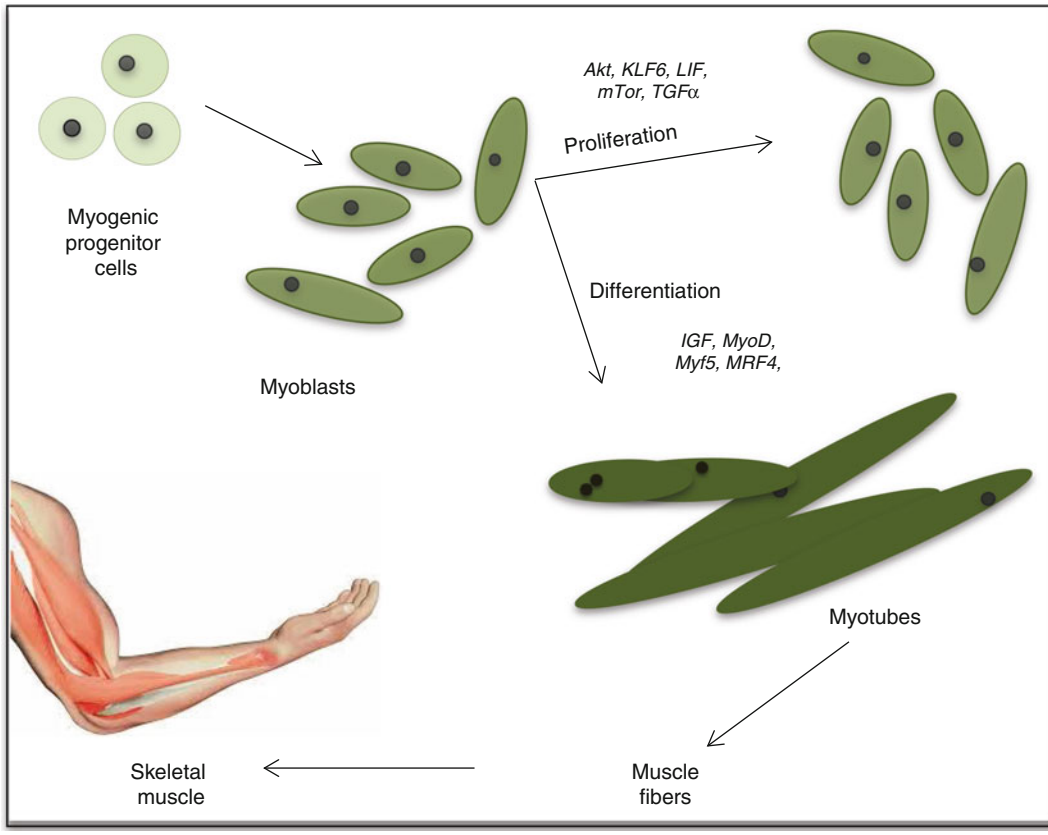


Fig. 4.6 Skeletal muscle cell myogenesis model (From Isaacson Dissertation – Myogenesis Model)

Dihydropirydine Receptor (DHPR) to change shape, and it is this allosteric modification of the DHPR that allows it to physically interact with the largest known mammalian channels, the Ryanodine Receptors (RyR) precisely located on the surface of the membrane of the SR. This DHPR-RyR contact, leads to the opening of the RyR, which brings about the release of calcium from the SR into the cytosol of the skeletal muscle cell. This rise in cytosolic calcium causes the binding sites on the actin filament to be exposed, allowing myofilaments heads to bind. The myosin filaments pull the actin filaments in, resulting in a shortening of the sarcomere. It is the shortening of sarcomere throughout the muscle fibers that causes muscle contraction. The process by which the electrical stimulation, or excitation is transferred into a mechanical contraction is called the excitation-contraction coupling (ECC) and is fundamental to skeletal muscle physiology [102–104]. The ECC is the cellular and molecular reason that we can execute from very fine controlled movements to the lifting of several hundred kilograms of weight.

The functional role of skeletal muscle to move and support the body has long been realized; it has only been recently that endocrine-like function of skeletal muscle has begun to be appreciated. Research associated with skeletal muscle secreted factors began primarily in relation to those produced in response to injury. For example, several myokines, prostaglandin, IL-6, and LIF, have been shown to enhance the myocyte differentiation after injury [105–108]. Muscle regeneration is an ongoing phenomenon throughout the life span, and provides an excellent opportunity for investigation into the endocrine function of this organ, as well as hope for targeted interventions to slow the process of muscle wasting. Two additional factors secreted by injured skeletal muscle are TGFα and TGFβ1 [106, 109]. These myokines

have an inhibitory effect on muscle cell proliferation and differentiation.

In addition to raising serum levels of IL-6, exercise has been found to induce a six-fold increase in mRNA of Chemokine CXC motif ligand-1 (CXCL-1) and a 2.4-fold increase in serum CXCL-1. A functional homolog for IL-8, murine CXCL-1, belongs to a group that has gained attention for its role in inflammation, chemotaxis, angiogenesis, neuroprotective activity, and tumor growth regulation and is associated with a decrease in visceral fat [110].

Obesity and type 2 diabetes have both reached epidemic proportions worldwide. As the body of knowledge related to myokines continues to expand, researchers are investigating the role of certain myokines, or more accurately the lack thereof, because of limited exercise and the possible connection to these chronic diseases [110]. Recently, a new myokine brought hope for the development of molecules to target fat tissue accumulation, since irisin was shown to regulate the conversion of 'bad' (white) fat into 'good' (brown) fat that is essential for thermogenesis in mice [111]. Since the original publication, 49 papers have been published on the effects of irisin. A recent study by Park [112] concluded that irisin might be directly associated with a higher risk of cardiovascular diseases and metabolic syndrome in humans, suggesting that augmented secretion of irisin by either adipocytes or muscle cells might occur to overcome an underlying irisin resistance, similar to the hyperinsulinemia seen in insulin resistance associated with obesity [112].

The list of myokines continues to grow, and includes IL-8, which has been shown to increase angiogenesis [113]; IL-5, which is an anabolic factor being investigated for its role in muscle-fat crosstalk; IL-7, which is being studied for its impact on satellite cells during myogenesis [114]; and brain-derived neurotrophic factor (BDNF) [115]. With a deeper understanding of skeletal muscle as an endocrine organ comes the promise of innovative approaches to the prevention and treatment of diseases and disorders throughout the body.

Interplay Between Bones and Muscles as Endocrine Organs

The conditions are determined in utero for the connection between bones and muscles, as they share a common mesenchymal precursor and experience organogenesis through a tightly orchestrated network of genes during intrauterine development. As mentioned, their anatomic proximity lends credence to the hypothesis that bones and muscles influence each other in a paracrine nature. Evidence of such a relationship exists as pathologic conditions are studied; specifically, some of the bone stress syndromes where inflammation localized to the muscle area underneath the periosteal region spreads into the bone itself. These situations support the paracrine relationship hypothesis, suggesting inflammatory molecules from adjacent muscle fibers may penetrate into this region of the bone. Another powerful clinical example of this paracrine relationship is the aforementioned muscle flap application to compounded bone fractures. The effect of this therapeutic approach is significantly faster healing for these fractured bones. Although the specific molecular mechanism of action is not completely understood, the introduction of muscle flaps has been used as a successful therapeutic approach to treat chronic osteomyelitis and to accelerate the healing of bone fractures [116]. These mechanisms might display further importance for bone and muscle healing after musculoskeletal injury.

Experiments performed using osteocyte and muscle cell lines have revealed that PGE_2 secretion from osteocytes is more than 1000 times greater than PGE_2 secretion from muscle cells. This excess amount of PGE_2 from osteocytes could interplay with injured muscles, which would aid in muscle regeneration and repair. Intriguingly, recent *in vitro* studies have provided support for a role of osteocyte secreted PGE_2 in aiding with the process of myogenesis [89]. While these studies were originally performed with the myogenic cell line C2C12, as shown in Fig. 4.7, PGE_2 signaling is also a potent stimulator of myogenic differentiation in primary myoblasts/myotubes.

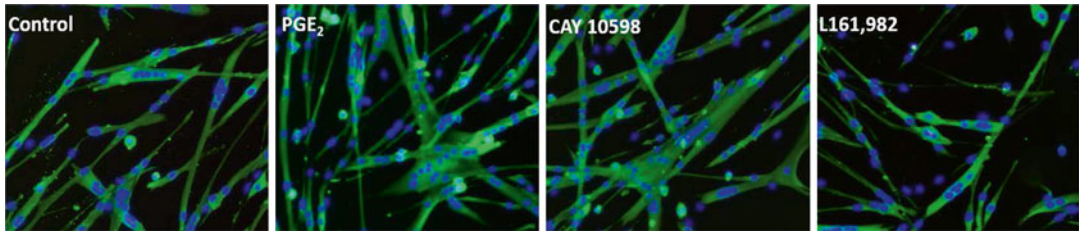


Fig. 4.7 PGE2 signaling modulates myogenesis of primary myoblast/myotubes. Representative images following treatment with PGE2, EP4 agonist CAY10598, and EP4 inhibitor L161,982 in 5-month old mouse primary myotubes, showing the same pattern previously published in C2C12 cells in Mo et al. [89]. Ingreen, myosin heavy chain, MHC and inblue: DAPI. Unpublished results by the Brotto Lab (Mo and Brotto Unpublished Results, 2015). It is evident that PGE2 and CAY 10598 promote myogenesis while L161,982 inhibitsit. PGE2 is a major osteokine secreted by osteocytes and one of the mediators of the bone-muscle crosstalk [89] (From Mo and Brotto Unpublished Results, 2015)

Recently developed transgenic animal models provide an excellent opportunity for researchers to gain further insight into this bone-muscle crosstalk, as in the case of the myostatin-deficient mouse. Myostatin, which was discussed earlier with regard to its pleiotropic characteristics, was discovered in the late 1990s to be a potent inhibitor of muscle growth. It is expressed during development and in adult skeletal muscle, serving as an important negative regulator of skeletal muscle growth [45, 117]. Myostatin appears to decrease myoblast proliferation. The myostatin-deficient mouse model has increased muscle size and strength, with individual muscles weighing significantly more than wild type mice [118]. Hamrick used this myostatin-deficient mouse model to investigate the effects of increased muscle mass on bone mineral content and density. He and his team found that although a consistent correlation was not found in all regions of the skeletal system, there was increased cortical bone mineral density in the distal femur and an increased periosteal circumference along the humerus [49, 119–121]. Another group used the same myostatin-deficient mouse model to look at the impact of the chronic loss of myostatin on multiple organ systems and found that it appeared to preserve bone density [122]. From a contrasting perspective, Zimmers investigated the effects of myostatin overexpression in an animal model and observed a profound loss of muscle and fat, mimicking the presentation seen in chronically ill patients and commonly referred to clinically as cachexia [118]. Further research into the disruption of myostatin is a worthy direction in an effort to preserve muscle mass in patients with chronic diseases.

As mentioned in a previous section, osteocalcin serves as a splendid example of bone as an endocrine organ [123]. This osteoblast-derived factor, circulating levels of which increase with exercise, binds to the GPRC6A receptor, affecting distant adipocytes and pancreatic β cells. Interestingly, osteoblasts also naturally express the osteo-testicular phosphatase gene (*Esp*), which inhibits the function of osteocalcin [69]. With this information in mind, it is of specific interest to the discussion of bone-muscle crosstalk that the *Gprc6a* knockout mouse displays the phenotype of decreased muscle mass, while the *Esp* knockout mouse has increased muscle mass. Through these observations, it can be proposed that osteocalcin, a known bone cell factor, may play a role in the regulation of muscle mass. This is the type of knowledge that promises a deeper understanding of sarcopenia; as osteocalcin could be a target for the development of therapies to prevent, delay, or slow the progression of this highly prevalent disorder associated with aging. If this knowledge is useful for sarcopenia, it is possible that it may also be useful for its associated disorder, osteoporosis.

The endocrine communication that continues to be revealed through effects of factors derived

from these tissues is not limited merely to a bone-muscle connection. There is a growing awareness that the factors secreted from tissues throughout the body impact the overall health of the individual. The significance of this dynamic interrelationship is becoming more apparent with the aging of the world's population and the concomitant rise of chronic diseases such as obesity, diabetes, and metabolic syndrome. According to the Centers for Disease Control and Prevention, the prevalence of obesity in the United States among adults 65 years of age and older is nearly 35 %; translating into more than 8 million older adults [52]. The American Diabetes Association website reports that nearly 25 % of adults aged 60 and over have diabetes, and it is also becoming clear that the prevalence of metabolic syndrome increases with age [62]. Recognizing the overwhelming implications for public health posed by sarcopenia alone, a distinguished team of researchers called for increased research investigating the factors involved in the pathogenesis of sarcopenia more than a decade ago [124]. Data from many studies published around that same time began to suggest that sarcopenia influenced the development of other chronic conditions such as cardiovascular and metabolic diseases. Since then, more evidence has been uncovered that sarcopenia is often linked to dyslipidemia, insulin resistance, and hypertension as well as a decline in immunologic function [71, 125].

As the understanding of the role of bones and muscles as endocrine organs, and insights into bone-muscle crosstalk begin to be translated into meaningful and innovative therapeutic approaches, unprecedented advances will be achieved in the fight against chronic diseases such as obesity, diabetes, osteoporosis, and sarcopenia.

Musculoskeletal Diseases: The Special Cases of Osteoporosis and Sarcopenia

People are living longer than any time in history due to the many advances in healthcare. In 1900, the life expectancy was only 47 years. By 1930, it increased to 60 years, and by the early 2000s, the life expectancy from birth had risen to more than 75 years. As the life expectancy climbs, there is a parallel increase in the percentage of the population aged 65 and older. Again, looking just back in time to 1900, only 4 % of the population was 65 and older, but that percentage nearly tripled to 13 % by 2008, and is projected to increase to an unprecedented 22 % by 2030 [126]. This has been reported as the largest demographic shift in history by experts in fields from finance to sociology [127, 128]. Many factors have contributed to this increased life expectancy, including the development of vaccines and antibiotics, improved nutrition, and processes to better the accessibility of clean water to more of the world's population.

Unfortunately, this trend of increasing age is accompanied by a corresponding increase in disability as aging adults experience a decline in physical functioning. The decline in functional reserve has been well documented throughout scientific and popular literature [129]. Nearly 300 diseases and injuries appear on the Global Burden of Disease (GBD) list, and a staggering 289 of those are known to cause disability. In the 2010 Global Burden of Disease (GBD) Study, researchers reported that the years lived with disability (YLD) per 100,000 people remained relatively constant over the years, until recently. With the increasing population of those who are 65 years of age and older, the YLD numbers have dramatically increased [130]. The seemingly undeniable fact of mortality is that aging is associated with the decline in function of nearly every system in the body along with the development of chronic conditions. Chronic diseases and disorders have a tremendous impact on individual health and healthcare expenditures, which has motivated much research into the prevalence of chronic conditions. Reports align and reveal that as many as 82 % of the older population in the U.S. has one or more chronic health conditions [131–133].

One of the body systems that experiences significant changes with aging is the musculoskeletal system. According to the 2010 Global Burden of Disease Study (GBD), musculoskeletal diseases are the second greatest cause of disability, affecting billions of people worldwide [130].

Disability leads to injury and a decline in function and independence. Rubenstein and Josephson reported that one in three community-dwelling older adults falls each year [134]. Fall-related injuries were responsible for more than two million Emergency Department visits and nearly 600,000 hospitalizations among older adults in 2009 [135, 136]. One of the most frightening injuries for an older adult to experience is a hip fracture. Ninety percent of hip fractures are the result of a fall, and the mortality rate 1-year post hip fracture is an astounding 25 %. It would seem the fear surrounding this injury is justified as only one in two older adults that experience a hip fracture return to their baseline level of activity [136]. There are many risk factors for falls, but primary among them is muscle weakness. The associated morbidity and mortality, especially hip fractures, is greatly increased among older adults, and is a significant health risk for those with osteoporosis. In addition to other chronic diseases and medication use, the decline in musculoskeletal health and function is a growing problem [74, 137, 138]. Loss of muscle mass and strength not only increases the individual's risk of falls, it impacts quality of life. Depp and Jeste reported that in the majority of cases, the very definition of "successful aging" is predicated by the absence of disability [73].

The musculoskeletal changes that occur not only impact the aging individual, they create a profound economic burden. Looking at sarcopenia alone, the healthcare costs in the year 2000 were $18.5 billion, which represented 1.5 % of the nation's total direct healthcare costs that year [139]. That percentage would translate into more than $40 billion a decade and a half later. Drawing from the 1995 Report of the National Osteoporosis Foundation [140], and adjusting for inflation and other factors to make the dollar values consistent, the same authors reported costs associated with osteoporotic fractures in the year 2000 to be $16.3 billion. Included in this price tag is the cost of inpatient care, nursing home care, outpatient care, emergency room visits, radiology services, orthopedic medical supplies, and outpatient medications. Even with all these aspects factored in, these costs may be conservative, considering that the United States Center for Disease Control and Prevention website, updated in September of 2013, reports the direct medical costs associated with fall-related injuries among the older adult population was $30 billion in 2010, and is projected to climb to nearly $55 billion by the year 2020 [141].

Osteoporosis

Osteoporosis is the most common metabolic bone disorder and is characterized by the progressive loss of bone mass. Bones are in a constant state of destruction and rebuilding, and in young, healthy individuals, the balance between bone formation and resorption is maintained. The decrease in bone density that has come to be known as osteoporosis appears to be the result of a growing imbalance of these two processes. The body of knowledge surrounding osteoporosis is growing as it is now recognized as the most common metabolic bone disease in the United States.

Evidence exists that the phenomenon of age related bone loss has afflicted mankind for centuries [142]. An English surgeon, Sir Astley Cooper was one of the first to document the changes he observed in bones of older adults: "With respect to the neck at the thigh-bone, a very principal cause of non-consolidation by bone is the advanced age at which it becomes obnoxious to fracture through that peculiar change which the part undergoes at this period of life without any apparent cause, but which renders it incapable of sustaining the superincumbent weight, and even in continuity insufficient to maintain its function; therefore it may be fairly supposed, when broken incompetent to set up a restorative action" [70]. The term, *osteoporosis,* is attributed to the French pathologist, Jean Lobstein, who used the term in a paper describing autopsy findings of holes in bones associated with fragility. In retrospect, it seems likely that he was actually using the term to describe osteogenesis imperfecta rather than osteoporosis [143].

Many definitions of osteoporosis have been offered over the years, with the most widely accepted being an operational definition based

upon bone mineral density (BMD). And, the most widely validated measure of BMD is dual energy X-ray absorptiometry (DXA). According to the World Health Organization (WHO) criteria, osteoporosis is defined as a bone mineral density (BMD) that falls greater than or equal to 2.5 standard deviations (SD) below the average value for young healthy women [144]. In recent years, there has been a growing debate about the use of DXA scan results. This diagnostic measure has proven to have high specificity, but low sensitivity; which means that a patient with a T-score below −2.5 has a high risk of fracture, but the patient with a T-score greater than −1.0, or within normal limits, is not immune to fracture. Clinicians and researchers have learned that many factors must be considered in determining the risk of an osteoporotic fracture in the aging patient.

Women are at greater risk of osteoporosis than men. Additional risk factors for osteoporosis include increased age, Caucasian or Asian ethnicity, postmenopausal status, late menarche or early menopause, low peak bone mass, a family history of osteoporosis or low trauma fracture, low dietary calcium, vitamin D and vitamin K, low levels of physical activity, smoking, excessive alcohol intake, and the use of certain medications such as steroids, anticonvulsants, immunosuppressants and heparin [72, 145–148]. Health care providers must consider all of these as they contemplate preventive and treatment options for their aging patients.

Treatment plans for those diagnosed with osteoporosis are related to these identified risk factors. The initial approach includes lifestyle modifications such as increased physical activity if possible, smoking cessation, and decreasing alcohol intake [149]. Beyond these lifestyle changes to reduce the risk of injury, treatment goals are aimed at slowing or stopping bone loss and/or facilitating bone formation. Supplementations often recommended include calcium, vitamin D, and, in some cases, hormone replacement therapy [150]. The primary pharmacologic intervention are antiresorptives. These pharmacological approaches are reviewed in depth in Chap. 12 of this textbook.

Sarcopenia

Skeletal muscle accounts for 38 and 31 % of the total body weight in men and women, respectively, and represents the largest single organ in the human body [151]. Thus, it is reasonable that the age-related anatomical and physiologic changes in skeletal muscle have a significant impact on the overall health of the individual. Irwin Rosenberg first proposed the term 'sarcopenia,' in 1988 to describe age related muscle wasting [152]. The term derives from the two Greek words, *sarx* (flesh) and *penia*, (loss). Because all individuals experience muscle wasting with age, the prevalence of sarcopenia with age is essentially 100 %. However, Rosenberg and others recognized that in many, the muscle loss that accompanied aging happened at a seemingly accelerated rate and contributed significantly to disability. In 1988, a group of researchers and clinicians convened for a meeting in Albuquerque, New Mexico to discuss various measurements used to assess the health and nutritional status of the elderly population. It was in a summary report following that historic meeting that Rosenberg first coined the term, 'sarcopenia.' He stated at that time his motivation for coining the term was to draw attention to this all too common disabling physiologic phenomenon. With a name came an increase in research conducted into the process and effects of age-related skeletal muscle wasting. And, in a reciprocal fashion, as the body of knowledge related to sarcopenia grows and develops, so grows the acceptance of sarcopenia as a condition with specific and measureable signs and symptoms. It is now recognized that sarcopenia has significant implications for the lives of individuals, for the nation and for the world.

In the mid-1990s, the simple measurement used to identify sarcopenia among older adults was the upper-arm circumference. Even with this crude method of identification, researchers began to see a correlation between the presence of sarcopenia and the older adults' mortality risk [153, 154]. In 1998, Baumgartner and his team suggested a modified approach to determining whether the muscle mass in an older adult was within normal limits, or whether it reflected a state

of compromised health, i.e. sarcopenia. From the research he and his colleagues were conducting on older adults in New Mexico, Baumgartner defined sarcopenia as a height adjusted to muscle mass of two standard deviations (SD) or more below the mean of a young reference population. With this as his measurement, he demonstrated the increasing prevalence of sarcopenia with aging. The prevalence of sarcopenia in the New Mexico Elder Health Survey was 14 % in those 65–69 years of age, compared with greater than 50 % in those 80 years of age and older [61]. Other researchers in the field of gerontology adopted this measurement standard in their investigations of age-related loss of muscle mass. The consistent use of measurements allows for more meaningful comparisons of research findings between studies.

Nearly all of the studies conducted prior to 2005 were cross-sectional, and focused on a correlation between sarcopenia and decreased muscle mass and the associated functional impairment leading to physical disability [124, 155–158]. At least one study in the early 2000s looked at the impact of muscle size and strength over time and reported a less than 5 % change in strength attributable to a corresponding change in muscle size [159]. In an 8-year follow up to the Cardiovascular Health Study, Janssen et al. [139] reported a 27 % increased risk of developing disability with sarcopenia when compared with individuals with normal muscle mass. Interestingly, at the beginning of that same study, the reported likelihood of having disability was 79 % greater in those with severe sarcopenia than in those with normal muscle mass. The longitudinal analysis was three times smaller than the cross-sectional analysis, reported at the baseline. This underscores the importance of not drawing conclusions too early in an investigation of data, and suggests that the sarcopenia-associated risk of functional impairment and physical disability reported in cross-sectional studies of older adults in the early 2000s may have been overestimated.

Questions surrounding a universally accepted definition of sarcopenia continue as clinicians and researchers search for specific age-related musculoskeletal changes that correlate most strongly with the risk of disability. Evidence is growing that the rate at which muscles become weaker is much faster than the rate at which they become smaller [160]. Research findings are supporting that it is the loss of muscle strength, even more than the loss of muscle mass, that carries the greatest risk of disability in the aging adult [102, 160, 161].

Some researchers refer to the ‘bone-muscle unit’ in deference to observations that bones respond to varying levels of mechanical strain imposed by muscle mass and strength. The varying levels of mechanical strain appear to be modulated primarily by hormonal effects systemically, citing gender differences over time as evidence [62]. There is undeniably much evidence in support of the strong correlation between bone and muscle strength [163, 164].

A deeper understanding of the physiological relevance of these bone and muscle endocrine properties may serve to bridge the gap between the mechanical and biochemical theories of bone-muscle interaction. A feasible way of interpreting the role of these interactions is that they may serve to sense and transduce biomechanical signals such as unloading, loading, inactivity, or exercise, and even perhaps the translation of systemic hormonal stimulation into effective biochemical signals. Another way of interpreting and bridging these two theories is that one specific form of interaction could work as a priming for the other, in that, the physical effects of contraction on bone cells may prime these cells for the simultaneous, consecutive or ulterior effects of a secreted molecule. The growing evidence of a mismatch between changes in muscle mass and muscle strength that accompany muscle unloading also lends support to the biochemical communication between tissues [66]. The suggestion that in addition to mechanical force, other factors contribute to increasing muscle strength came more than three decades ago. In their work with isometric training, McDonagh and colleagues made experimental observations that led them to postulate “that the increase in the force of maximal voluntary isometric contraction must be related to factors other than the force-generating capacity of the muscle fibres themselves” [165].

In his work with the New Mexico Elder Survey, Baumgartner observed that, as many as 15 % of

individuals with sarcopenia are also obese. The sarcopenic-obese older adult captured his attention because in his cross-sectional study examining older adults in the New Mexico Aging Process Study, he found this subsector of the elderly population to be at especially high risk of physical disability [166]. The decline in both lean muscle mass and bone density poses an even greater risk to independence and safety of the older adult. The appreciation of this risk has inspired research into this phenomenon. Findings of such research suggest an increase in catabolic cytokines such as interleukin-6 (IL-6), as well as inflammatory markers such as C-reactive protein and sedimentation rate [157, 167]. Interestingly, many of these same factors observed in the development of obesity are secreted by adipocytes [168, 169].

In 2004, Baumgartner and his team set out to replicate as a longitudinal study, the findings of their 2000 cross-sectional study, based upon the same cohort of individuals in New Mexico [170]. Looking at the problem over time, they found that neither sarcopenia alone nor obesity alone increased the older adult's risk of functional impairment when compared with those with a normal body composition. Sarcopenic-obese individuals, however, had a 2.5 times greater risk of functional impairment [170]. A partial explanation for this could be related to the decreased resting metabolic rate that corresponds to the reduced skeletal muscle mass of sarcopenia [171].

Since the mid-2000s, several researchers have investigated the combination of sarcopenia and obesity, specifically concerned with the risk for physical disability. The findings of some researchers support an increased risk of physical disability in sarcopenic-obese older adults [172, 173], while the findings of other researchers do not support this notion [65, 174]. Of interest is the recognition that between research groups, and even within some research groups, conflicting results are obtained with regard to the question of sarcopenic-obesity and the increased risk for physical disability. It is possible that these conflicting results are the consequence, in part, of having no single definition of sarcopenia that is widely accepted within the research and clinical arenas. This experience should provide ample motivation to come to a consensus on the matter.

Attempts to understand the cause of an age related loss of muscle mass and strength have predominantly focused on the loss of skeletal muscle fibers, especially type II fibers. In recent years researchers have begun to delve into a wide variety of mechanisms involved in the pathophysiological mechanisms of sarcopenia including nutritional factors, activity levels, alterations in protein metabolism, and the impact of changing levels of hormones. Walrand and colleagues published a review that shed light on what many had begun to observe; suggesting that sarcopenia impacts the development of other chronic conditions such as cardiovascular and metabolic diseases [175]. Sarcopenia is beginning to be linked to dyslipidemia, insulin resistance and hypertension as well as a decline in immunologic function [71, 125].

Gaining momentum is yet another element to this issue; that age-related decreases in muscle strength result from a combination of loss of muscle mass (atrophy) and reduced muscle specific force (i.e., muscle force per unit of cross-sectional area), suggesting reduced muscle quality. Data is gathering to show that it is principally the weakness that accompanies sarcopenia, not the loss of muscle size *per se* that contributes to disability [62, 159, 161]. It is possible that the disproportionate loss of force and power compared to loss of muscle mass originates inside the muscle fibers themselves, due to defects on the excitation-contraction coupling (ECC) process that ultimately lead to reduced availability of calcium to be released during each cycle of contraction-relaxation [66, 102, 176]. Reflecting on the physiology behind muscle contraction, it is reasonable to postulate that factors released from distant tissues could influence the steps leading up to skeletal muscle contraction. The mismatch observed between muscle mass and strength, might at least in part, be explained by other tissue factors that influence the EC coupling, such as reduced calcium release from the sarcoplasmic reticulum (see Fig. 4.8).

It has also been noted that store-operated calcium entry is reduced in aged muscle cells. In a recent review, the argument is made that there is most likely a link between dysfunctional intracellular calcium homeostasis, the newly discovered modulatory genes, and biochemical

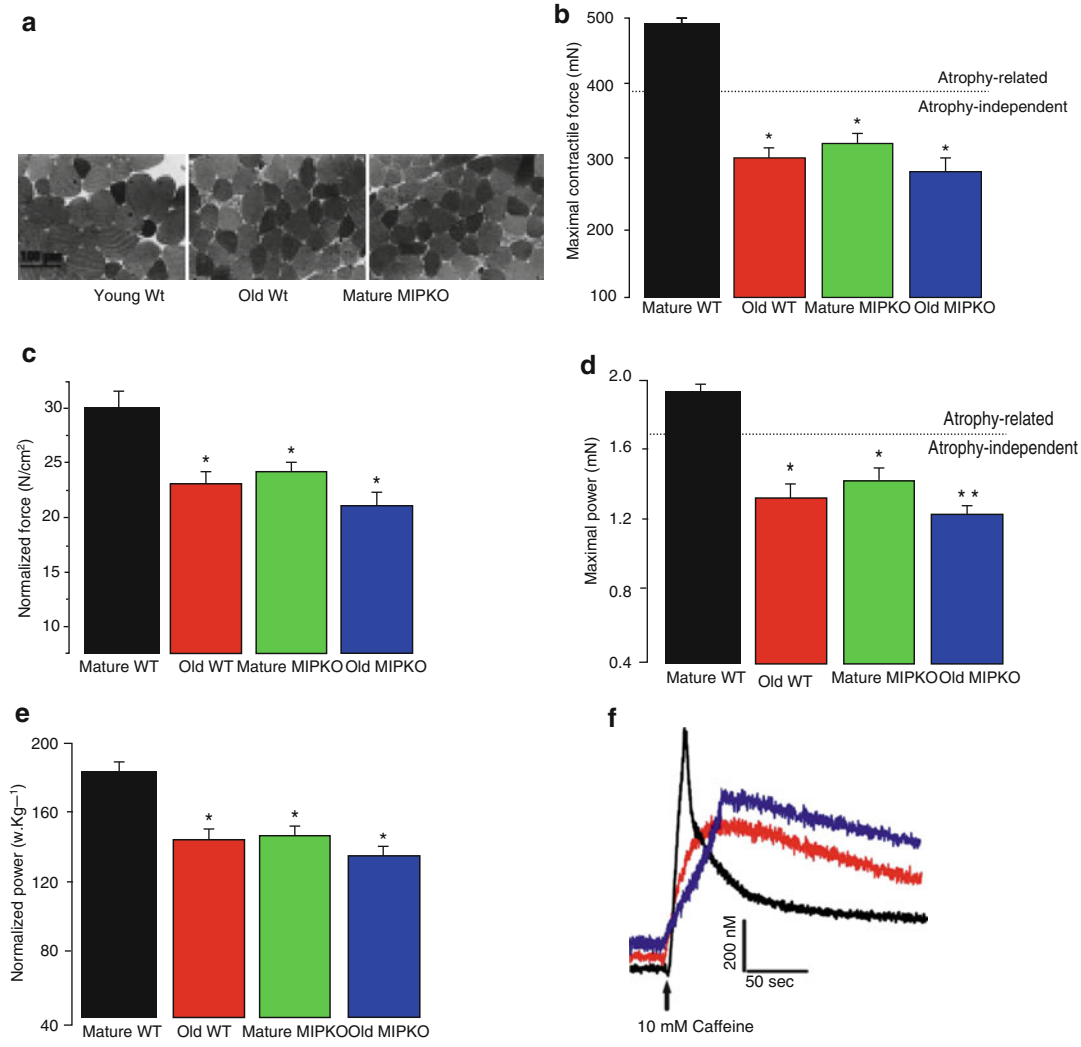


Fig. 4.8 Evidence for muscle atrophy, decreased contractile force, and reduced power in skeletal muscles suggested similarity from old WT and MIPKO mice. In all figures, the black bars are mature, wild type mice, the red bars are old, wild type mice, the green bars are mature MIPKO mice, and the blue bars are old, MIPKO mice. (**a**) Typical Toluidine blue-stained cross sections of EDL muscles from young Wt, old Wt, and mature MIPKO mice. The cross-sectional areas of old Wtand MIPKO cells are significantly reduced compared with those of the young Wt. (**b**) Maximal contractile force in EDL muscle for each genotype. Atrophy (decrease in muscle cross-sectional area) can explain ~1/2 of the drop in total force (note the *dotted horizontal line*), but does not account for the complete decrease in contractile force. (**c**) Data from **b**, except that force is normalized per cross-sectional area (N/cm^2). This figure illustrates the atrophy-independent component of contractile dysfunction. (**d**) Maximal power in EDL muscle from all four animal models. (**e**) Data from panel Dwas normalized per cross sectional area of muscles. It shows that a significant drop in power is atrophy-independent. Data is the average ± SE of 24 EDL muscles from 12 mice for each genotype. * indicates a significant difference ($p < 0.01$) between the control muscles and a particular genotype. ** indicates a significant difference ($p < 0.01$) between the old MIPKO mice and the old Wtand mature MIPKO mice (FROM Romero-Suarez et al. [176])

factors secreted by other body tissues, which is illustrated in Fig. 4.9.

Additional health risks experienced by sarcopenic older adults include insulin resistance and the development of type 2 diabetes mellitus. Srikanthan, Hevener, and Karlamangla conducted a study to investigate the relationship between sarcopenia, obesity and age-related insulin

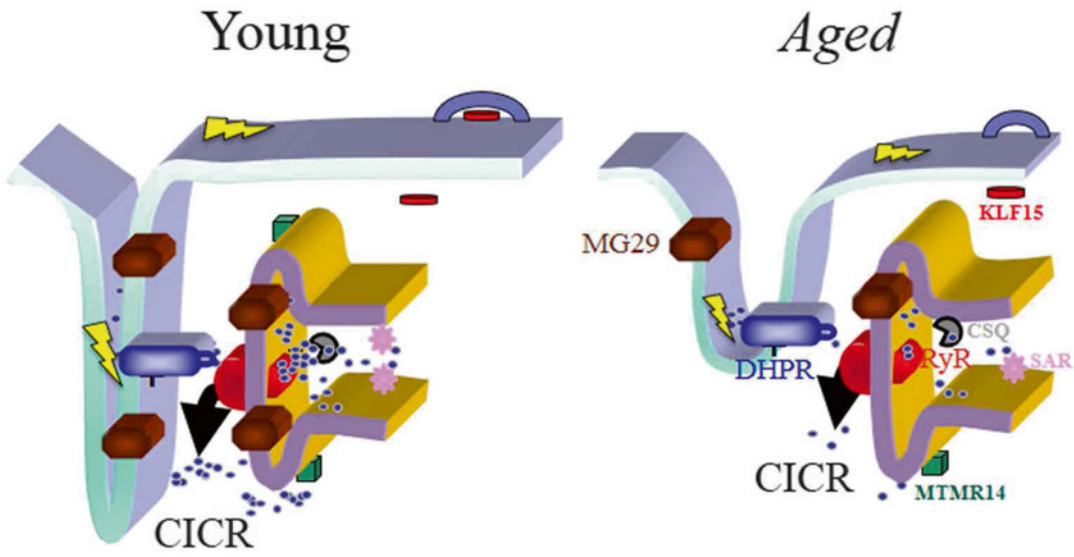


Fig. 4.9 Schematic drawing of the triad junction, the chief site of the E-C coupling process in skeletal muscles. The predicted localization of the four genes/proteins emphasized in this review article is shown and they are represented in different colors along with the Dihydropyridine Receptor (DHPR), the Ryanodine Receptortype1 (RyR1) and Calsequestrin (CSQ). In youngmusclesE-C coupling is effectively maintained through coordinated actions of the E-C coupling machinery and the optimal participation of MG29, MTMR14, SAR, and KLF15. Their concentration and/or effectiveness is reduced with aging, which associates with structural changes of the triad junction itself. Together these biochemical and morphological changes contribute to the reduced coupling between depolarization of the sarcolemma and contraction due to the reduced calcium release capacity of aged muscles. In summary, "E-C coupling quality" is reduced in aged muscles, and becomes a key factor to reduced muscle quality during aging. The steps of the E-C coupling process are described in detail in the text. In skeletal muscles, depolarization of the sarcolemma and its invaginations (t-tubules) represented by the lightning bolt in yellow color alters the configuration of the DHPR, which modifies its interaction with RyR1, leading to the dominant type of calcium release in skeletal muscle (depolarization-induced calcium release, DICR). This initial release phase can be further amplified by a secondary mechanism, calcium-induced calcium release (CICR), the main release mechanism in cardiac muscles. The structural deformation as well as the lack of organized triads is a hallmark of aged muscles and also common in other diseases covered in this article. Not detailed in this figure is the process of calcium entry or re-entry, store-operated calcium entry (SOCE), responsible for continual refilling of the sarcoplasmic reticulum (SR). SOCE is also reduced with aging, which we have postulated contributes to sarcopenia and to the un-matching between muscle mass and muscle contractile force during aging, since force/power decrease significantly more than the observed decrease in muscle mass. We foresee that new generations of drugs could be developed to specifically target the different steps of E-C coupling in disease states to increase efficiency of Ca2+ handling. F. Altered Ca+2 homeostasis is present in muscle fibers from old Wtand MIPKO mice. Original traces representative of caffeine-induced Fura-2 Ca+2 transients in mature Wt (*black trace*), old Wt (*red trace*), and mature MIPKO FDB muscle fibers (*blue trace*). Examples shown are representative of 6–12 muscle fibers from 3 mice, and data were normalized to the intracellular Ca+2 concentrations in nM (From Manring et al. [102], doi:10.3389/fphys.2014.00037. eCollection 2014. Review)

resistance. In their cross-sectional analysis of the National Health and Nutrition Examination Survey III (NANES III), they concluded that sarcopenia, independent of obesity, is associated with compromised glucose metabolism [177]. In support of that analysis, another study conducted around the same time concurred that type 2 diabetes was associated with an increased risk of sarcopenia [178]. A relationship between diabetes and sarcopenia certainly makes physiologic sense from the perspective that skeletal muscle represents the largest target tissue for insulin-mediated glucose uptake. A decline in muscle mass with aging is, therefore, associated with a decrease in sites for glucose uptake, which would be further exacerbated by a decline in physical activity. Along with this, data supports an increase in triglycerides with aging, which have been indicted both in age-related mitochondrial damage and with blocking of ability of insulin to

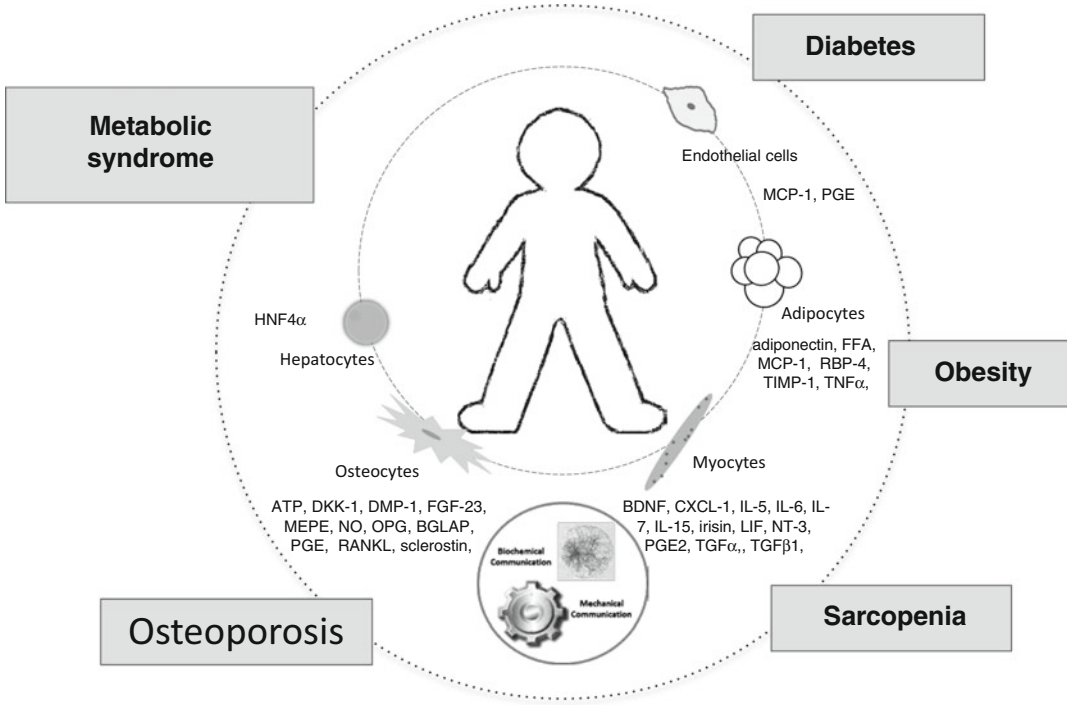


Fig. 4.10 Bone-muscle crosstalk, interactions with other tissues, and impact on chronic diseases. This original drawing illustrates the concept that interactions among different tissues throughout the organism are abundant and much more complex than previously realized. In this larger context, bone–muscle cross talk remains both physiologically and pathologically relevant but is also seen as being affected by other tissues of the body. At the center of this figure is the outline of an individual, the patient. The smaller circle, closest to the patient, lists cells discussed in the text, along with factors they are known to secrete. The dashed line connecting these cells indicates that they are connected biochemically through the impact that their secreted factors have on one another. The larger circle surrounding the patient lists a number of conditions and diseases impacted by the biochemical interactions between cells listed and others. Special significance for multi-tissue/organ cross talk is revealed by pathological conditions such as obesity, diabetes, and metabolic syndrome. The dotted line of this larger circle indicates the developing understanding that these conditions and diseases impact one another. These conditions seem to directly influence sarcopenia and osteoporosisasdetailed in the text (From Isaacson and Brotto [182])

facilitate glucose entry into the muscle cell. All of these phenomena contribute to an increase in blood glucose. Insulin is a potent anabolic hormone that impacts glucose, protein and lipid metabolism, and may play a significant role in all of this as well. It facilitates glucose uptake, inhibits hepatic glucose uptake and triglyceride production, inhibits skeletal muscle protein synthesis and inhibits adipose tissue lipolysis [179]. Recognizing this relationship, research conducted by Lee et al. provided data supporting a direct relationship between insulin resistance, the loss of lean muscle mass and the gain of fat mass in men aged 65 and older [180]. The chronic complications of diabetes mellitus affect systems throughout the body; including bones. Individuals with type 1 diabetes mellitus have lower bone mass density, with impaired bone formation believed to be the primary cause [181]. Patients with type 1- or type 2-diabetic patients experience hypercalciuria during times of glycosuria. This increased loss of calcium has been hypothesized to contribute to impaired bone quality observed with diabetes, although the direct effects of this loss of calcium on skeletal muscle function remains elusive. As more is understood about these chronic conditions, the connections between them are becoming undeniable. Recognizing these connections and conducting research from this multifactorial perspective will deepen understanding and further the development of meaningful interventions (Fig. 4.10).

The Role of Cartilage, Ligaments, and Tendons in Bone-Muscle Crosstalk

Crosstalk in MSK Development

As previously mentioned in this chapter, tissues of the musculoskeletal (MSK) system have been traditionally studied as individual and autonomous entities, in spite of being functionally intimately associated. This is especially true for bones, muscles, and tendons, which are commonly referred to as the *musculoskeletal unit.* This interrelationship is more noticeably characterized by a biomechanical interdependence, which is essential for body movement. Tendons, in most cases, connect muscles to bones, as muscles contract and shorten, they pull tendons, which in their turn pull bones, resulting in movement. This way, a weakness in any component should imply in loss of functionality of the whole unit. In addition to bones, muscles, and tendons, other tissues are also part of the MSK system, such as ligaments, which are responsible for bone to bone connection and essential for joint stability, and cartilaginous tissues. At the articular ends of bones, hyaline cartilage is closely associated with bone tissue as they form cartilaginous joints.

More recently, the concept that the communication between MSK tissues may extend beyond their biomechanical relationship has been gaining momentum as novel evidence in this direction is acquired through new research. In this case, MSK tissues would *talk* by exchanging chemical factors, in a paracrine or even endocrine way, that is, factors produced by one tissue would exert a determined effect on another tissue of the MSK system. Earlier in the chapter, we presented evidence about this biochemical crosstalk between bones and muscles. However, what about other tissues of the MSK system? Is it reasonable to expect that they also communicate via chemical factors? Or, alternatively, do they merely fulfill an essentially mechanical function?

In order to answer these intriguing questions, first we turn our attention to the development of the MSK system, where the importance of a crosstalk, biomechanical and biochemical, has been demonstrated. The events that characterize MSK embryologic development are quite complex and the objective of this section is not to present a comprehensive review of the topic, rather we will solely focus on findings that point to a biochemical crosstalk between tissues of the MSK system during development. Furthermore, we will restrict our discussion to vertebrates, more specifically using limb development as a model [184]. Muscles, tendons, and bones progenitor cells originate from different somites (i.e., divisions) of the mesoderm, respectively, the myotome, the syndetome, and the sclerotome. Two regions critical for the development of the MSK unit (muscle-tendon-bone): the myotendinous junction and the entheses, are specialized regions representing the muscle-tendon and tendon-bone interfaces, respectively. Correct assembly of these regions, which requires close interactions between these tissues, is crucial for the proper functioning of the MSK system.

Experimental evidence has shown that, in addition to the most flagrant role of mechanical load, the biochemical communication between bone, tendon, and muscle is crucial to their proper development. For example, scleraxis (Scx), a tendon marker, regulates the genetic expression of bone morphogenic protein-4 (*Bmp4*) in tendon cells. When *Bmp4* expression was blocked in mice, it led to a partial loss of bone ridges [183], suggesting a role of factors secreted by tendon on bone ridge formation. In addition, syndetome-induction, which will initiate tendon formation in mouse embryos, is associated with fibroblast growth factors (FGFs), FGF-4 and FGF-6 in mice, and FGF-8 in chicken [64, 185], only expressed in the myotome. This induction is a consequence of the activation of Scx expression and other tendon markers [64, 186] (Fig. 4.11). Down-regulation of these tendon markers in muscle-less and aneural conditions was reverted by the administration of exogenous FGF4, demonstrating an unequivocal biochemical dependence of tendon formation from muscle [187]. On the other hand, muscle development, initially characterized by increased proliferation of myogenic cells with later adjustment to normal

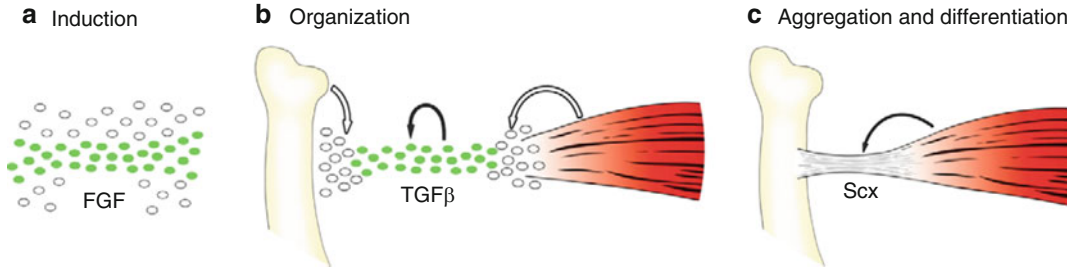


Fig. 4.11 Tissue interactions required for tendon progenitor induction in vertebrate embryos. Induction of tendon progenitors, identified as Scx-expressing cells, depends on a unique set of tissue interactions in different parts of the embryo. Each panel shows tendon progenitor distributionby whole-mount in situ hybridization (ISH) with an Scxprobe. The line across each upper image shows the orientation of the section schematized beneath, which highlights the relevant tissue interactions (with tendon progenitors shown in *green*; muscle progenitors in *red*; cartilage in *yellow*). (**a**) Whole-mount ScxISH on E10.5 mouse embryo and a schematic of a frontal trunk section, showing somite pairs (*squares*) and the neural tube (*gray*). Skeletal tissue derives from the sclerotome(Sc) of somites, whereas the musculature arises from the myotome(m). The tendon progenitors are found in the syndetome(S, *green*), a stripe of sclerotomecells at the junction between two adjacent myotomes. Scxexpression in syndetomecells is induced by FGFs secreted from the adjacent myotomes (*arrows*). (**b**) Whole-mount ScxISH on E10.5 mouse limb bud and a schematized sagittal section through the limb bud. In the early limb bud, Scxis expressed in mesodermal cells directly under the dorsal and ventral ectoderm. Scxexpression at this stage depends on ectoderm (*curved arrows*) and not on a signal from the myoblasts or from pre-chondrogeniccells. (**c**) Whole mount ScxISH on E12.5 mouse limb and a schematized sagittal section through the autopod. In the differentiating autopod, Scxis expressed in subectodermalmesoderm along the differentiating skeletal elements. Scxexpression along the differentiating digits can be induced by a signal from the skeletal condensations (*straight arrow*), and the sub-ectodermal position of the tendon progenitors suggests a role for the ectoderm (*curved arrows*) in tendon induction as well. *A* anterior, *D* distal, *P* posterior, *Pr* proximal, *nt* neural tube (From Schweitzer et al. [183])

morphology, happens because of controlled cell death modulated by local apoptotic factor(s). Interestingly, only muscle fibers that are not part of a stable myotendinous junction are affected, suggesting a role for tendon in muscle that belies morphogenesis. Retinoic acid, produced by both tendon and muscle, has been suggested as a potential apoptotic factor with an important role in mediating muscle apoptosis and muscle-tendon assembly [188].

Bone-Cartilage Crosstalk

Like other interactions between contiguous tissues of the MSK system, mechanical load is an integral part of their relationship and biomechanical crosstalk is indisputable. In this way, defective bone remodeling affects its mechanical properties, and, consequently, modifies how load is transmitted to cartilage, which ultimately results in altered local strains, and cartilage weakening and disease. Several studies have shown that initiation of osteoarthritis (OA) is preceded by increased osteoclastic activity and subchondral bone resorption [68], but it is not clear if it happens only because of mechanical causes or if other factors are also involved. Despite this almost ubiquitous mechanical influence and the difficulty of removing the mechanical influence in this relationship, there is evidence that also points to a biochemical crosstalk between subchondral bone and cartilage in OA. In mice, over-expression of the EPHB4 receptor in osteoblasts was able to protect against OA induced by medial meniscus destabilization. In this case, OA was not initially related to a previously altered mechanical environment, and molecular changes in bone were able to deter OA development, which clearly suggests a role for factor(s) produced by bone in this process, and a bone-cartilage crosstalk [189]. There is also evidence that the hepatocyte growth-factor (HGF) may be part of the bone-cartilage crosstalk in OA. HGF expression and production in human subchondral osteoblasts are increased in OA, while the protein, but not the gene, can be detected in the articular cartilage, suggesting that

subchondral bone could be the origin of that HGF. Other potential players in the bone-cartilage crosstalk are RANK ligand (RANKL) and osteoprotegerin (OPG). Interestingly, though both molecules are produced by bone and cartilage cells, RANK receptor is expressed only in human OA chondrocytes [190]. How does this crosstalk happen? First, there is evidence that small molecules can easily diffuse between the bone marrow and the articular space, suggesting that, at least for small molecules, a direct exchange of biochemical factors between subchondral bone and articular cartilage is possible in a paracrine fashion [189, 191]. Second, during the pathogenesis of OA, vascular penetration in cartilage would expose the chondrocytes to cytokines and growth factors, such as VEGF, NGF, IL-1, IL-6, HGF, or IGF-1, from subchondral bone [192]. Overall, the demonstration of the bone-cartilage crosstalk indicates that targeting subchondral bone is a viable therapeutic approach in the OA treatment [193].

Tendon-Muscle Crosstalk

We have mentioned that during development there is strong evidence pointing to a biochemical crosstalk between muscle and tendon. Is there similar evidence post-development? Although the crosstalk between MSK tissues is a recently new research topic and the factors supposedly responsible for the crosstalk are yet to be identified, there are subtle but unquestionable indications that the relationship between muscles and tendons go beyond their biomechanical dependence.

Tendinopathies are common overuse injuries in sports and are often associated with aging. Tendons are difficult to heal, and most of the time the mechanical properties of the tissue are poorer when compared to the normal tissue. Clinicians have known for quite a long time that eccentric (i.e. lengthening contraction), not concentric (i.e. shortening contraction), training is the most effective conservative treatment to promote healing of tendon diseases, including Achilles and patellar tendinopathies [63, 194]. In eccentric training muscle contraction occurs at the same time that the muscles and tendons are stretching or remain stretched [63]. Despite overwhelming clinical evidence, the mechanisms of how eccentric contraction improves tendon healing remain unknown. The answer may be in how the expression of growth factors, such as TGFβ-1 and IGF-1, respond to eccentric and concentric training in tendons and muscles. Heinemeier et al. exposed rats to short-term strength training consisting of pure shortening (concentric), lengthening (eccentric), or static plantar extensors contraction. Strength training in the Achilles tendon, regardless of the type of contraction, increased the expression of TGFβ-1 and IGF-1, even though the force produced was higher during the eccentric contractions. In the gastrocnemius muscle, there was similar upregulation of growth factors; however, the effect of lengthening was significantly greater than the effect of shortening [195]. The fact that muscle, but not tendon, responded differently depending on the type of strength training strongly suggests that if eccentric contractions have superior effect on tendon healing, it may be caused by one or more muscle factors produced during eccentric but not concentric contraction.

Transgenic mice are useful models to study the role of specific cytokines in different tissues. The *mdx* mouse is the classical animal model for Duchenne muscular dystrophy. Dystrophin is a cytoplasmatic protein that forms a complex that connects the cytoskeleton of the muscle fiber to the surrounding extracellular matrix. Without the dystrophin-complex, the sarcolemma becomes fragile and as the muscle fibers contract the muscle is damaged. As a result, *mdx* skeletal muscles are ~20 % weaker than normal muscles. Rizzuto et al. found that in dystrophin-deficient (*mdx*) mice, tendons are also affected by an increase in the number of dead cells, more energy dissipation during dynamic loading, and a significant loss of the elastic properties of the tissue. Furthermore, these functional changes suggest that *mdx* tendon experience similar alterations to those found in *mdx* muscles (reduction of viable cells and higher inflammatory response). It could be argued that a weaker muscle would cause a loss in tendon mechanical properties, but the similarity in response to missing dystrophin could also mean that either the protein has

a role in tendon homeostasis or that there is a paracrine communication between muscles and tendons [196].

The existence of a crosstalk between tissues of the MSK system, in development and adult life, are crucial for a better understanding of the biology of theses tissues and may open the door to strategies that would improve the regeneration of these tissues, especially those that are difficult to heal.

Concluding Remarks and Future Directions

In the year 2000, United Nations member states signed the United Nations Millennium Declaration agreeing to work toward the achievement of eight Millennium Development Goals (MDGs) by the year 2030. Among these are the goals to improve health and combat disease. While major issues related to health care education and access, such as proper diet, exercise levels, and a host of social factors remain critical to be addressed, if humanity is to achieve the WHO health goals, all of us must do more. Even in face of all these challenges, however, humans are living longer due in large part to basic improvements in health conditions and reductions in absolute levels of poverty or misery.

Life expectancy in Japan has reached almost 83 years and the oldest human on record has lived to 122 years of age. Very simple metabolic and telomerase estimations give us the clue that humans could live to 125 years of age. This increasing life expectancy poses a unique set of challenges. On the one hand, there is the desire to live a longer and healthier life, but the cost seems quite high since morbidities and co-morbidities combine to afflict in particular older adults. Musculoskeletal diseases alone affect almost 2 billion humans in the planet and the large majority of them are older persons. The puzzle that is facing us is that while living a long life is desirable; it is really the quality of such life that matters the most.

As MSK scientists are trying to put the pieces of this puzzle together, they have come across some very interesting new ideas. There is no doubt that bones-tendons-muscles come together in a unit of mechanical coupling where physical forces are constantly shaping the relationships between these tissues. What is relatively new is the "kine"; the endocrine-like role that these tissues play. It seems that the human body is significantly more endocrine than we had ever anticipated and the MSK players are no different from other parts of the body.

Thus, in this complex interaction of physical forces and secreted factors (myokines, osteokines, tenokines), these tissues interact both physically and biochemically in ways about which we are still learning. However, it is even more complex. Behind these interactions, there are complex genetic signaling pathways apparently shared among these tissues, and this pleiotropy might itself influence the way these tissues respond to physical and biochemical forces and factors.

In a world filled with uncertainty, there is one certainty; the MSK field is poised to bring many new developments and advancements as we improve our understanding of the MSK system and how different tissues interact and prime other in heath and disease. If we learn for example to control or modulate the secretion or to mimic the effects of the "kines", many MSK conditions could be treated or improved, including the twin diseases of aging, osteoporosis and sarcopenia. One last and very positive aspect of this field is that its basic research is continuing to push new boundaries of cell biological understanding, thus facilitating the development of new technologies that will benefit science and humankind in general.

References

1. Pourquie O. Vertebrate somitogenesis. Annu Rev Cell Dev Biol. 2001;17:311–50. doi:10.1146/annurev.cellbio.17.1.311.
2. Land C, Schoenau E. Fetal and postnatal bone development: reviewing the role of mechanical stimuli and nutrition. Best Pract Res Clin Endocrinol Metab. 2008;22(1):107–18. doi:10.1016/j.beem.2007.09.005.
3. Rauch F, Schoenau E. The developing bone: slave or master of its cells and molecules? Pediatr Res.

2001;50(3):309–14.doi:10.1203/00006450-200109000-00003.
4. Gunter KB, Almstedt HC, Janz KF. Physical activity in childhood may be the key to optimizing lifespan skeletal health. Exerc Sport Sci Rev. 2012;40(1):13–21. doi:10.1097/JES.0b013e318236e5ee.
5. Recker R, Lappe J, Davies K, Heaney R. Characterization of perimenopausal bone loss: a prospective study. J Bone Miner Res Off J Am Soc Bone Miner Res. 2000;15(10):1965–73. doi:10.1359/jbmr.2000.15.10.1965.
6. Hu MC, Shiizaki K, Kuro-o M, Moe OW. Fibroblast growth factor 23 and Klotho: physiology and pathophysiology of an endocrine network of mineral metabolism. Annu Rev Physiol. 2013;75:503–33. doi:10.1146/annurev-physiol-030212-183727.
7. Novotny SA, Warren GL, Hamrick MW. Aging and the muscle-bone relationship. Physiology. 2015;30:8–16.
8. Arden NK, Spector TD. Genetic influences on muscle strength, lean body mass, and bone mineral density: a twin study. J Bone Miner Res Off J Am Soc Bone Miner Res. 1997;12(12):2076–81. doi:10.1359/jbmr.1997.12.12.2076.
9. Costa AM, Breitenfeld L, Silva AJ, Pereira A, Izquierdo M, Marques MC. Genetic inheritance effects on endurance and muscle strength: an update. SportsMed.2012;42(6):449–58.doi:10.2165/11650560-000000000-00000.
10. Prior SJ, Roth SM, Wang X, Kammerer C, Miljkovic-Gacic I, Bunker CH, Wheeler VW, Patrick AL, Zmuda JM. Genetic and environmental influences on skeletal muscle phenotypes as a function of age and sex in large, multigenerational families of African heritage. J Appl Physiol. 2007;103(4):1121–7. doi:10.1152/japplphysiol.00120.2007.
11. Silventoinen K, Magnusson PK, Tynelius P, Kaprio J, Rasmussen F. Heritability of body size and muscle strength in young adulthood: a study of one million Swedish men. Genet Epidemiol. 2008;32(4):341–9. doi:10.1002/gepi.20308.
12. Cheng Y, Rachagani S, Canovas A, Mayes MS, Tait Jr RG, Dekkers JC, Reecy JM. Body composition and gene expression QTL mapping in mice reveals imprinting and interaction effects. BMC Genet. 2013;14:103. doi:10.1186/1471-2156-14-103.
13. Guo YF, Zhang LS, Liu YJ, Hu HG, Li J, Tian Q, Yu P, Zhang F, Yang TL, Guo Y, Peng XL, Dai M, Chen W, Deng HW. Suggestion of GLYAT gene underlying variation of bone size and body lean mass as revealed by a bivariate genome-wide association study. Hum Genet. 2013;132(2):189–99. doi:10.1007/s00439-012-1236-5.
14. Hai R, Pei YF, Shen H, Zhang L, Liu XG, Lin Y, Ran S, Pan F, Tan LJ, Lei SF, Yang TL, Zhang Y, Zhu XZ, Zhao LJ, Deng HW. Genome-wide association study of copy number variation identified gremlin1 as a candidate gene for lean body mass. J Hum Genet. 2012;57(1):33–7. doi:10.1038/jhg.2011.125.
15. Keildson S, Fadista J, Ladenvall C, Hedman AK, Elgzyri T, Small KS, Grundberg E, Nica AC, Glass D, Richards JB, Barrett A, Nisbet J, Zheng HF, Ronn T, Strom K, Eriksson KF, Prokopenko I, Consortium M, Consortium D, Mu TC, Spector TD, Dermitzakis ET, Deloukas P, McCarthy MI, Rung J, Groop L, Franks PW, Lindgren CM, Hansson O. Expression of phosphofructokinase in skeletal muscle is influenced by genetic variation and associated with insulin sensitivity. Diabetes. 2014;63(3):1154–65. doi:10.2337/db13-1301.
16. Kuo T, Lew MJ, Mayba O, Harris CA, Speed TP, Wang JC. Genome-wide analysis of glucocorticoid receptor-binding sites in myotubes identifies gene networks modulating insulin signaling. Proc Natl Acad Sci U S A. 2012;109(28):11160–5. doi:10.1073/pnas.1111334109.
17. Liu XG, Tan LJ, Lei SF, Liu YJ, Shen H, Wang L, Yan H, Guo YF, Xiong DH, Chen XD, Pan F, Yang TL, Zhang YP, Guo Y, Tang NL, Zhu XZ, Deng HY, Levy S, Recker RR, Papasian CJ, Deng HW. Genome-wide association and replication studies identified TRHR as an important gene for lean body mass. Am J Hum Genet. 2009;84(3):418–23. doi:10.1016/j.ajhg.2009.02.004.
18. Perusse L, Rankinen T, Rauramaa R, Rivera MA, Wolfarth B, Bouchard C. The human gene map for performance and health-related fitness phenotypes: the 2002 update. Med Sci Sports Exerc. 2003;35(8):1248–64. doi:10.1249/01.MSS.0000078938.84161.22.
19. Thomis MA, De Mars G, Windelinckx A, Peeters MW, Huygens W, Aerssens J, Beunen GP. Genome-wide linkage scan for resistance to muscle fatigue. Scand J Med Sci Sports. 2011;21(4):580–8. doi:10.1111/j.1600-0838.2009.01082.x.
20. Windelinckx A, De Mars G, Huygens W, Peeters MW, Vincent B, Wijmenga C, Lambrechts D, Delecluse C, Roth SM, Metter EJ, Ferrucci L, Aerssens J, Vlietinck R, Beunen GP, Thomis MA. Comprehensive fine mapping of chr12q12-14 and follow-up replication identify activin receptor 1B (ACVR1B) as a muscle strength gene. Eur J Hum Genet EJHG. 2011;19(2):208–15. doi:10.1038/ejhg.2010.173.
21. Duncan EL, Danoy P, Kemp JP, Leo PJ, McCloskey E, Nicholson GC, Eastell R, Prince RL, Eisman JA, Jones G, Sambrook PN, Reid IR, Dennison EM, Wark J, Richards JB, Uitterlinden AG, Spector TD, Esapa C, Cox RD, Brown SD, Thakker RV, Addison KA, Bradbury LA, Center JR, Cooper C, Cremin C, Estrada K, Felsenberg D, Gluer CC, Hadler J, Henry MJ, Hofman A, Kotowicz MA, Makovey J, Nguyen SC, Nguyen TV, Pasco JA, Pryce K, Reid DM, Rivadeneira F, Roux C, Stefansson K, Styrkarsdottir U, Thorleifsson G, Tichawangana R, Evans DM, Brown MA. Genome-wide association study using extreme truncate selection identifies novel genes affecting bone mineral density and fracture risk. PLoS Genet. 2011;7(4):e1001372. doi:10.1371/journal.pgen.1001372.
22. Estrada K, Styrkarsdottir U, Evangelou E, Hsu YH, Duncan EL, Ntzani EE, Oei L, Albagha OM, Amin N, Kemp JP, Koller DL, Li G, Liu CT, Minster RL, Moayyeri A, Vandenput L, Willner D, Xiao SM,

Yerges-Armstrong LM, Zheng HF, Alonso N, Eriksson J, Kammerer CM, Kaptoge SK, Leo PJ, Thorleifsson G, Wilson SG, Wilson JF, Aalto V, Alen M, Aragaki AK, Aspelund T, Center JR, Dailiana Z, Duggan DJ, Garcia M, Garcia-Giralt N, Giroux S, Hallmans G, Hocking LJ, Husted LB, Jameson KA, Khusainova R, Kim GS, Kooperberg C, Koromila T, Kruk M, Laaksonen M, Lacroix AZ, Lee SH, Leung PC, Lewis JR, Masi L, Mencej-Bedrac S, Nguyen TV, Nogues X, Patel MS, Prezelj J, Rose LM, Scollen S, Siggeirsdottir K, Smith AV, Svensson O, Trompet S, Trummer O, van Schoor NM, Woo J, Zhu K, Balcells S, Brandi ML, Buckley BM, Cheng S, Christiansen C, Cooper C, Dedoussis G, Ford I, Frost M, Goltzman D, Gonzalez-Macias J, Kahonen M, Karlsson M, Khusnutdinova E, Koh JM, Kollia P, Langdahl BL, Leslie WD, Lips P, Ljunggren O, Lorenc RS, Marc J, Mellstrom D, Obermayer-Pietsch B, Olmos JM, Pettersson-Kymmer U, Reid DM, Riancho JA, Ridker PM, Rousseau F, Slagboom PE, Tang NL, Urreizti R, Van Hul W, Viikari J, Zarrabeitia MT, Aulchenko YS, Castano-Betancourt M, Grundberg E, Herrera L, Ingvarsson T, Johannsdottir H, Kwan T, Li R, Luben R, Medina-Gomez C, Palsson ST, Reppe S, Rotter JI, Sigurdsson G, van Meurs JB, Verlaan D, Williams FM, Wood AR, Zhou Y, Gautvik KM, Pastinen T, Raychaudhuri S, Cauley JA, Chasman DI, Clark GR, Cummings SR, Danoy P, Dennison EM, Eastell R, Eisman JA, Gudnason V, Hofman A, Jackson RD, Jones G, Jukema JW, Khaw KT, Lehtimaki T, Liu Y, Lorentzon M, McCloskey E, Mitchell BD, Nandakumar K, Nicholson GC, Oostra BA, Peacock M, Pols HA, Prince RL, Raitakari O, Reid IR, Robbins J, Sambrook PN, Sham PC, Shuldiner AR, Tylavsky FA, van Duijn CM, Wareham NJ, Cupples LA, Econs MJ, Evans DM, Harris TB, Kung AW, Psaty BM, Reeve J, Spector TD, Streeten EA, Zillikens MC, Thorsteinsdottir U, Ohlsson C, Karasik D, Richards JB, Brown MA, Stefansson K, Uitterlinden AG, Ralston SH, Ioannidis JP, Kiel DP, Rivadeneira F. Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture. Nat Genet. 2012;44(5):491–501. doi:10.1038/ng.2249.

23. Karasik D, Hsu YH, Zhou Y, Cupples LA, Kiel DP, Demissie S. Genome-wide pleiotropy of osteoporosis-related phenotypes: the Framingham Study. J Bone Miner Res Off J Am Soc Bone Miner Res. 2010;25(7):1555–63. doi:10.1002/jbmr.38.
24. Lee YH, Choi SJ, Ji JD, Song GG. Pathway analysis of genome-wide association study for bone mineral density. Mol Biol Rep. 2012;39(8):8099–106. doi:10.1007/s11033-012-1657-1.
25. Oei L, Hsu YH, Styrkarsdottir U, Eussen BH, de Klein A, Peters MJ, Halldorsson B, Liu CT, Alonso N, Kaptoge SK, Thorleifsson G, Hallmans G, Hocking LJ, Husted LB, Jameson KA, Kruk M, Lewis JR, Patel MS, Scollen S, Svensson O, Trompet S, van Schoor NM, Zhu K, Buckley BM, Cooper C, Ford I, Goltzman D, Gonzalez-Macias J, Langdahl BL, Leslie WD, Lips P, Lorenc RS, Olmos JM, Pettersson-Kymmer U, Reid DM, Riancho JA, Slagboom PE, Garcia-Ibarbia C, Ingvarsson T, Johannsdottir H, Luben R, Medina-Gomez C, Arp P, Nandakumar K, Palsson ST, Sigurdsson G, van Meurs JB, Zhou Y, Hofman A, Jukema JW, Pols HA, Prince RL, Cupples LA, Marshall CR, Pinto D, Sato D, Scherer SW, Reeve J, Thorsteinsdottir U, Karasik D, Richards JB, Stefansson K, Uitterlinden AG, Ralston SH, Ioannidis JP, Kiel DP, Rivadeneira F, Estrada K. A genome-wide copy number association study of osteoporotic fractures points to the 6p25.1 locus. J Med Genet. 2014;51(2):122–31. doi:10.1136/jmedgenet-2013-102064.
26. Ran S, Pei YF, Liu YJ, Zhang L, Han YY, Hai R, Tian Q, Lin Y, Yang TL, Guo YF, Shen H, Thethi IS, Zhu XZ, Deng HW. Bivariate genome-wide association analyses identified genes with pleiotropic effects for femoral neck bone geometry and age at menarche. PLoS One. 2013;8(4):e60362. doi:10.1371/journal.pone.0060362.
27. Rivadeneira F, Styrkarsdottir U, Estrada K, Halldorsson BV, Hsu YH, Richards JB, Zillikens MC, Kavvoura FK, Amin N, Aulchenko YS, Cupples LA, Deloukas P, Demissie S, Grundberg E, Hofman A, Kong A, Karasik D, van Meurs JB, Oostra B, Pastinen T, Pols HA, Sigurdsson G, Soranzo N, Thorleifsson G, Thorsteinsdottir U, Williams FM, Wilson SG, Zhou Y, Ralston SH, van Duijn CM, Spector T, Kiel DP, Stefansson K, Ioannidis JP, Uitterlinden AG, Genetic Factors for Osteoporosis C. Twenty bone-mineral-density loci identified by large-scale meta-analysis of genome-wide association studies. Nat Genet. 2009;41(11):1199–206. doi:10.1038/ng.446.
28. Savage SA, Mirabello L, Wang Z, Gastier-Foster JM, Gorlick R, Khanna C, Flanagan AM, Tirabosco R, Andrulis IL, Wunder JS, Gokgoz N, Patino-Garcia A, Sierrasesumaga L, Lecanda F, Kurucu N, Ilhan IE, Sari N, Serra M, Hattinger C, Picci P, Spector LG, Barkauskas DA, Marina N, de Toledo SR, Petrilli AS, Amary MF, Halai D, Thomas DM, Douglass C, Meltzer PS, Jacobs K, Chung CC, Berndt SI, Purdue MP, Caporaso NE, Tucker M, Rothman N, Landi MT, Silverman DT, Kraft P, Hunter DJ, Malats N, Kogevinas M, Wacholder S, Troisi R, Helman L, Fraumeni Jr JF, Yeager M, Hoover RN, Chanock SJ. Genome-wide association study identifies two susceptibility loci for osteosarcoma. Nat Genet. 2013;45(7):799–803. doi:10.1038/ng.2645.
29. Zhang L, Choi HJ, Estrada K, Leo PJ, Li J, Pei YF, Zhang Y, Lin Y, Shen H, Liu YZ, Liu Y, Zhao Y, Zhang JG, Tian Q, Wang YP, Han Y, Ran S, Hai R, Zhu XZ, Wu S, Yan H, Liu X, Yang TL, Guo Y, Zhang F, Guo YF, Chen Y, Chen X, Tan L, Zhang L, Deng FY, Deng H, Rivadeneira F, Duncan EL, Lee JY, Han BG, Cho NH, Nicholson GC, McCloskey E, Eastell R, Prince RL, Eisman JA, Jones G, Reid IR, Sambrook PN, Dennison EM, Danoy P, Yerges-Armstrong LM, Streeten EA, Hu T, Xiang S, Papasian CJ, Brown MA, Shin CS, Uitterlinden AG, Deng HW. Multistage genome-wide association meta-analyses identified two new loci for bone

mineral density. Hum Mol Genet. 2014;23(7):1923–33. doi:10.1093/hmg/ddt575.
30. Gupta M, Cheung CL, Hsu YH, Demissie S, Cupples LA, Kiel DP, Karasik D. Identification of homogeneous genetic architecture of multiple genetically correlated traits by block clustering of genome-wide associations. J Bone Miner Res Off J Am Soc Bone Miner Res. 2011;26(6):1261–71. doi:10.1002/jbmr.333.
31. Karasik D, Cohen-Zinder M. Osteoporosis genetics: year 2011 in review. Bonekey Rep. 2012;1:114. doi:10.1038/bonekey.2012.114.
32. Karasik D, Kiel DP. Evidence for pleiotropic factors in genetics of the musculoskeletal system. Bone. 2010;46(5):1226–37. doi:10.1016/j.bone.2010.01.382.
33. Karasik D, Zhou Y, Cupples LA, Hannan MT, Kiel DP, Demissie S. Bivariate genome-wide linkage analysis of femoral bone traits and leg lean mass: Framingham study. J Bone Miner Res Off J Am Soc Bone Miner Res. 2009;24(4):710–8. doi:10.1359/jbmr.081222.
34. Sun L, Tan LJ, Lei SF, Chen XD, Li X, Pan R, Yin F, Liu QW, Yan XF, Papasian CJ, Deng HW. Bivariate genome-wide association analyses of femoral neck bone geometry and appendicular lean mass. PLoS One. 2011;6(11):e27325. doi:10.1371/journal.pone.0027325.
35. Edmondson DG, Lyons GE, Martin JF, Olson EN. Mef2 gene expression marks the cardiac and skeletal muscle lineages during mouse embryogenesis. Development. 1994;120(5):1251–63.
36. Kramer I, Baertschi S, Halleux C, Keller H, Kneissel M. Mef2c deletion in osteocytes results in increased bone mass. J Bone Miner Res Off J Am Soc Bone Miner Res. 2012;27(2):360–73. doi:10.1002/jbmr.1492.
37. Cloutier P, Lavallee-Adam M, Faubert D, Blanchette M, Coulombe B. A newly uncovered group of distantly related lysine methyltransferases preferentially interact with molecular chaperones to regulate their activity. PLoS Genet. 2013;9(1):e1003210. doi:10.1371/journal.pgen.1003210.
38. Huang J, Hsu YH, Mo C, Abreu E, Kiel DP, Bonewald LF, Brotto M, Karasik D. METTL21C is a potential pleiotropic gene for osteoporosis and sarcopenia acting through the modulation of the NF-kappaB signaling pathway. J Bone Miner Res Off J Am Soc Bone Miner Res. 2014;29(7):1531–40. doi:10.1002/jbmr.2200.
39. Kimonis VE, Fulchiero E, Vesa J, Watts G. VCP disease associated with myopathy, Paget disease of bone and frontotemporal dementia: review of a unique disorder. Biochim Biophys Acta. 2008;1782(12):744–8. doi:10.1016/j.bbadis.2008.09.003.
40. McPherron AC, Lawler AM, Lee SJ. Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member. Nature. 1997;387(6628):83–90. doi:10.1038/387083a0.
41. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nat Rev Endocrinol. 2012;8(8):457–65. doi:10.1038/nrendo.2012.49.
42. Clop A, Marcq F, Takeda H, Pirottin D, Tordoir X, Bibe B, Bouix J, Caiment F, Elsen JM, Eychenne F, Larzul C, Laville E, Meish F, Milenkovic D, Tobin J, Charlier C, Georges M. A mutation creating a potential illegitimate microRNA target site in the myostatin gene affects muscularity in sheep. Nat Genet. 2006;38(7):813–8. doi:10.1038/ng1810.
43. Grobet L, Martin LJ, Poncelet D, Pirottin D, Brouwers B, Riquet J, Schoeberlein A, Dunner S, Menissier F, Massabanda J, Fries R, Hanset R, Georges M. A deletion in the bovine myostatin gene causes the double-muscled phenotype in cattle. Nat Genet. 1997;17(1):71–4. doi:10.1038/ng0997-71.
44. Kambadur R, Sharma M, Smith TP, Bass JJ. Mutations in myostatin (GDF8) in double-muscled Belgian Blue and Piedmontese cattle. Genome Res. 1997;7(9):910–6.
45. McPherron AC, Lee SJ. Double muscling in cattle due to mutations in the myostatin gene. Proc Natl Acad Sci U S A. 1997;94(23):12457–61.
46. Mosher DS, Quignon P, Bustamante CD, Sutter NB, Mellersh CS, Parker HG, Ostrander EA. A mutation in the myostatin gene increases muscle mass and enhances racing performance in heterozygote dogs. PLoS Genet. 2007;3(5), e79. doi:10.1371/journal.pgen.0030079.
47. Zhang GX, Zhao XH, Wang JY, Ding FX, Zhang L. Effect of an exon 1 mutation in the myostatin gene on the growth traits of the Bian chicken. Anim Genet. 2012;43(4):458–9. doi:10.1111/j.1365-2052.2011.02274.x.
48. Williams MS. Myostatin mutation associated with gross muscle hypertrophy in a child. N Engl J Med. 2004;351(10):1030–1; author reply 1030–1.
49. Elkasrawy MN, Hamrick MW. Myostatin (GDF-8) as a key factor linking muscle mass and bone structure. J Musculoskelet Neuronal Interact. 2010;10(1):56–63.
50. Williams NG, Interlichia JP, Jackson MF, Hwang D, Cohen P, Rodgers BD. Endocrine actions of myostatin: systemic regulation of the IGF and IGF binding protein axis. Endocrinology. 2011;152(1):172–80. doi:10.1210/en.2010-0488.
51. Perrini S, Laviola L, Carreira MC, Cignarelli A, Natalicchio A, Giorgino F. The GH/IGF1 axis and signaling pathways in the muscle and bone: mechanisms underlying age-related skeletal muscle wasting and osteoporosis. J Endocrinol. 2010;205(3):201–10. doi:10.1677/JOE-09-0431.
52. Fakhouri TH, Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity among older adults in the United States, 2007–2010. NCHS Data Brief. 2012;106:1–8.
53. Landry PS, Marino AA, Sadasivan KK, Albright JA. Effect of soft-tissue trauma on the early periosteal response of bone to injury. J Trauma. 2000;48(3):479–83.
54. Stein H, Perren SM, Cordey J, Kenwright J, Mosheiff R, Francis MJ. The muscle bed–a crucial factor for fracture healing: a physiological concept. Orthopedics. 2002;25(12):1379–83.

55. Utvag SE, Iversen KB, Grundnes O, Reikeras O. Poor muscle coverage delays fracture healing in rats. Acta Orthop Scand. 2002;73(4):471–4. doi:10.1080/00016470216315.
56. Zacks SI, Sheff MF. Periosteal and metaplastic bone formation in mouse minced muscle regeneration. Lab Invest J Tech Methods Pathol. 1982;46(4):405–12.
57. Aydin A, Memisoglu K, Cengiz A, Atmaca H, Muezzinoglu B, Muezzinoglu US. Effects of botulinum toxin A on fracture healing in rats: an experimental study. J Orthop Sci Off J Jpn Orthop Assoc. 2012;17(6):796–801. doi:10.1007/s00776-012-0269-x.
58. Harry LE, Sandison A, Paleolog EM, Hansen U, Pearse MF, Nanchahal J. Comparison of the healing of open tibial fractures covered with either muscle or fasciocutaneous tissue in a murine model. J Orthop Res Off Publ Orthop Res Soc. 2008;26(9):1238–44. doi:10.1002/jor.20649.
59. Reverte MM, Dimitriou R, Kanakaris NK, Giannoudis PV. What is the effect of compartment syndrome and fasciotomies on fracture healing in tibial fractures? Injury. 2011;42(12):1402–7. doi:10.1016/j.injury.2011.09.007.
60. Agas D, Marchetti L, Hurley MM, Sabbieti MG. Prostaglandin F2alpha: a bone remodeling mediator. J Cell Physiol. 2013;228(1):25–9. doi:10.1002/jcp.24117.
61. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, Garry PJ, Lindeman RD. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol. 1998;147(8):755–63.
62. Beltran-Sanchez H, Harhay MO, Harhay MM, McElligott S. Prevalence and trends of metabolic syndrome in the adult U.S. population, 1999–2010. J Am Coll Cardiol. 2013;62(8):697–703. doi:10.1016/j.jacc.2013.05.064.
63. Camargo PR, Alburquerque-Sendin F, Salvini TF. Eccentric training as a new approach for rotator cuff tendinopathy: review and perspectives. World J Orthop. 2014;5(5):634–44. doi:10.5312/wjo.v5.i5.634.
64. Charvet B, Ruggiero F, Le Guellec D. The development of the myotendinous junction. A review. Muscles Ligaments Tendons J. 2012;2(2):53–63.
65. Choquette S, Bouchard DR, Doyon CY, Senechal M, Brochu M, Dionne IJ. Relative strength as a determinant of mobility in elders 67–84 years of age. A nuage study: nutrition as a determinant of successful aging. J Nutr Health Aging. 2010;14(3):190–5.
66. Clark BC, Fernhall B, Ploutz-Snyder LL. Adaptations in human neuromuscular function following prolonged unweighting: I. Skeletal muscle contractile properties and applied ischemia efficacy. J Appl Physiol. 2006;101(1):256–63. doi:10.1152/japplphysiol.01402.2005.
67. Clark BC, Manini TM. Sarcopenia =/= dynapenia. J Gerontol A Biol Sci Med Sci. 2008;63(8):829–34.
68. Cohen-Solal M, Funck-Brentano T, Hay E. Animal models of osteoarthritis for the understanding of the bone contribution. Bonekey Rep. 2013;2:422. doi:10.1038/bonekey.2013.156.
69. Coiro V, Volpi R, Cataldo S, Magotti MG, Maffei ML, Giumelli C, Araldi A, Volpi L, Chiodera P. Effect of physiological exercise on osteocalcin levels in subjects with adrenal incidentaloma. J Endocrinol Invest. 2012;35(4):357–8.
70. Cooper A. A treatise on dislocations, and on fractures of the joints. Philadelphia: Lea and Blanchard; 1844.
71. Cosqueric G, Sebag A, Ducolombier C, Thomas C, Piette F, Weill-Engerer S. Sarcopenia is predictive of nosocomial infection in care of the elderly. Br J Nutr. 2006;96(5):895–901.
72. Cummings SR, Black DM, Nevitt MC, Browner W, Cauley J, Ensrud K, Genant HK, Palermo L, Scott J, Vogt TM. Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. Lancet. 1993;341(8837):72–5.
73. Depp CA, Jeste DV. Definitions and predictors of successful aging: a comprehensive review of larger quantitative studies. Am J Geriatr Psychiatry Off J Am Assoc Geriatric Psychiatry. 2006;14(1):6–20. doi:10.1097/01.JGP.0000192501.03069.bc.
74. Di Monaco M, Vallero F, Di Monaco R, Tappero R. Prevalence of sarcopenia and its association with osteoporosis in 313 older women following a hip fracture. Arch Gerontol Geriatr. 2011;52(1):71–4. doi:10.1016/j.archger.2010.02.002.
75. Ducy P, Desbois C, Boyce B, Pinero G, Story B, Dunstan C, Smith E, Bonadio J, Goldstein S, Gundberg C, Bradley A, Karsenty G. Increased bone formation in osteocalcin-deficient mice. Nature. 1996;382(6590):448–52.
76. Liu R, Schindeler A, Little DG. The potential role of muscle in bone repair. J Musculoskelet Neuronal Interact. 2010;10(1):71–6.
77. Schindeler A, Liu R, Little DG. The contribution of different cell lineages to bone repair: exploring a role for muscle stem cells. Differ Res Biol Divers. 2009;77(1):12–8. doi:10.1016/j.diff.2008.09.007.
78. Griffin XL, Costa ML, Parsons N, Smith N. Electromagnetic field stimulation for treating delayed union or non-union of long bone fractures in adults. Cochrane Database Syst Rev. 2011;4:CD008471. doi:10.1002/14651858.CD008471.pub2.
79. Leon-Salas WD, Rizk H, Mo C, Weisleder N, Brotto L, Abreu E, Brotto M. A dual mode pulsed electromagnetic cell stimulator produces acceleration of myogenic differentiation. Recent Pat Biotechnol. 2013;7(1):71–81.
80. Elkasrawy M, Immel D, Wen X, Liu X, Liang LF, Hamrick MW. Immunolocalization of myostatin (GDF-8) following musculoskeletal injury and the effects of exogenous myostatin on muscle and bone healing. J Histochem Cytochem Off J Histochem Soc. 2012;60(1):22–30. doi:10.1369/0022155411425389.
81. Frost HM. Perspectives: a proposed general model of the "mechanostat" (suggestions from a new skeletal-biologic paradigm). Anat Rec. 1996;244(2):139–47. doi:10.1002/

(SICI)1097-0185(199602)244:2<139::AID--AR1>3.0.CO;2-X.
82. Toledo FG, Goodpaster BH. The role of weight loss and exercise in correcting skeletal muscle mitochondrial abnormalities in obesity, diabetes and aging. Mol Cell Endocrinol. 2013;379(1–2):30–4. doi:10.1016/j.mce.2013.06.018.
83. Toledo FG, Menshikova EV, Ritov VB, Azuma K, Radikova Z, DeLany J, Kelley DE. Effects of physical activity and weight loss on skeletal muscle mitochondria and relationship with glucose control in type 2 diabetes. Diabetes. 2007;56(8):2142–7. doi:10.2337/db07-0141.
84. Yang J. Enhanced skeletal muscle for effective glucose homeostasis. Prog Mol Biol Transl Sci. 2014;121:133–63. doi:10.1016/B978-0-12-800101-1.00005-3.
85. Marotti G, Ferretti M, Muglia MA, Palumbo C, Palazzini S. A quantitative evaluation of osteoblast-osteocyte relationships on growing endosteal surface of rabbit tibiae. Bone. 1992;13(5):363–8.
86. Urist MR. Bone: formation by autoinduction. Science. 1965;150(3698):893–9.
87. Klein-Nulend J, Burger EH, Semeins CM, Raisz LG, Pilbeam CC. Pulsating fluid flow stimulates prostaglandin release and inducible prostaglandin G/H synthase mRNA expression in primary mouse bone cells. J Bone Miner Res Off J Am Soc Bone Miner Res. 1997;12(1):45–51. doi:10.1359/jbmr.1997.12.1.45.
88. Hartke JR, Lundy MW. Bone anabolic therapy with selective prostaglandin analogs. J Musculoskelet Neuronal Interact. 2001;2(1):25–31.
89. Mo C, Romero-Suarez S, Bonewald L, Johnson M, Brotto M. Prostaglandin E2: from clinical applications to its potential role in bone- muscle crosstalk and myogenic differentiation. Recent Pat Biotechnol. 2012;6(3):223–9.
90. Raisz LG. Prostaglandins and bone: physiology and pathophysiology. Osteoarthritis Cartilage/OARS Osteoarthritis Res Soc. 1999;7(4):419–21. doi:10.1053/joca.1998.0230.
91. Yoshida K, Oida H, Kobayashi T, Maruyama T, Tanaka M, Katayama T, Yamaguchi K, Segi E, Tsuboyama T, Matsushita M, Ito K, Ito Y, Sugimoto Y, Ushikubi F, Ohuchida S, Kondo K, Nakamura T, Narumiya S. Stimulation of bone formation and prevention of bone loss by prostaglandin E EP4 receptor activation. Proc Natl Acad Sci U S A. 2002;99(7):4580–5. doi:10.1073/pnas.062053399.
92. Winkler DG, Sutherland MK, Geoghegan JC, Yu C, Hayes T, Skonier JE, Shpektor D, Jonas M, Kovacevich BR, Staehling-Hampton K, Appleby M, Brunkow ME, Latham JA. Osteocyte control of bone formation via sclerostin, a novel BMP antagonist. EMBO J. 2003;22(23):6267–76. doi:10.1093/emboj/cdg599.
93. Shimada T, Kakitani M, Yamazaki Y, Hasegawa H, Takeuchi Y, Fujita T, Fukumoto S, Tomizuka K, Yamashita T. Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. J Clin Invest. 2004;113(4):561–8. doi:10.1172/JCI19081.
94. Bonewald LF, Wacker MJ. FGF23 production by osteocytes. Pediatr Nephrol. 2013;28(4):563–8. doi:10.1007/s00467-012-2309-3.
95. Martin A, Liu S, David V, Li H, Karydis A, Feng JQ, Quarles LD. Bone proteins PHEX and DMP1 regulate fibroblastic growth factor Fgf23 expression in osteocytes through a common pathway involving FGF receptor (FGFR) signaling. FASEB J Off Publ Feder Am Soc Exp Biol. 2011;25(8):2551–62. doi:10.1096/fj.10-177816.
96. Karsenty G, Wagner EF. Reaching a genetic and molecular understanding of skeletal development. Dev Cell. 2002;2(4):389–406.
97. Lajeunesse D, Kiebzak GM, Frondoza C, Sacktor B. Regulation of osteocalcin secretion by human primary bone cells and by the human osteosarcoma cell line MG-63. Bone Miner. 1991;14(3):237–50.
98. Ducy P, Zhang R, Geoffroy V, Ridall AL, Karsenty G. Osf2/Cbfa1: a transcriptional activator of osteoblast differentiation. Cell. 1997;89(5):747–54.
99. Lee NK, Sowa H, Hinoi E, Ferron M, Ahn JD, Confavreux C, Dacquin R, Mee PJ, McKee MD, Jung DY, Zhang Z, Kim JK, Mauvais-Jarvis F, Ducy P, Karsenty G. Endocrine regulation of energy metabolism by the skeleton. Cell. 2007;130(3):456–69.
100. Nag AC, Foster JD. Myogenesis in adult mammalian skeletal muscle in vitro. J Anat. 1981;132(Pt 1):1–18.
101. Shefer G, Van de Mark DP, Richardson JB, Yablonka-Reuveni Z. Satellite-cell pool size does matter: defining the myogenic potency of aging skeletal muscle. Dev Biol. 2006;294(1):50–66. doi:10.1016/j.ydbio.2006.02.022.
102. Manring H, Abreu E, Brotto L, Weisleder N, Brotto M. Novel excitation- contraction coupling related genes reveal aspects of muscle weakness beyond atrophy – new hopes for treatment of musculoskeletal diseases. Front Physiol. 2014;5(37).
103. Pan Z, Brotto M, Ma J. Store-operated Ca2+ entry in muscle physiology and diseases. BMB Rep. 2014;47(2):69–79.
104. Rios E, Pizarro G, Stefani E. Charge movement and the nature of signal transduction in skeletal muscle excitation-contraction coupling. Annu Rev Physiol. 1992;54:109–33. doi:10.1146/annurev.ph.54.030192.000545.
105. Goldspink DF, Goldspink G. The role of passive stretch in retarding muscle atrophy. In: Nix WA, Vrbová G, editors. Electrical stimulation and neuromuscular disorders. Berlin Heidelberg: Springer; 1986. p. 91–100. doi:10.1007/978-3-642-71337-8_10.
106. Kurek JB, Bower JJ, Romanella M, Koentgen F, Murphy M, Austin L. The role of leukemia inhibitory factor in skeletal muscle regeneration. Muscle Nerve. 1997;20(7):815–22.
107. Pedersen BK, Febbraio MA. Muscle as an endocrine organ: focus on muscle-derived interleukin-6. Physiol Rev. 2008;88(4):1379–406. doi:10.1152/physrev.90100.2007.
108. Pedersen BK, Steensberg A, Fischer C, Keller C, Keller P, Plomgaard P, Febbraio M, Saltin B. Searching for the exercise factor: is IL-6 a candidate? J Muscle Res Cell Motil. 2003;24(2–3):113–9.

109. Li Y, Huard J. Differentiation of muscle-derived cells into myofibroblasts in injured skeletal muscle. Am J Pathol. 2002;161(3):895–907. doi:10.1016/S0002-9440(10)64250-2.
110. Pedersen L, Olsen CH, Pedersen BK, Hojman P. Muscle-derived expression of the chemokine CXCL1 attenuates diet-induced obesity and improves fatty acid oxidation in the muscle. Am J Physiol Endocrinol Metab. 2012;302(7):E831–40. doi:10.1152/ajpendo.00339.2011.
111. Seale P, Bjork B, Yang W, Kajimura S, Chin S, Kuang S, Scime A, Devarakonda S, Conroe HM, Erdjument-Bromage H, Tempst P, Rudnicki MA, Beier DR, Spiegelman BM. PRDM16 controls a brown fat/skeletal muscle switch. Nature. 2008;454(7207):961–7. doi:10.1038/nature07182.
112. Park KH, Zaichenko L, Brinkoetter M, Thakkar B, Sahin-Efe A, Joung KE, Tsoukas MA, Geladari EV, Huh JY, Dincer F, Davis CR, Crowell JA, Mantzoros CS. Circulating irisin in relation to insulin resistance and the metabolic syndrome. J Clin Endocrinol Metab. 2013;98(12):4899–907. doi:10.1210/jc.2013-2373.
113. Nielsen AR, Pedersen BK. The biological roles of exercise-induced cytokines: IL-6, IL-8, and IL-15. Appl Physiol Nutr Metab=Physiologie appliquee, nutrition et metabolisme. 2007;32(5):833–9. doi:10.1139/H07-054.
114. Pedersen BK, Akerstrom TC, Nielsen AR, Fischer CP. Role of myokines in exercise and metabolism. J Appl Physiol. 2007;103(3):1093–8. doi:10.1152/japplphysiol.00080.2007.
115. Matthews VB, Astrom MB, Chan MH, Bruce CR, Krabbe KS, Prelovsek O, Akerstrom T, Yfanti C, Broholm C, Mortensen OH, Penkowa M, Hojman P, Zankari A, Watt MJ, Bruunsgaard H, Pedersen BK, Febbraio MA. Brain-derived neurotrophic factor is produced by skeletal muscle cells in response to contraction and enhances fat oxidation via activation of AMP-activated protein kinase. Diabetologia. 2009;52(7):1409–18. doi:10.1007/s00125-009-1364-1.
116. Chan JK, Harry L, Williams G, Nanchahal J. Soft-tissue reconstruction of open fractures of the lower limb: muscle versus fasciocutaneous flaps. Plast Reconstr Surg. 2012;130(2):284e–95. doi:10.1097/PRS.0b013e3182589e63.
117. Joulia-Ekaza D, Cabello G. The myostatin gene: physiology and pharmacological relevance. Curr Opin Pharmacol. 2007;7(3):310–5. doi:10.1016/j.coph.2006.11.011.
118. Zimmers TA, Davies MV, Koniaris LG, Haynes P, Esquela AF, Tomkinson KN, McPherron AC, Wolfman NM, Lee SJ. Induction of cachexia in mice by systemically administered myostatin. Science. 2002;296(5572):1486–8. doi:10.1126/science.1069525.
119. Hamrick MW. Increased bone mineral density in the femora of GDF8 knockout mice. The Anatomical Record. 2003;272A(1):388–91. doi:10.1002/ar.a.10044.
120. Hamrick MW, McPherron AC, Lovejoy CO. Bone mineral content and density in the humerus of adult myostatin-deficient mice. Calcified Tissue International. 2002;71(1):63–8. doi:10.1007/s00223-001-1109-8.
121. Hamrick MW, Samaddar T, Pennington C, McCormick J. Increased muscle mass with myostatin deficiency improves gains in bone strength with exercise. Journal of Bone and Mineral Research. 2005;21(3):477–83. doi:10.1359/JBMR.051203.
122. Morissette MR, Stricker JC, Rosenberg MA, Buranasombati C, Levitan EB, Mittleman MA, Rosenzweig A. Effects of myostatin deletion in aging mice. Aging Cell. 2009;8(5):573–83. doi:10.1111/j.1474-9726.2009.00508.x.
123. Karsenty G, Ferron M. The contribution of bone to whole-organism physiology. Nature. 2012;481(7381):314–20. doi:10.1038/nature10763.
124. Morley JE, Baumgartner RN, Roubenoff R, Mayer J, Nair KS. Sarcopenia. J Lab Clin Med. 2001;137(4):231–43. doi:10.1067/mlc.2001.113504.
125. Karakelides H, Nair KS. Sarcopenia of aging and its metabolic impact. Curr Top Dev Biol. 2005;68:123–48. doi:10.1016/S0070-2153(05)68005-2.
126. Haber D. Health promotion and aging. 5th ed. New York: Springer Publishing Company; 2013.
127. Bloom DE, Canning D. Booms, busts, and echoes. International Monetary Fund. 2006. http://www.imf.org/external/pubs/ft/fandd/2006/09/bloom.htm. Accessed 3 43.
128. Hayutin A, Beals M, Borges E. The aging workforce: a Chartbook of demographic shifts. Stanford center of longevity. 2013. http://longevity3.stanford.edu/wp-content/uploads/2013/09/The_Aging_U.S.-Workforce.pdf.
129. Muravchick S. Preoperative assessment of the elderly patient. Anesthesiol Clin North America. 2000;18(1):71–89. vi.
130. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, Abraham J, Ackerman I, Aggarwal R, Ahn SY, Ali MK, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Bahalim AN, Barker-Collo S, Barrero LH, Bartels DH, Basanez MG, Baxter A, Bell ML, Benjamin EJ, Bennett D, Bernabe E, Bhalla K, Bhandari B, Bikbov B, Bin Abdulhak A, Birbeck G, Black JA, Blencowe H, Blore JD, Blyth F, Bolliger I, Bonaventure A, Boufous S, Bourne R, Boussinesq M, Braithwaite T, Brayne C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C, Buchbinder R, Buckle G, Budke CM, Burch M, Burney P, Burstein R, Calabria B, Campbell B, Canter CE, Carabin H, Carapetis J, Carmona L, Cella C, Charlson F, Chen H, Cheng AT, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahiya M, Dahodwala N, Damsere-Derry J, Danaei G, Davis A, De Leo D, Degenhardt L, Dellavalle R, Delossantos A, Denenberg J, Derrett S, Des Jarlais DC, Dharmaratne SD, Dherani M, Diaz-Torne C, Dolk H, Dorsey ER, Driscoll T, Duber H, Ebel B, Edmond K, Elbaz A, Ali SE, Erskine H, Erwin PJ, Espindola P, Ewoigbokhan SE, Farzadfar F, Feigin V, Felson DT, Ferrari A, Ferri CP, Fevre EM,

Finucane MM, Flaxman S, Flood L, Foreman K, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabbe BJ, Gabriel SE, Gakidou E, Ganatra HA, Garcia B, Gaspari F, Gillum RF, Gmel G, Gosselin R, Grainger R, Groeger J, Guillemin F, Gunnell D, Gupta R, Haagsma J, Hagan H, Halasa YA, Hall W, Haring D, Haro JM, Harrison JE, Havmoeller R, Hay RJ, Higashi H, Hill C, Hoen B, Hoffman H, Hotez PJ, Hoy D, Huang JJ, Ibeanusi SE, Jacobsen KH, James SL, Jarvis D, Jasrasaria R, Jayaraman S, Johns N, Jonas JB, Karthikeyan G, Kassebaum N, Kawakami N, Keren A, Khoo JP, King CH, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lalloo R, Laslett LL, Lathlean T, Leasher JL, Lee YY, Leigh J, Lim SS, Limb E, Lin JK, Lipnick M, Lipshultz SE, Liu W, Loane M, Ohno SL, Lyons R, Ma J, Mabweijano J, MacIntyre MF, Malekzadeh R, Mallinger L, Manivannan S, Marcenes W, March L, Margolis DJ, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGill N, McGrath J, Medina-Mora ME, Meltzer M, Mensah GA, Merriman TR, Meyer AC, Miglioli V, Miller M, Miller TR, Mitchell PB, Mocumbi AO, Moffitt TE, Mokdad AA, Monasta L, Montico M, Moradi-Lakeh M, Moran A, Morawska L, Mori R, Murdoch ME, Mwaniki MK, Naidoo K, Nair MN, Naldi L, Narayan KM, Nelson PK, Nelson RG, Nevitt MC, Newton CR, Nolte S, Norman P, Norman R, O'Donnell M, O'Hanlon S, Olives C, Omer SB, Ortblad K, Osborne R, Ozgediz D, Page A, Pahari B, Pandian JD, Rivero AP, Patten SB, Pearce N, Padilla RP, Perez-Ruiz F, Perico N, Pesudovs K, Phillips D, Phillips MR, Pierce K, Pion S, Polanczyk GV, Polinder S, Pope 3rd CA, Popova S, Porrini E, Pourmalek F, Prince M, Pullan RL, Ramaiah KD, Ranganathan D, Razavi H, Regan M, Rehm JT, Rein DB, Remuzzi G, Richardson K, Rivara FP, Roberts T, Robinson C, De Leon FR, Ronfani L, Room R, Rosenfeld LC, Rushton L, Sacco RL, Saha S, Sampson U, Sanchez-Riera L, Sanman E, Schwebel DC, Scott JG, Segui-Gomez M, Shahraz S, Shepard DS, Shin H, Shivakoti R, Singh D, Singh GM, Singh JA, Singleton J, Sleet DA, Sliwa K, Smith E, Smith JL, Stapelberg NJ, Steer A, Steiner T, Stolk WA, Stovner LJ, Sudfeld C, Syed S, Tamburlini G, Tavakkoli M, Taylor HR, Taylor JA, Taylor WJ, Thomas B, Thomson WM, Thurston GD, Tleyjeh IM, Tonelli M, Towbin JA, Truelsen T, Tsilimbaris MK, Ubeda C, Undurraga EA, van der Werf MJ, van Os J, Vavilala MS, Venketasubramanian N, Wang M, Wang W, Watt K, Weatherall DJ, Weinstock MA, Weintraub R, Weisskopf MG, Weissman MM, White RA, Whiteford H, Wiersma ST, Wilkinson JD, Williams HC, Williams SR, Witt E, Wolfe F, Woolf AD, Wulf S, Yeh PH, Zaidi AK, Zheng ZJ, Zonies D, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2163–96. doi:10.1016/S0140-6736(12)61729-2.

131. McLaughlin SJ, Connell CM, Heeringa SG, Li LW, Roberts JS. Successful aging in the United States: prevalence estimates from a national sample of older adults. J Gerontol B Psychol Sci Soc Sci. 2010;65B(2):216–26. doi:10.1093/geronb/gbp101.
132. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. Arch Intern Med. 2002; 162(20):2269–76.
133. Wu SY, Green A. Projection of chronic illness prevalence and cost inflation. National Centers for Health Statistics. 2000. http://www.nationalhealthcouncil.org.
134. Rubenstein LZ, Josephson KR. Falls and their prevention in elderly people: what does the evidence show? Med Clin North Am. 2006;90(5):807–24. doi:10.1016/j.mcna.2006.05.013.
135. Auron-Gomez M, Michota F. Medical management of hip fracture. Clin Geriatr Med. 2008;24(4):701–719, ix. doi:10.1016/j.cger.2008.07.002.
136. Bradley SM. Falls in older adults. Mount Sinai J Med, New York. 2011;78(4):590–595. doi:10.1002/msj.20280.
137. Scott D, Blizzard L, Fell J, Jones G. The epidemiology of sarcopenia in community living older adults: what role does lifestyle play? J Cachex Sarcopenia Muscle. 2011;2(3):125–34. doi:10.1007/s13539-011-0036-4.
138. Walsh MC, Hunter GR, Livingstone MB. Sarcopenia in premenopausal and postmenopausal women with osteopenia, osteoporosis and normal bone mineral density. Osteoporos Int J Establ Result Cooper Between Eur Found Osteoporosional Osteoporos Found USA. 2006;17(1):61–7. doi:10.1007/s00198-005-1900-x.
139. Janssen I, Shepard DS, Katzmarzyk PT, Roubenoff R. The healthcare costs of sarcopenia in the United States. J Am Geriatr Soc. 2004;52(1):80–5.
140. Ray NF, Chan JK, Thamer M, Melton 3rd LJ. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the National Osteoporosis Foundation. J Bone Miner Res Off J Am Soc Bone Miner Res. 1997;12(1):24–35. doi:10.1359/jbmr.1997.12.1.24.
141. CDC. National Vital Statistics Report. 2013. http://www.cdc.gov/nchs/nvss.htm.
142. Zaki ME, Hussein FH, Banna RAE-SE. Osteoporosis among ancient Egyptians. Int J Osteoarchaeol. 2009;19(1):78–89. doi:10.1002/oa.978.
143. Schapira D, Schapira C. Osteoporosis: the evolution of a scientific term. Osteoporos Int J Establ Result Cooper Between Eur Found Osteoporose Natl Osteoporos Found USA. 1992;2(4):164–7.
144. WHO. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis, WHO Technical Report Series, No. 843 edn. Geneve: World Health Organization; 1994.
145. Schwartz AV, Nevitt MC, Brown Jr BW, Kelsey JL. Increased falling as a risk factor for fracture among older women: the study of osteoporotic

fractures. Am J Epidemiol. 2005;161(2):180–5. doi:10.1093/aje/kwi023.
146. Taylor BC, Schreiner PJ, Stone KL, Fink HA, Cummings SR, Nevitt MC, Bowman PJ, Ensrud KE. Long-term prediction of incident hip fracture risk in elderly white women: study of osteoporotic fractures. J Am Geriatr Soc. 2004;52(9):1479–86. doi:10.1111/j.1532-5415.2004.52410.x.
147. Vermeer C, Knapen MH, Schurgers LJ. Vitamin K and metabolic bone disease. J Clin Pathol. 1998;51(6):424–6.
148. Versluis RG, Papapoulos SE, de Bock GH, Zwinderman AH, Petri H, van de Ven CM, Springer MP. Clinical risk factors as predictors of postmenopausal osteoporosis in general practice. Br J Gen Pract J Royal Coll Gen Pract. 2001;51(471):806–10.
149. Body JJ, Bergmann P, Boonen S, Boutsen Y, Bruyere O, Devogelaer JP, Goemaere S, Hollevoet N, Kaufman JM, Milisen K, Rozenberg S, Reginster JY. Non-pharmacological management of osteoporosis: a consensus of the Belgian Bone Club. Osteoporos Int J Establ Result Cooper Between Eur Foundation for Osteoporos Natl Osteoporos Found USA. 2011;22(11):2769–88. doi:10.1007/s00198-011-1545-x.
150. Rizzoli R, Boonen S, Brandi ML, Burlet N, Delmas P, Reginster JY. The role of calcium and vitamin D in the management of osteoporosis. Bone. 2008;42(2):246–9. doi:10.1016/j.bone.2007.10.005.
151. Janssen I, Ross R. Linking age-related changes in skeletal muscle mass and composition with metabolism and disease. J Nutr Health Aging. 2005;9(6):408–19.
152. Rosemberg I. Summary comments: epidemiological and methodological problems in determining nutritional status of older persons. Am J Clin Nutr. 1989;50:1231–3.
153. Muhlethaler R, Stuck AE, Minder CE, Frey BM. The prognostic significance of protein-energy malnutrition in geriatric patients. Age Ageing. 1995;24(3):193–7.
154. Prothro JW, Rosenbloom CA. Body measurements of black and white elderly persons with emphasis on body composition. Gerontology. 1995;41(1):22–38.
155. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. J Am Geriatr Soc. 2002;50(5):889–96.
156. Newman AB, Kupelian V, Visser M, Simonsick E, Goodpaster B, Nevitt M, Kritchevsky SB, Tylavsky FA, Rubin SM, Harris TB, Health ABCSI. Sarcopenia: alternative definitions and associations with lower extremity function. J Am Geriatr Soc. 2003;51(11):1602–9.
157. Roubenoff R. Physical activity, inflammation, and muscle loss. Nutr Rev. 2007;65(12):S208–12.
158. Vandervoort AA, Symons TB. Functional and metabolic consequences of sarcopenia. Can J Appl Physiol. 2001;26(1):90–101.
159. Hughes VA, Frontera WR, Wood M, Evans WJ, Dallal GE, Roubenoff R, Fiatarone Singh MA. Longitudinal muscle strength changes in older adults: influence of muscle mass, physical activity, and health. J Gerontol A Biol Sci Med Sci. 2001;56(5):B209–17.
160. Mitchell WK, Williams J, Atherton P, Larvin M, Lund J, Narici M. Sarcopenia, dynapenia, and the impact of advancing age on human skeletal muscle size and strength; a quantitative review. Front Physiol. 2012;3:260. doi:10.3389/fphys.2012.00260.
161. Goodpaster BH, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, Simonsick EM, Tylavsky FA, Visser M, Newman AB. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. J Gerontol A Biol Sci Med Sci. 2006;61(10):1059–64.
162. Lang TF. The bone-muscle relationship in men and women. J Osteoporos. 2011;2011:702735. doi:10.4061/2011/702735.
163. Wang Q, Alen M, Nicholson P, Suominen H, Koistinen A, Kroger H, Cheng S. Weight-bearing, muscle loading and bone mineral accrual in pubertal girls–a 2-year longitudinal study. Bone. 2007;40(5):1196–202. doi:10.1016/j.bone.2006.12.054.
164. Zanchetta JR, Plotkin H, Alvarez Filgueira ML. Bone mass in children: normative values for the 2–20-year-old population. Bone. 1995;16(4 Suppl):393S–9.
165. McDonagh MJ, Hayward CM, Davies CT. Isometric training in human elbow flexor muscles. The effects on voluntary and electrically evoked forces. J Bone Joint Surg. 1983;65(3):355–8.
166. Baumgartner RN. Body composition in healthy aging. Ann N Y Acad Sci. 2000;904:437–48.
167. Roubenoff R, Hughes VA. Sarcopenia: current concepts. J Gerontol A Biol Sci Med Sci. 2000;55(12):M716–24.
168. Roubenoff R. Excess baggage: sarcopenia, obesity, and cancer outcomes. Lancet Oncol. 2008;9(7):605–7. doi:10.1016/S1470-2045(08)70160-8.
169. Schrager MA, Metter EJ, Simonsick E, Ble A, Bandinelli S, Lauretani F, Ferrucci L. Sarcopenic obesity and inflammation in the InCHIANTI study. J Appl Physiol. 2007;102(3):919–25. doi:10.1152/japplphysiol.00627.2006.
170. Baumgartner RN, Wayne SJ, Waters DL, Janssen I, Gallagher D, Morley JE. Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. Obes Res. 2004;12(12):1995–2004. doi:10.1038/oby.2004.250.
171. Lammes E, Akner G. Resting metabolic rate in elderly nursing home patients with multiple diagnoses. J Nutr Health Aging. 2006;10(4):263–70.
172. Bouchard DR, Janssen I. Dynapenic-obesity and physical function in older adults. J Gerontol A Biol Sci Med Sci. 2010;65(1):71–7. doi:10.1093/gerona/glp159.
173. Janssen I. Morbidity and mortality risk associated with an overweight BMI in older men and women. Obesity. 2007;15(7):1827–40. doi:10.1038/oby.2007.217.
174. Bouchard DR, Dionne IJ, Brochu M. Sarcopenic/obesity and physical capacity in older men and

women: data from the Nutrition as a Determinant of Successful Aging (NuAge)-the Quebec longitudinal Study. Obesity. 2009;17(11):2082–8. doi:10.1038/oby.2009.109.
175. Walrand S, Guillet C, Salles J, Cano N, Boirie Y. Physiopathological mechanism of sarcopenia. Clin Geriatr Med. 2011;27(3):365–85. doi:10.1016/j.cger.2011.03.005.
176. Romero-Suarez S, Shen J, Brotto L, Hall T, Mo C, Valdivia HH, Andresen J, Wacker M, Nosek TM, Qu CK, Brotto M. Muscle-specific inositide phosphatase (MIP/MTMR14) is reduced with age and its loss accelerates skeletal muscle aging process by altering calcium homeostasis. Aging. 2010;2(8):504–13.
177. Srikanthan P, Hevener AL, Karlamangla AS. Sarcopenia exacerbates obesity-associated insulin resistance and dysglycemia: findings from the National Health and Nutrition Examination Survey III. PLoS One. 2010;5(5):e10805. doi:10.1371/journal.pone.0010805.
178. Kim TN, Park MS, Yang SJ, Yoo HJ, Kang HJ, Song W, Seo JA, Kim SG, Kim NH, Baik SH, Choi DS, Choi KM. Prevalence and determinant factors of sarcopenia in patients with type 2 diabetes: the Korean Sarcopenic Obesity Study (KSOS). Diabetes Care. 2010;33(7):1497–9. doi:10.2337/dc09-2310.
179. Magkos F, Wang X, Mittendorfer B. Metabolic actions of insulin in men and women. Nutrition. 2010;26(7–8):686–93. doi:10.1016/j.nut.2009.10.013.
180. Lee CG, Boyko EJ, Strotmeyer ES, Lewis CE, Cawthon PM, Hoffman AR, Everson-Rose SA, Barrett-Connor E, Orwoll ES, Osteoporotic Fractures in Men Study Research G. Association between insulin resistance and lean mass loss and fat mass gain in older men without diabetes mellitus. J Am Geriatr Soc. 2011;59(7):1217–24. doi:10.1111/j.1532-5415.2011.03472.x.
181. Hofbauer LC, Brueck CC, Singh SK, Dobnig H. Osteoporosis in patients with diabetes mellitus. J Bone Miner Res Off J Am Soc Bone Miner Res. 2007;22(9):1317–28. doi:10.1359/jbmr.070510.
182. Isaacson J, Brotto M. Physiology of Mechanotransduction: How Do Muscle and Bone "Talk" to One Another? Clinical Reviews in Bone and Mineral Metabolism. 2014;12(2):77–85.
183. Schweitzer R, Zelzer E, Volk T. Connecting muscles to tendons: tendons and musculoskeletal development in flies and vertebrates. Development. 2010;137(17):2807–17. doi:10.1242/dev.047498.
184. Pineault KM, Wellik DM. Hox genes and limb musculoskeletal development. Curr Osteoporos Rep. 2014;12(4):420–7. doi:10.1007/s11914-014-0241-0.
185. Blitz E, Viukov S, Sharir A, Shwartz Y, Galloway JL, Pryce BA, Johnson RL, Tabin CJ, Schweitzer R, Zelzer E. Bone ridge patterning during musculoskeletal assembly is mediated through SCX regulation of Bmp4 at the tendon-skeleton junction. Dev Cell. 2009;17(6):861–73. doi:10.1016/j.devcel.2009.10.010.
186. Edom-Vovard F, Duprez D. Signals regulating tendon formation during chick embryonic development. Dev Dyn Off Publ Am Assoc Anat. 2004;229(3):449–57. doi:10.1002/dvdy.10481.
187. Edom-Vovard F, Schuler B, Bonnin MA, Teillet MA, Duprez D. Fgf4 positively regulates scleraxis and tenascin expression in chick limb tendons. Dev Biol. 2002;247(2):351–66.
188. Rodriguez-Guzman M, Montero JA, Santesteban E, Ganan Y, Macias D, Hurle JM. Tendon-muscle cross-talk controls muscle bellies morphogenesis, which is mediated by cell death and retinoic acid signaling. Dev Biol. 2007;302(1):267–80. doi:10.1016/j.ydbio.2006.09.034.
189. Findlay DM, Atkins GJ. Osteoblast-chondrocyte interactions in osteoarthritis. Curr Osteoporos Rep. 2014;12(1):127–34. doi:10.1007/s11914-014-0192-5.
190. Funck-Brentano T, Cohen-Solal M. Crosstalk between cartilage and bone: when bone cytokines matter. Cytokine Growth Factor Rev. 2011;22(2):91–7. doi:10.1016/j.cytogfr.2011.04.003.
191. Pan J, Zhou X, Li W, Novotny JE, Doty SB, Wang L. In situ measurement of transport between subchondral bone and articular cartilage. J Orthop Res Off Publ Orthop Res Soc. 2009;27(10):1347–52. doi:10.1002/jor.20883.
192. Yuan XL, Meng HY, Wang YC, Peng J, Guo QY, Wang AY, Lu SB. Bone-cartilage interface crosstalk in osteoarthritis: potential pathways and future therapeutic strategies. Osteoarthritis Cartilage/OARS Osteoarthritis Res Soc. 2014;22(8):1077–89. doi:10.1016/j.joca.2014.05.023.
193. Tat SK, Lajeunesse D, Pelletier J-P, Martel-Pelletier J. Targeting subchondral bone for treating osteoarthritis: what is the evidence? Best Pract Res Clin Rheumatol. 2010;24:51–70.
194. Loppini M, Maffulli N. Conservative management of tendinopathy: an evidence-based approach. Muscles Ligaments Tendons J. 2011;1(4):134–7.
195. Heinemeier KM, Olesen JL, Haddad F, Langberg H, Kjaer M, Baldwin KM, Schjerling P. Expression of collagen and related growth factors in rat tendon and skeletal muscle in response to specific contraction types. J Physiol. 2007;582(Pt 3):1303–16. doi:10.1113/jphysiol.2007.127639.
196. Rizzuto E, Musaro A, Catizone A, Del Prete Z. Measuring tendon properties in mdx mice: cell viability and viscoelastic characteristics. J Biomech. 2009;42(14):2243–8. doi:10.1016/j.jbiomech.2009.06.041.

Sex Steroids and Aging Bone

5

Jane A. Cauley

Introduction

Sex steroids play key roles in the development and maintenance of the skeleton in both men and women. Historically, it was thought that sex steroids were gender specific: estrogen was important for women and testosterone (T), for men. However, research over the past several decades has demonstrated a key role for estrogen in maintaining skeletal integrity in men. Thus, a unitary model for involutional osteoporosis has been proposed [1] that identifies estrogen deficiency as a cause of the accelerated phase of bone loss in women and the slower age related phase of bone loss in both men and women. It is also likely that androgens play a role, although evidence supporting their role is stronger in laboratory and clinical experiments than population studies.

In this chapter, the evidence supporting a role for sex steroids in maintaining the skeleton into old age is reviewed. The focus is on both estrogen and T, in men and women from an epidemiologic perspective.

J.A. Cauley, DrPH
Department of Epidemiology,
Graduate School of Public Health,
University of Pittsburgh, Pittsburgh,
PA 15261, USA
e-mail: jcauley@edc.pitt.edu

Methodologic Issues

It is important to acknowledge the difficulty in evaluating this literature. Older hormone assays lacked sufficient sensitivity to be reliable. Most estradiol (E2) assays were originally developed for pre-menopausal women and lack the sensitivity to measure the very low levels that are typical of post-menopausal women. These assays could discriminate pre-from post-menopausal women but could not discriminate between post-menopausal women with very low levels. Measurements in pre-menopausal women need to be standardized across the menstrual cycle. In the Study of Women's Health Across the Nation (SWAN), we used a standard protocol that specified that the blood be obtained in the 2–5 day window of the early follicular phase of the menstrual cycle. However, in women with irregular menstrual cycles or in women who were beginning to transition into menopause, this standardization was increasingly difficult. Whether or not the sample was drawn according to the protocol influenced our results [2].

Two major methods are used to measure E2: indirect and direct immunoassays. Indirect assays typically include an initial extraction step before the radioimmunoassay (RIA). In contrast, direct assays do not involve extraction. A recent study compared four direct assay and three indirect assay methods and found that indirect E2 assays correlated more highly with mass spectrometry [3].

G. Duque, D.P. Kiel (eds.), *Osteoporosis in Older Persons: Advances in Pathophysiology and Therapeutic Approaches*, DOI 10.1007/978-3-319-25976-5_5

The extraction step in indirect assays removes cross-reacting substances that interfere with the assay. Mass spectrometry is the reference standard for measuring both male and female sex hormones [4, 5]. Newer approaches to the assessment of sex steroids specifically using mass spectrometry have been developed to reduce or eliminate interfering substances and now serve us the reference methods for sex steroids assays [6, 7]. However, until these methods are widely available, extraction based indirect methods are preferable over direct assays.

Many of the more recent studies have used mass spectrometry methods. Two comparisons of immunoassays and mass spectrometry have been carried out in men. A study of 213 men aged 22–91 years showed very high correlations for serum T and bioavailable T (BioT) comparing the 2 methods (r = 0.90 and 0.95, respectively) [8]. Within the US MrOS, MrOS Sweden and the European Male Aging Study, the spearman correlation between the 2 assays for serum E2 ranged from 0.53 to 0.76 [9]. However, serum E2 correlated with the C-reactive protein using the immunoassay but not the mass spectrometry suggesting that inflammation may interfere with the immunoassay results. Nevertheless, the correlations with areal BMD [9] and volumetric BMD [8] were similar across the 2 assays. This suggests that we can, indeed, interpret earlier results of studies which relied on immunoassays.

In addition, the biosynthesis of androgens and estrogens is complex, differs in men and women and in pre and post-menopausal women. Many enzymes are involved in the production and metabolism of steroid hormones [10]. Androgens and estrogens are correlated. In post-menopausal women and men, androgens serve as the major precursor to E2. Free unbound and bioavailable hormone levels (the portion loosely bound to albumin) are highly correlated with each other and to the total hormone concentration. Nevertheless, most findings are generally stronger for the bioavailable hormone. Finally, in most studies, a single concentration of estrogen or T is available and the within person variability in the hormone concentration will lead to some misclassification and weaken the findings.

Sex Steroids and Age

Testosterone and E2 levels, especially the free or bioavailable fractions decline with increasing age in both men and women and the decline may lead to some of the most important sequels of aging. In addition to skeletal strength, the decline in sex steroids could relate to declines in physical function, changes in cognition and quality of life.

Using sex steroid data from the Mayo Clinic (data chosen because results are derived from the same laboratory), differences in total and BioT and E2 by gender across ages is shown in Figs. 5.1 and 5.2 [11, 12]. Testosterone levels are higher in men than women at every age group. As expected, younger pre-menopausal women have higher E2 levels than younger men but this trend is reversed among the older women. Total E2 levels are 76 % higher and bioavailable E2 (BioE2) levels are almost threefold higher on average in older men than in older women. In these data, the greatest declines were observed in the bioavailable fraction and not the total hormone. Nevertheless, there may be substantial individually variability in the age-related decline in sex steroid hormones [13], suggesting that targeting risk factors that contribute to the decline could prevent fractures.

Sex Steroids and Bone Mineral Density (BMD)

Women

Serum estrogen measures have been consistently linked with appendicular and axial bone mineral density (BMD) measures in post-menopausal women [14–23]. In pre-menopausal women, total E2 and BioE2 were unrelated to BMD at the hip [15] or spine [24]. The strongest hormonal predictor of BMD in pre and early peri-menopausal women was follicle stimulating hormone levels (FSH) [24].

SWAN also evaluated the decline in BMD in relation to the final menstrual period (FMP) [25]. BMD trajectories were divided into 3 segments: the pre-transmenopause (5 years to 1 year before

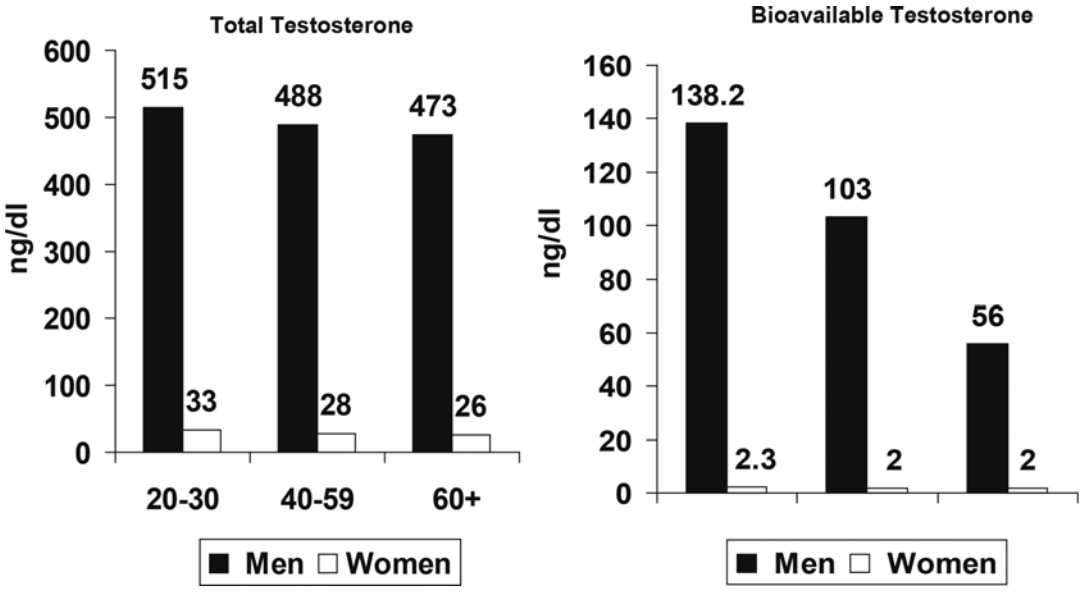


Fig. 5.1 Total and bioavailable testosterones by age: men and women

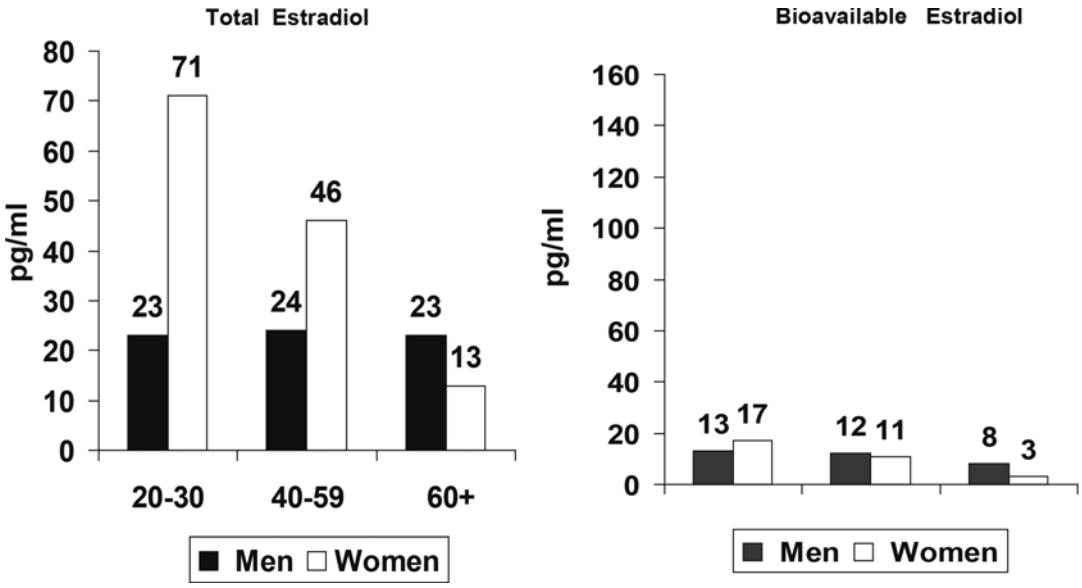


Fig. 5.2 Total and bioavailable estradiol by age: men and women

the FMP); transmenopause (1 year before to 2 years after FMP) and post-menopause (2–5 years after the FMP). During the 10-year observation, the rates and cumulative amounts of bone loss were greatest during the initial years after the FMP, termed the transmenopause. Cumulative, 10-year lumbar spine BMD loss was 10.6 %; 7.38 % was lost during the transmenopause. Cumulative femoral neck loss was 9.1 %; 5.8 % was lost during the transmenopause. Black race/ethnicity was related to slower loss rates, whereas the opposite was true of Japanese and Chinese women. Faster rates of lumbar spine BMD loss across the menopause transition compared to

femoral neck BMD were also reported in a small sample of White women enrolled in the Michigan Bone Health Study [24]. Greater BMD loss in the lumbar spine may reflect the greater proportion of trabecular bone at the lumbar spine.

SWAN also examined the relations between sex steroids and gonadotropins and menopause-related BMD loss [26]. Higher levels of FSH (but not E2) predicted faster rates of lumbar spine BMD loss in the pre-transmenopausal and transmenopausal phases. During the third phase, starting 2 years post-menopause, lower levels of E2 (but not FSH) predicted higher rates of LS loss. Sex steroids and gonadotropins did not predict BMD loss during any phase at the FN site. Our finding that higher FSH and lower E2 were related to LS but not femoral bone loss could be due to statistical power – the ability to detect associations is greater at the lumbar spine, because the rate of bone loss is 50 % higher than that at the femoral neck [25]. Or, it may be that the lumbar spine, due to the predominance of trabecular bone, is more sensitive to the effects of changing hormones during the menopause transition [27].

The observations from SWAN that FSH (and not E2) [2, 26] is related to perimenopausal bone loss is controversial. Investigations into the role of FSH and bone loss using mouse models produced conflicting findings. One group reported that FSH receptor null (FORKO) mice are hypogonadal, but have normal bone mass [28]. However, these mice also have high testosterone levels, which may be bone-protective. Another group reported that FORKO mice do have reduced bone mass and that bilateral oophorectomy reduced their testosterone levels, leading to bone mass values similar to oophorectomized control mice [29]. However, a randomized controlled trial in which postmenopausal women were randomized to leuprolide acetate or placebo (along with an aromatase inhibitor in each group) found that FSH suppression did not affect bone turnover markers [30]. It may be that FSH is a more sensitive marker of declining E2 levels early in the MT, especially in studies such as SWAN that measure annual sex steroids during the early follicular phase, when estrogen is at its cyclic nadir. But, it may also mean we can measure FSH more accurately than E2. SWAN uses a direct assay to measure E2 and these E2 levels may be inaccurate because of cross-reactivity.

The association between T and BMD in older post-menopausal women is less consistent with some reports showing associations with one BMD site and not others [16, 19, 20] or free T and not total T [16, 18]. In contrast to findings with respect to E2, total BioT levels were positively correlated with BMD in pre-menopausal women [15].

Longitudinally, low E2 concentrations are associated with faster rates of bone loss in older post-menopausal women [21, 31, 32] but not in pre-menopausal women [2, 24, 31, 33–35]. Nevertheless, within a group of pre-menopausal women, women with lower estrogens experienced faster rates of bone loss [36]. Follow-up in most of these studies was <4 years and it's possible that over longer periods of time, estrogen levels could predict rates of bone loss. In the 12 year study of Rannevik et al, after about 3 years post-menopausally, E2 correlated with rates of bone loss [37]. Testosterone was not correlated with changes in BMD [2, 34, 35] except for a single study. Bone loss over a 2–8 year follow-up was related to lower androgens in premenopausal women but to both lower androgens and estrogens in post-menopausal women [31].

Men

Two "Experiments of Nature" [38] have provided essential information about the importance of estrogen to the male skeleton. An alpha-estrogen receptor deficient male was found to have high circulating estrogens, normal T levels but very low BMD [39]. Three men with an aromatase deficiency, rendering these men estrogen deficient were found to have very low BMD and all responded well to estrogen replacement [40, 41].

Population studies of older men have reported positive correlations between total E2 and/or BioE2 in both older and younger men [15, 42–48]. The relationships tended to be stronger for BioE2 than total E2 [15, 44]. In contrast, there

is little evidence that total or BioT is correlated with BMD in older or younger men, at least in the range of normal T [15, 43, 47, 49, 50]. In the Framingham Study, BMD at any site did not differ in hypogonadal men compared to eugonadal men [46]. In the US MrOS study the proportion of men who were hypogonadl (T <200 ng/dl, 6.9 nmol/L) and E2 deficient (E2 < 10 pg/ml, 36.7 pmol/L) was greater in men with hip BMD T-score below −2.5 [51].

The relative contribution of T and estrogen in regulating bone resorption and formation in men was examined by eliminating endogenous T and estrogen production in 59 older men, average age 68 years [52], and then replacing either T, E2 or both. Bone resorption markers increased significantly in the absence of both T and E2. Administration of E2 alone prevented the increase in bone resorption but administration of T had no effect. In contrast, both T and E2 individually maintained levels of bone formation. Thus, although correlations between BMD and T levels are usually not apparent, T appears to influence bone formation.

An interesting paper by Araujo tested whether differences in sex hormones could explain racial differences in BMD [53]. Total and free T were higher in Black and Hispanic men with little difference in comparison to White men. Positive correlations were observed between E2 and BMD in Black, Hispanic and White men but there was no evidence that E2 could account for the differences in BMD across race/ethnic groups [53].

Other cross-sectional studies have shown associations between sex steroid hormone levels and BMD. In the nationally representative third National Health and Nutrition Examination Survey (NHANES III), the odds of low bone mass (T-score −1 to <2.5 SD) was 3.8 (1.87–7.78) and 1.69 (0.95–2.98) for those with lowest free T and free E2, respectively (p-trend across quartiles, free T, $p \leq 0.001$; E2, $p = 0.04$); absolute cutoffs for quartiles, not provided. Men with lowest SHBG had a 60 % lower risk of having low bone mass. Although there was no association across quartiles of E2, men with total E2 < 20 ng/l had a lower BMD than men with normal E2 [54].

Cross-sectional studies have consistently shown an important role for estrogen in determining the skeleton but it is unclear whether estrogen contributes to peak skeletal mass or affects bone loss in men. Low total BioE2 concentrations were associated with faster rates of bone loss in older men [55–57]. There was no association between total or BioT concentrations and change in BMD [56]. Similarly, the rate of increase in BMD in younger men (age 22–39) was correlated with total and BioE2 but not with total or BioT [55]. SHBG has been shown to correlate with cortical bone in men at the age of peak skeletal mass [58]. Of importance, a threshold level for BioE2 below which aging men begin to lose bone was suggested [55]. Elderly men with BioE2 < median (40 pmol/L) had significantly higher rates of bone loss and levels of bone resorption markers than men with higher BioE2 levels. This subset of older men may be the most likely to benefit from preventive efforts.

The US MrOS Study also supports a threshold for BioE2 regarding rates of bone loss. Men with the lowest BioE2 (<39.7 pmol/L) lost significantly greater BMD in comparison with men with the highest BioE2 (≥66.0 pmol/L) [59]. Above this level, the rate of BMD loss did not differ. However, the spline analysis did not identify a significant threshold perhaps because we measured areal BMD, a mix of cortical and trabecular BMD and this threshold may be most important for cortical volumetric BMD [12]. The MrOS results are also consistent with a threshold of BioE2 for fracture risk [60, 61] although the threshold level was slightly lower than described for BMD. The US MrOS Study also found a significant threshold for SHBG [59]. Men with SHBG above 50.9 nmol/L experienced significantly faster rates of BMD loss. This threshold is consistent with the MrOS Sweden where men with SHBG in the highest quartile (52.5 nmol/L) had an increased risk of fractures [60]. In US MrOS, a threshold for SHBG and fracture risk was also identified, although the threshold was higher at ≥59.1 nmol/L [61]. The results suggest a nonlinear relationship between SHBG and rates of bone loss and fracture. A metaanalysis of all of

these studies would be helpful in defining the threshold for BioE2 and SHBG.

We also showed that the odds of rapid hip bone loss (annualized rate of hip bone loss −3 % per year) was three fold higher in men who were T deficient and two fold higher among men who were estrogen deficient [51]. Analyses from MrOS suggested that the strongest association between sex steroids, SHBG, bone loss and fracture were in analyses when the combination of all three measures were considered [59, 61]. Men who had the lowest BioE2 (<39.7 pmol/L), the lowest BioT (<5.43 nmol/L), and the highest SHBG (≥62.9 nmol/L) experienced an annualized rate of bone loss that was three times faster than men with high BioE2, high BioT, and low SHBG. These results suggest that each hormone plays a role in maintaining BMD longitudinally. Delineating each hormone's role in maintaining BMD is complex because the bioavailable measures were derived from mass action equations that include SHBG. Nevertheless, future research should consider the role of each individual hormone and their interactions on maintaining BMD.

Estrone is a biologically weaker estrogen than E2 but circulates at greater concentrations. Estrone was moderately correlated with BioE2, but the relative importance of estrone is unknown in comparison with BioE2 [59]. We found modest correlations between estrone and baseline BMD (r=0.09). Longitudinally, BioE2 was strongly linked with BMD loss, but estrone was not. The associations of BioE2 with BMD and BMD loss were independent of estrone, suggesting that BioE2 is the predominant estrogen in older men [59].

Among Japanese men, no association was reported between total E2 and rates of bone loss but free T was significantly related to change in BMD over 3 years but not longer [62]. They used a direct assay and it is not clear why they measured free T but not free E2. The body mass index (BMI) of these Japanese men (23.3 kg/m^2) was very different from that of US men in the MrOS Study (27.5 kg/m^2).

The MrOS Hong Kong Study used GC-MS to measure sex steroids in 1489 Chinese men and reported inverse associations between total E2 and BioE2 and rates of bone loss [63]. The difference in results between these 2 studies of Asians may have reflected the difference in laboratory methods.

Sex Steroids, Volumetric BMD and Skeletal Structure

All previous studies used areal BMD measures and were unable to examine the associations between sex steroids and trabecular and cortical bone separately or to structural parameters. Khosla et al have recently published three key papers [11, 12, 64]. As shown in Fig. 5.3 (women) and Fig. 5.4 (men), the "threshold" theory exists only for cortical bone. At all cortical sites, volumetric BMD was associated with BioE2 at low but not high BioE2. Trabecular bone on the other hand, was correlated with BioE2 both above and below the median. The authors speculate that reductions in BioE2 levels to below the threshold will result in greater decreases in trabecular bone than cortical bone. Cortical bone on the other hand is not sensitive to declining BioE2 levels until they decline past the threshold. This theory is consistent with the observation that menopause related bone loss primarily affects trabecular and not cortical bone. Further studies are needed to confirm this observation. Improved assays are needed to identity the specific cutpoint. In the papers described above, the "cutpoint" was the median level and it differed in both men and women.

None of the structural parameters (vertebral area, bone area, subendocortical area, cortical area, and trabecular microstructural measures) were related to BioE2 or BioT in young men or pre-menopausal women. In older men and women, both BioE2 or BioT were related to many of these structural parameters and to trabecular microarchitecture [11, 12].

In a longitudinal study of 108 women followed over the menopause for 15 years, there was an increase in periosteal apposition, leading to an increase in skeletal size [65]. This increase in size

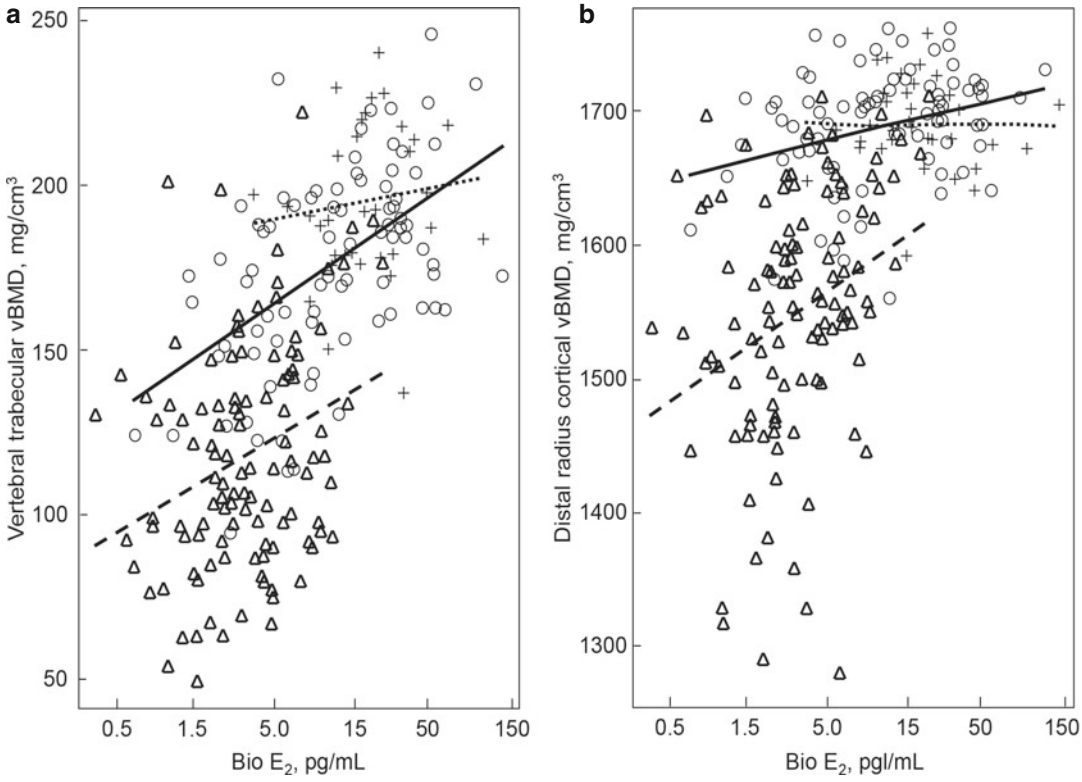


Fig. 5.3 (**a**) Relationship between trabecular vBMD at the vertebrae and serum BioE2 levels in group A (age 20–39) (*dotted lines*, *crosses*), group B (age 40–59) (*solid lines*, *circles*), and group C (age ≥60) (*dashed lines*, *triangles*) (all women). Slopes are as follows: group A, 4.4; group B, 14.9; and group C, 12.9. (**b**) Relationship between cortical vBMD at the distal radius and serum BioE2 levels in group A (age 20–39) (*dotted lines*, *crosses*), group B (age 40–59) (*solid lines*, *circles*), and group C (age ≥60) (*dashed lines*, *triangles*). Slopes are as follows: group A, –0.01; group B, 12.4; and group C, 36.3. Note that BioE2 levels are on a log scale (By permission of The Endocrine Society [11])

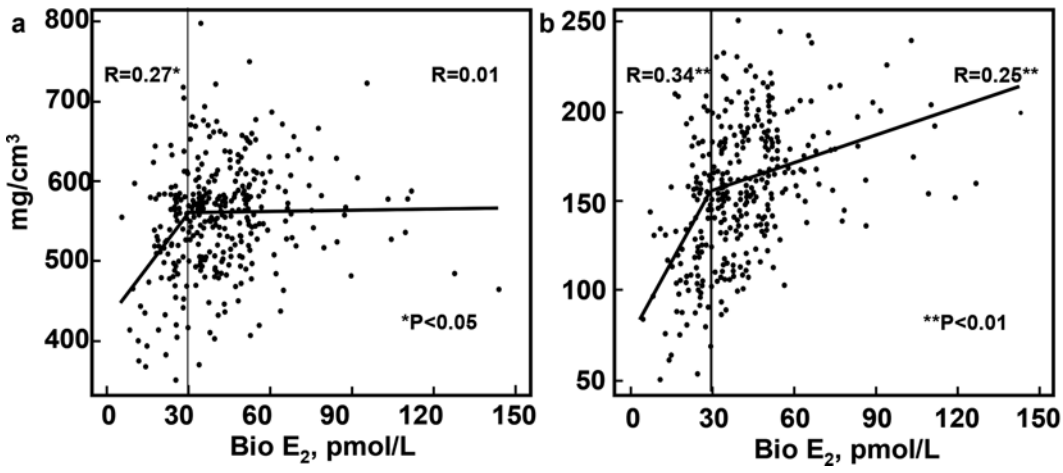


Fig. 5.4 (**a**) Femur neck cortical vBMD and (**b**) vertebral trabecular vBMD as a function of BioE2 levels below and above 30 pM in Rochester, MN, men (By permission of *Journal of Bone Mineral Research* [12])

in part compensates for the loss in bone strength due to post-menopausal bone loss. Of importance, post-menopausal serum E2 levels were highly correlated with changes in the periosteal diameter. These results support a role for estrogens in maintaining bone size parameters.

Most fractures occur after the age of 65 and are attributed to greater loss of cortical than trabecular bone [66]. Increase in cortical porosity due to intracortical remodeling reduces bone strength. Vandenput et al showed that E2 and free E2 are inversely correlated with cortical porosity at least in older men [67]. There was no relationship with T levels. These results may suggest that low E2 levels may predispose individuals to fracture because low E2 levels lead to greater cortical porosity.

The association between serum E2 and T to bone microarchitecture was recently reported from the Structure of the Aging Men's Bones (STRAMBO) cohort [68]. Among men age 65 or older, E2 was a major determinant of cortical bone, especially if T levels were low. Other cross-sectional studies have shown E2 but not T to be correlated with hip strength variables beyond areal BMD in older men [69].

Sex Steroids and Fractures

Women

Early case control studies comparing sex steroids in women with and without a fracture were conflicting [70–73]. These contradictory results may have reflected the small sample sizes, biased selections of cases and controls, alterations in hormones resulting from the fracture itself and use of low sensitivity assays. Prevalent vertebral fractures were less common among women who had an E2 level >5 pg/ml (18 pmol/L): The multiple adjusted odds ratio was 0.4 (95 % confidence intervals, 0.2–0.8) [17]. In contrast, in the Rancho Bernardo Study, the prevalence of vertebral fractures was not related to either total or BioE2 or BioT in older women [74] although earlier reports from this cohort showed a relationship between estimated BioT (but not E2) and height loss [75].

The prospective studies of endogenous hormones and fracture are summarized in Table 5.1 [76–85]. In the Study of Osteoporotic Fractures (SOF), women with E2 below the sensitivity of the assay (<5 pg/ml (18 pmol/L)), had a 2½ fold increased risk of a hip fracture (Relative Risk (RR) = 2.5; 1.4–4.6) even after adjusting for age and body weight [76]. Adjustment for BMD attenuated the RR slightly to 1.9(1.0–3.6) suggesting that at least part of this association reflected the higher BMD among women with higher endogenous concentrations of E2. Of importance, the RR remained significant suggesting that E2 may have other effects which contribute to their effect on fractures.

Women with low free T had an increased risk of hip but not vertebral fracture but this was not significant after adjusting for E2 [76]. The risk of hip fracture increased with increasing serum concentrations of SHBG but this association appeared to be slightly dependent upon body weight. The combination of low E2 and high SHBG was associated with an age-adjusted 14 fold increase in hip and 12 fold increase in vertebral fractures.

The OFELY cohort of French women were about 10 years younger on average than women in SOF [77]. In this study, low E2 (defined as lowest Quartile (<39.6 pmol/L) was associated with an increased risk of fracture. Neither SHBG or T were significantly related to fracture, although there was a trend of increasing fracture with increasing SHBG. Adjustment for BMD or bone turnover had little effect. The authors estimated that women with both high resorption markers and low E2 had a threefold increased risk of fracture.

In the French Epidemiology of Osteoporosis (EPIDOS) Study, low concentrations of E2 were unrelated to hip fractures, even after exploring various cutoffs from <10.8 pmol/L (2 % of subjects) to <25.2 pmol/L (38 % of subjects) [78]. However, women with *high* (≥36 pmol/L) concentrations were protected (RR = 0.66 (0.44–0.98)). Women with the highest levels of SHBG (Quartile IV) had a 2.5 fold (1.4–4.6) increased

Table 5.1 Summary of prospective studies of endogenous sex steroid hormones and fracture in older women. Hazard ratio (95 % confidence interval) shown unless otherwise noted

Author	Study population	Outcomes	Assay	Results		
Cummings (1998) [76] USA	SOF cohort (n = 9704) Age = ≥ 65 years Mean age = 73 years (controls) Exclude hormone users Controls (n = 274) randomly selected from cohort	Hip fracture (n = 133) Vertebral fracture (n = 138) Mean follow-up = 5.9 years	RIA	**E2** (<18 pmol/L) **Free T** (<2.4 pmol/L) **SHBG** (≥34.7 nmol/L)	Vertebral fracture RR (95 % CI) 2.5 (1.4–4.2) 1.4 (0.8–2.4) 2.3 (1.2–4.4) Adjusted for age & weight	Hip fracture RR (95 % CI) 2.5 (1.4–4.6) 1.6 (1.0–2.7) 2.0 (1.1–3.9) Adjusted for age & weight
Garnero (2000) [77] France	OFELY cohort (n = 1039) Mean age = 64 years Excluded pre-menopausal Excluded if on active bone agents Controls (n = 380)	Vertebral fracture (n = 30) Peripheral fracture (n = 35) Mean follow-up = 5 years	RIA	**E2** (<39.6 pmol/L) **SHBG** (>40.2 nmol/L) T (lowest Quartile[b])	Any fracture RR (95 % CI) 2.2 (1.2–4.0)[a] 1.6 (0.9–2.9)[a] 1.4 (0.7–2.8)[a] [a]Adjusted age, prevalent vertebral fracture and activity [b]Levels of T not specified	
Chapurlat (2000) [78] France	EPIDOS cohort (n = 7598) Mean age = 82 years Controls (n = 636)	Hip fracture (n = 212) Mean follow-up = 3.3 years	RIA	**E2** (≤18 pmol/L) (≥36 pmol/L) **SHBG** (>25.8 mg/L)	RR (95 % CI) unadjusted 1.07 (0.6–1.87) 0.66 (0.44–0.98) 0.75 (0.49, 1.12)	
Goderie-Plomp (2004) [79] Netherlands	Rotterdam cohort (n = 4878) Age = ≥ 55 Mean age = 68 years Age matched Controls (n = 339)	Vertebral fracture (n = 115) Mean follow-up = 6.5 years	RIA	**E2** (≤15.5 pmol/L) **SHBG** (<42.9 nmol/L) **T**	RR (95 % CI) 2.09 (1.26–3.46)[a] 0.51(0.30–0.87)[a] No association (results not shown) [a]Adjusted for age, weight	
Devine (2005) [80] Australia	(n = 1499 women) Mean age = 75 years	Incident fracture (n = 151) Mean follow-up = 3 years	RIA	**E2** (pmol/L) **SHBG** (nmol/L) **FEI**	Cases (Mean) 24.0 54.5 0.40	Control (Mean) 25.0 50.0 0.49	p-value 0.08 0.02 0.002

(continued)

Table 5.1 (continued)

Author	Study population	Outcomes	Assay	Results			
Sipila (2006) [81] Finland	(n = 175 women) Age = ≥ 75 years	Incident fracture (n = 121) Mean follow-up = 10 year	RIA	**E2** (nmol/L) >0.066 0.022–0.066 <0.0.22 **SHBG** (nmol/L) >91.5 42.6–91.5 <42.6	RR (95 % CI)[a] 1.00 Referent 2.00 (0.86–4.63) 2.53 (1.03–6.19) 1.00 Referent[a] 1.34 (0.66–2.69) 1.65 (0.67–4.05) [a]Adjusted for muscle strength, height, BMD.		
Kuchuk (2007) [98] Netherlands	LASA (n = 634) Mean age = 75.5 years	Low trauma fracture Incident fracture (n = 65) Follow-up = 3 years	RIA	Results in women only reported for subset with known levels of mobility and exercise. **BioE2** (<median) HR = 2.39 (1.28–4.48) Adjusted for BMI, corticosteroid use, alcohol, smoking, chronic disease, mobility and exercise.			
Bjornerem (2007, 2011) [101] Norway	Tromso Study (n = 1386) Mean age = ≈65 years	Non-vertebral fracture No fracture (n = 1105) Fracture (n = 281) Follow-up = 8.4 years	RIA	**Free E2** **Free T** **SHBG** [a]HR per SD increase (Unadjusted)	0.93 (0.82–1.05)[a] 1.00 (0.90–1.12)[a] 1.23 (1.10–1.37)[a]		
Prince (2007) [84] Australia	(n = 1500) Mean age = 75 years	Clinical spine fracture (n = 70) Radiographic spine fracture (n = 89) Follow-up = 5 years	RIA	 **Total E2** (pmol/L) **SHBG** (nmol/L) (Mean levels) Free E2 index (<0.35) [a]p < 0.05 vs no fracture	Clinical spine fracture 22.5[a] 61.2[a] HR = 2.18 (1.11–4.28)	Radiographic spine fracture 23.5[a] 62.0[a] HR = 1.77 (1.02–3.07)	No fracture 25.0 54.5

Lee (2008) [3] US	WHI-OS Nested case control Cases (n = 400) Controls (n = 400) Mean age = 70.8 years	Hip fracture Median follow-up = 7 years	RIA	**BioE2** (pg/mL) <5.1 5.1–< 8.2 ≥8.2 **Bio T** (ng/dl) <9 9–< 14 ≥14 **SHBG** (ug/dl) <1.2 1.2–< 1.7 ≥1.7	Age-adjusted 1.00 Referent 0.83 (0.59–1.16) 0.44 (0.29–0.66) 1.00 Referent 0.72 (0.51–1.02) 0.62 (0.44–0.88) 1.00 Referent 1.25 (0.86–1.82) 1.90 (1.31–2.74)	Risk factors[a] 1.00 Referent 1.20 (0.78–1.85) 0.97 (0.54–1.73) 1.00 Referent 0.78 (0.51–1.18) 0.63 (0.39–1.00) 1.00 Referent 1.13 (0.73–1.74) 1.63 (1.02–2.59)
				[a]MV adjusted for BMI, smoking, parity, corticosteroid use, physical functioning, parental history of hip fracture, calcium intake, diabetes.		
Roddam (2009) [97] United Kingdom	Premenopausal women Cases (n = 46) Controls (n = 89) Mean age = 35 years Postmenopausal women Cases (n = 235) Controls (n = 470) Mean age = 62 years	Any non-digit fracture	RIA	Premenopausal women (Matched on days of menses)		
				Doubling free **E2** Doubling free **T** Doubling **SHBG**		0.83 (0.58–1.18) 0.59 (0.38–0.91) 1.10 (0.59–2.07)
				Postmenopausal women		
				Free E2 (pmol/L)		
				<0.17 0.17–<0.33 ≥0.33		1.00 Referent 0.89 (0.59–1.35) 0.62 (0.38–1.02)
				Free T (pmol/L)		
				<8.52 8.52–<15.97 ≥15.95		1.00 Referent 0.96 (0.63–1.44) 0.83 (0.52–1.31)
				SHBG (nmol/L)		
				<48 48–<70 ≥70		1.00 Referent 1.05 (0.68–1.63) 1.05 (0.66–1.66)

(continued)

Table 5.1 (continued)

Author	Study population	Outcomes	Assay	Results		
Cauley (2010) [82] US	WHI-HT Nested case control Age = 65 years Cases (n = 750) Controls (n = 750)	Hip fracture (n = 231) All fractures (n = 519) Matched controls; average follow-up = 6.53 years	RIA	**BioE2** (pg/mL) ≤4.0 >4.0–≤6.1 >6.1–≤9.9 ≥9.9 p trend **SHBG** (ug/dl) ≤0.87 >0.87–≤1.21 ≥1.21–≤1.67 ≥1.67 p trend	Hip fracture[a] 1.00 Referent 0.65 (0.38–1.13) 0.78 (0.46–1.33) 0.80 (0.42–1.50) 0.496 1.00 Referent 2.11 (1.08–4.14) 2.69 (1.37–5.29) 4.01 (1.98–8.15) 0.002	All fracture[a] 1.00 Referent 0.77 (0.56–1.04) 0.93 (0.70–1.25) 0.91 (0.66–1.24) 0.39 1.00 Referent 1.29 (0.95–1.74) 1.12 (0.82–1.53) 1.53 (1.11–2.12) 0.048
				[a]Matching variables of age, ethnicity, randomization date; previous fracture, BMI, diabetes, health status.		
Finigan (2012) [83] United Kingdom	OPUS (n = 797 women) Mean age = 66.9 years	Vertebral fracture (n = 39) Non-spine fracture (n = 119) Average follow-up = 6 years	Immunoassay	**E2** (pg/mL) <8.15 **SHBG** (nmol/L) >59.4	Vertebral fracture OR = 2.97 (1.52–5.82) OR = 1.48 (0.73–3.01)	Non-vertebral fracture OR = 1.26 (0.80–1.97) OR = 1.16 (0.75–1.77)
				Adjusted for age, BMI, BMD, bone turnover, fracture history, use of antiresorptive therapy.		
Moberg (2013) [85] Sweden	Lund Area Study (n = 6917) Mean age = 56.8 years	Fracture (n = 409) Average follow-up = 8.4 years	Immunoassay	All fractures **E2** (pmol/L) **T** (nmol/L) **SHBG** (nmol/L)		0.96 (0.79–1.16) 0.98 (0.75–1.27) 1.30 (0.80–2.11)
				Adjusted for age, BMI and smoking. Unit for HR not reported		

[a]Lowest quartile cutpoint: not available

Abbreviations: *adj* adjusted, *fx* fracture, *E2* estradiol, *T* testosterone, *SHBG* sex hormone binding globulin, *RR* relative risk, *95 % CI* 95 % confidence intervals, *HR* hazard ratio, *OR* odds ratio, *SOF* Study of Osteoporotic Fractures, *OFELY* Os des Femmes de Lyon, *LASA* Longitudinal Aging Study Amsterdam, *WHI-OS* Women's Health Initiative-Observational Study, *WHI-HT* Women's Health Initiative-Hormone Trial, *OPUS* Osteoporosis and Ultrasound Study, *FEI* free estrogen index

risk of hip fracture in comparison to women with the lowest SHBG (Quartile 1).

In the Rotterdam Study of vertebral fractures, mean age 68 years, low E2 was associated with an increased risk and low SHBG, a decreased risk of vertebral fractures, independent of BMD [79]. Women with a combination of both low E2 and high SHBG had a 7.8 fold (2.7–22.5) increased risk of vertebral fractures. Testosterone was not related to fractures in this study.

Two studies examined the association of endogenous hormones to any type of incident fractures [80, 81]. In these studies, low E2, or a measure of free estrogen index were associated with increased fractures. In the Finnish Study, SHBG was unrelated to fracture risk.

A nested case control study within the Women's Health Initiative Observation Study (WHI-OS) [3] examined the association between endogenous sex hormones and hip fracture. In separate bivariate models, women with BioE2 > 8.2 pg/ml had a 56 % lower risk and women with BioT >14 ng/dl had a 38 % lower risk of hip fracture. Women with SHBG >1.7 ng/dl had a 90 % increased risk. However, BioE2 was no longer significant in models with all 3 hormones and other risk factors. BioT and SHBG remained strong predictors in these multivariable adjusted models.

In a second report from WHI, there was no evidence that the effect of hormone therapy on fracture risk reduction differed by baseline E2 or SHBG [82]. Across all quartiles of E2 and SHBG, women randomized to hormone therapy, experience a 50 % reduction in fracture. Multivariate models examining the main effect of sex steroids on fracture showed a significant effect of SHBG but not BioE2 on fracture risk.

The lack of an association with BioE2 conflicts with other studies. The women in WHI were heavier and younger with higher BioE2 than women in other studies and the authors speculate that the relation of endogenous estrogen and hip fracture may be weaker in these women. The WHI studies were also substantially larger than previous studies.

The Osteoporosis and Ultrasound Study (OPUS) found an association of lower E2 (<8.15 pg/ml) and vertebral fractures [83]. There was no association between E2 and non-vertebral fractures or between SHBG and any fracture. This study was unique in its examination of morphometric vertebral fractures and inclusion of both BMD and bone turnover in the models. However, power was low in this study.

Similarly, E2 was lower and SHBG were higher among women with vertebral fractures versus women with no fracture [84]. There was no difference in the levels between women with a clinical versus radiographic fracture. A low free E2 index (<0.35) was associated with an increased risk of clinical (HR = 2.18; 95 %, 1.11–4.28) and radiographic (HR = 1.77; 95 % CI, 1.02–3.07) vertebral fractures. Nevertheless, the sensitivity of this index for predicting vertebral fracture was only about 44 % with area under the receiver operating curves of 0.59 suggesting that inclusion of sex steroid hormones in prediction models is not much better than chance alone.

The Swedish Women's Health in the Lund Area Study [85] found no association between total E2, T or SHBG and fracture. An increased fracture risk was observed in women with low androstenedione and androstenedione/SHBG ratio. These women were considerably younger than most previous studies and was unique in its inclusion of androstenedione.

Taken together, these studies suggest an association between E2 and fracture. Of importance, these associations were found across several different cohorts, representing women with an average age ranging from 64 to 82 years, recruited from several different countries. Nevertheless, the results are confined to Caucasian women and little is known about sex steroids and fracture in other ethnic groups. Asian women have a high rate of hip fracture [86] and it will be important to study whether E2 predicts fracture in these women, especially since their body weight tends to be lower than Caucasians [87]. Testosterone was not related to fractures in these women and the association between SHBG was inconsistent. Future studies should use state of the art assays for T and include the free or BioT.

Men

A number of case control or cross-sectional studies have examined the role of sex steroids and fractures in older men. The prevalence of T deficiency was reported to be higher among men with hip fracture [88, 89] in comparison to controls. E2 levels were lower and SHBG higher in two small studies of men with idiopathic osteoporosis [90, 91], but not in other studies [92]. In the Rancho Bernardo cohort, men with a prevalent vertebral fracture had lower total and BioE2 but there was no difference in T [74]. Finally, E2 and T levels were similar in men with and without a vertebral fracture but SHBG levels were higher in the fracture group [93]. These retrospective studies are limited by their small sample size (ranging from 12 to 81) and their highly select nature of the cases and controls.

Since the publication of the first edition, there has been a large increase in the number of longitudinal studies examining sex steroid hormones and fractures in older men, Table 5.2 [79, 94–101]. In the early studies, the number of cases of fractures was extremely small, ranging from 22 to 54. The association between circulating sex steroids and prevalent fracture was examined in 2908 older men enrolled in MrOS Sweden [96]. Total E2 and T were measured using RIA and free E2, calculated using mass action equations and a fixed concentration of albumin. Free E2 < median was not associated with prevalent fractures although men with free E2 in the 10th percentile had a significant higher prevalence of all fractures and x-ray verified vertebral fractures. On the other hand, free T was related to all prevalent fractures, osteoporosis related fractures and vertebral fractures with odds ratios ranging from 1.26 to 1.77 for those men with free T < median. Information on the absolute levels of these cutoffs was not provided in the manuscript.

In the Framingham cohort, Amin and colleagues showed that men with total E2 (<18.1 pg/ml) had a threefold increased risk of hip fracture even after adjusting for age, BMI, height and smoking [46]. There was no association between total T and hip fracture. However, men with both low E2 (<17.2 pg/ml) and T (<3.85 ng/ml) had the greatest risk of hip fracture (adjusted hazard ratio (HR) = 6.5 (95 % CI), 2.9–14.3).

In the Longitudinal Aging Study of Amsterdam (LASA), men with BioE2 and BioT < median, the HR for low trauma fractures was 2.20; 95 % CI, 1.08–4.50 and 1.54; 95 % CI, 0.81–2.93, respectively [98]. When men and women were combined, the HR for total T achieved statistical significance. The absolute level of the median E2 and T was not defined.

In the MrOS Sweden Study, men with total E2 > 16.0 pg/ml had a reduced incidence of all fractures, non-vertebral fractures and clinical vertebral fractures [60]. There was no association across quartiles of total T and fracture but men with the highest free T (>99 pg/ml) has a lower risk of any fracture (HR = 0.47; 95 % CI, 0.31–0.71), non-vertebral fracture, (HR = 0.26; 95 %, 0.12–0.57) and a clinical vertebral fractures (HR = 0.31; 95 % CI, 0.14–0.69). Men with the highest SHBG (>52.5 nM) had a significantly increased risk of any fracture and clinical vertebral fractures. The relationship between E2 and fracture risk was non-linear with a strong relationship at a level of <16 pg/ml for E2.

Meier et al was the first to examine the association between endogenous sex steroid hormone and fractures using state-of-the-art mass spectroscopy [99]. One standard deviation decrease in total E2 and total T was associated with an increased risk of low trauma fractures with the HR slightly strongest for total T. Adjustment for SHBG comparing men with the lowest T (<294 ng/dl) with the highest (≥559 ng/dl), the HR for fracture was 2.26; 95 % CI, 1.20–4.20. Comparing men with the lowest E2 (<14 pg/ml) versus the highest, (>25.6 pg/ml), the HR was 1.61; 95 % CI, 0.90–2.80. The HR in models adjusting for BMD attenuated the associations slightly suggesting that BMD may mediate the association of sex steroid hormones and fracture.

In the US MrOS Study, men with BioE2, <11.4 pg/ml; BioT, <163.5 ng/dl or SHBG, >59.1 nM had a significantly increased risk of non-vertebral fracture in separate models [61]. However, the association between BioT and fracture was attenuated after adjusting for BioE2. In

Table 5.2 Summary of prospective studies of endogenous sex steroid hormones and fracture in older men. Hazard ratio (95 % confidence intervals) shown unless otherwise noted

Author	Population	Outcomes	Assay	Results			
Nyquist (1998) [94] Sweden	(n=242 men) Mean age=67 years	All fracture (n=22) Mean follow-up=7 years	RIA		Fracture (mean)	No fracture (mean)	
				T (nmol/L)	16.7	17.2	
				SHBG (nmol/L)	2.3	2.6	
Center (2000) [95] Australia	Dubbo cohort, (n=437) Mean age=72 years	All fracture (n=54) Mean follow-up=1.7 years "Minor" fracture (n=30) "Major" fracture (n=24	RIA		No fracture (mean)	Minor fracture (mean)	Major fracture (mean)
				E2 (pg/ml)	70	65	71
				Free T (pmol/L)	40	42	36
				SHBG (nmol/L)	40	41	54[a]
				[a]p<0.05 vs no fracture			
Goderie-Plomp (2004) [79] (Netherlands)	Rotterdam cohort, (n=3105) Mean age=66 years Age matched controls, randomly chosen (n=133)	Incident vertebral fracture (n=45) Mean follow-up=6.5 years	RIA	**E2** (pmol/L) <40.5 **SHBG** (nmol/L) <34.2	OR (95 % CI) 1.37 (0.6–3.1) 0.75 (0.34–1.7)		
				Adjusted for age and weight			
Amin (2006) US	Framingham Cohort (N=793 men) Mean age=71 years	Hip fracture (n=39) Follow-up=up to 18 years	RIA	**E2** (pg/ml) 2.0–<18.1 >18.2–34.2 ≥34.3	HR (95 % CI) 3.1 (1.4–16.9) 0.9 (0.4–2.0) 1.00 Referent		
				T (nmol/L) ≤3.85 3.85–5.29 >5.30	 1.8 (0.8–3.8) 0.8 (0.4–2.8) 1.00 Referent		

(continued)

Table 5.2 (continued)

Author	Population	Outcomes	Assay	Results			
				Adjusted for age, BMI, height, smoking.			
Mellstrom (2006) [60] Sweden	MrOS Sweden Study (n = 2639) Mean age = 75.4 years	Any fracture (n = 209) Non vertebral fracture (n = 83) Clinical vertebral fracture (n = 67) Follow-up = 3.3 years	GC-MS	**Total E2** (pg/ml)	All fracture	Non-vertebral fracture	Clinical vertebral fracture
				<16	1.00 Referent	1.00 Referent	1.00 Referent
				16–≤20.3	0.40 (0.3–0.6)	0.44 (0.2–0.8)	0.45 (0.2–0.9)
				>20.3–≤25.3	0.53 (0.4–0.8)	0.50 (0.3–0.9)	0.43 (0.2–0.9)
				>25.3	0.60 (0.4–0.9)	0.49 (0.3–0.9)	0.40 (0.2–0.8)
				Total T (ng/ml)			
				<3.36	1.00 Referent	1.00 Referent	1.00 Referent
				>3.36–≤4.38	0.67 (0.5–1.0)	0.64 (0.4–1.2)	0.71 (0.4–1.4)
				>4.38–≤5.54	0.63 (0.4–1.0)	0.72 (0.4–1.3)	0.41 (0.2–0.9)
				>5.54	0.89 (0.6–1.3)	0.51 (0.3–1.0)	0.76 (0.4–1.5)
				SHBG (nM)			
				≤28.8	1.00 Referent	1.00 Referent	1.00 Referent
				>28.8–≤38.7	0.76 (0.5–1.2)	0.47 (0.2–1.0)	0.94 (0.4–2.2)
				>38.7–≤52.5	1.30 (0.9–2.0)	1.00 (0.5–1.8)	1.96 (0.9–3.1)
				≥52.5	1.79 (1.2–2.6)	1.48 (0.8–2.6)	2.07 (1.0–4.3)
				All adjusted for age. HR (95 % CI).			
Kuchuk (2007) [98] Netherlands	LASA (N = 623 men) Age = 75.6 years	Low trauma fracture (n = 44) Follow-up = 3 years	RIA	**BioE2** (men only) <median HR = 2.20 (1.08–4.50)[a] >median HR = Referent **Bio T** (men only) (pmol/L) <median HR = 1.54 (0.81–2.93)[a] **Bio E2** (men & women combined) <median HR = 1.53 (1.02–2.29)[a] [a]Adjusted for BMI, corticosteroids use, alcohol, smoking & chronic disease.			

Meier (2008) [99] Australia	Dubbo cohort (n = 609) Mean age ≈ 73 years	Low trauma fracture (n = 113) Median follow-up = 5.8 years	LC-MS/MS		All Fracture
				E2 (pg/mL)	HR = 1.21 (1.0–1.5)[a, b]
				T (ng/dL)	HR = 1.48 (1.2–1.8)[a, b]
				E2 (pg/mL), <14	HR = 1.61 (0.94–2.77)[c]
				T (ng/dL), <294	HR = 2.26 (1.2–4.2)[c]
				[a]HR per standard deviation decrease. [b]Adjusted for SHBG. [c]Adjusted for SHBG, age, weight.	
LeBlanc (2009) [61] US	MrOS Study Cases (n = 342) Controls (N = 1738)	Non-vertebral fracture Follow-up = 4.7 years	GC-MS		Non-vertebral fracture
				BioE2 (pg/mL), <11.4	HR = 1.48 (1.18–1.86)[a]
				Bio T (ng/dl), <163.5	HR = 1.28 (1.00–1.64)
				SHBG (nM), >59.1	HR = 1.44 (1.14–1.82)
				[a]Adjusted for age, race, BMI.	
Roddam (2009) [97] United Kingdom	EPIC-Oxford Cases (n = 155 men) Controls (n = 309 men)	Any non-digit fracture (N = 155) Follow-up = 5 years	RIA	**Free E2** (pmol/L)	Non-digit fracture
				<1.2	1.00 Referent
				>1.2–<1.7	RR = 0.52 (0.3–1.01)
				≥1.7	RR = 0.46 (0.2–0.9)
				Free T (pmol/L)	
				<283	1.00 Referent
				>283–<371	RR = 1.06 (0.6–1.8)
				≥371	RR = 0.89 (0.5–1.6)
				SHBG (nmol/L)	
				<32	1.00 Referent
				>32–<45	RR = 1.39 (0.8–2.5)
				≥45	RR = 1.20 (0.7–2.2)
				Adjusted for BMI, cycling, exercise, alcohol.	

(continued)

Table 5.2 (continued)

Author	Population	Outcomes	Assay	Results	
Bjornerem (2007, 2011) [101] Norway	Tromso Study (n = 1364)	Non-vertebral fracture No fracture (n = 1259) Fracture (n = 105) Follow-up = 8.4 years	RIA	 **Free E2** **Free T** **SHBG**	HR per 1 SD increase unadjusted HR = 1.04 (0.9–1.1) HR = 1.02 (0.9–1.2) HR = 1.26 (1.1–1.5)
Woo (2012) [63] Hong Kong	(n = 1489) Mean age = 72.5 years	Fractures (n = 108) Non-vertebral fractures (n = 59) Hip fractures (n = 31) Follow-up = 4 years	GC-MS	**Total E2** (pg/ml) <18.84 **BioE2** (pg/mL) <12.26 **Free T** (ng/dl) <8.65 **SHBG** (nmol/L) >60.7	<u>All fractures</u> HR = 1.48 (0.98–2.23) HR = 1.54 (1.03–2.31) HR = 1.31 (0.86–1.99) HR = 0.94 (0.59–1.50)
				Adjusted for age, smoking, calcium, BMI, physical activity and muscle mass.	
Hsu (2015) [102] Australia	CHAMP Study (n = 1705) Mean age = 76.9 years	Fractures (n = 168) Hip fractures (n = 43) Non-vertebral fractures (n = 137) Follow-up = 6 years	LC-MS/MS	 **Total E2** **Total T** **SHBG**	<u>All fractures (HR per 1 SD decrease)</u> HR = 1.04 (0.9–1.2) HR = 1.01 (0.9–1.2) HR = 0.88 (0.8–1.0)
				Adjusted for age, BMI, smoking, physical activity and comorbidities.	

Abbreviations: *E2* estradiol, *T* testosterone, *SHBG* sex hormone binding globulin, *BIO* bioavailable, *LASA* Longitudinal Aging Study Amsterdam, *HR* hazard ratio, *CI* confidence intervals, *OR* odds ratio, *EPIC-Oxford* European Prospective Investigation of Cancer – Oxford, *CHAMP* Concord Health and Aging in Men

the combined model men with low BioE2, low BioT and high SHBG had the highest risk of fracture, HR = 3.4; 95 % CI, 2.2–5.3.

Similarly, men enrolled in the EPIC-Oxford Study were followed for 5 years for incident non-digit fractures [97]. An inverse association was observed for free E2 but not for free T or SHBG. In contrast, the Tromso Study reported no association between E2 or T and fracture but men with highest SHBG had an increased risk of fracture that was attenuated and no longer significant after adjusting for BMD [101].

Hsu studied an Australian cohort and found no association for total E2, T or SHBG and fractures after adjusting for age, BMI, smoking status and comorbidity [102]. This study also included dihydrotestosterone and estrone and neither hormone was related to fracture in the univariate or multivariate models. This study was limited because of its high loss to follow-up rate.

Finally, all previous studies were carried out in men who for the most part were of European descent. Woo et al followed 1489 Chinese men for up to 4 years. Total E2 and BioE2 were related to fracture risk but there was no association with T or SHBG [63].

Summary

This review clearly supports a key role for E2 in the maintenance of skeletal integrity in both men and women. Testosterone is also important, especially in older men and in maintaining bone formation although the epidemiologic data do not support a strong independent role for T and fractures at least in women and men with T in the normal range. Most of the available research has focused on correlations with areal BMD. More information is needed on other aspects of skeletal strength including bone size, geometry and the micro architecture of bone. The possibility of a "threshold" level of E2 in both men and women and differential effects on trabecular and cortical bone needs to be confirmed. Prospective studies of sex hormones and fracture in women generally show a strong relationship between serum E2 and subsequent fracture risk. Nevertheless, until mass spectrometry is routinely available, clinical use of E2 as a marker of risk is not recommended. There has been a major growth in the prospective data on sex hormones and fractures in men. Many earlier studies relying on RIA did not show an association between total or bioavailable E2 or T. Larger studies published more recently show an inverse association between E2 and fracture [60, 61, 63, 98, 99]. Two well characterized cohort studies reported an inverse association with BioT and fracture [61, 98]. There has been one prospective study showing an association between total T and subsequent fracture [99]. For the most part, higher SHBG was related to a higher risk of fracture. However, various fracture outcomes have been examined and each paper adjusted for different sets of confounding variables. BMD was not consistently adjusted for in the models.

Sex steroid hormones have been linked to frailty [103]. In particular, low levels of T are independently associated with more frailty in older men and greater loss of lean mass [104]. Thus, testosterone could influence fracture and skeletal health through an effect on muscle mass and physical performance.

Emerging from these data is the hypothesis that all these sex hormones significantly influences fracture risk. As part of MrOS, men with low BioE2, low BioT and high SHBG experienced faster rates of bone loss and more fractures [59, 61]. Further research should examine the combination of these various sex hormones and skeletal outcomes.

Fractures are clearly multifactorial and a combination of biomarkers may be essential in identifying high risk individuals. For example, in MrOS, 25-hydroxyvitamin D (25(OH)D) <20 ng/ml was associated with greater rates of hip bone loss and hip fracture [100, 105]. There was no association between 25(OH)D and non-spine fracture. However, 25(OH)D in combination with low BioE2, BioT or SHBG had an increased risk of non-spine fracture and major osteoporotic fracture, Fig. 5.5 [106]. These results suggest that a multifactorial approach may be optimal in identifying endocrine influences on bone health.

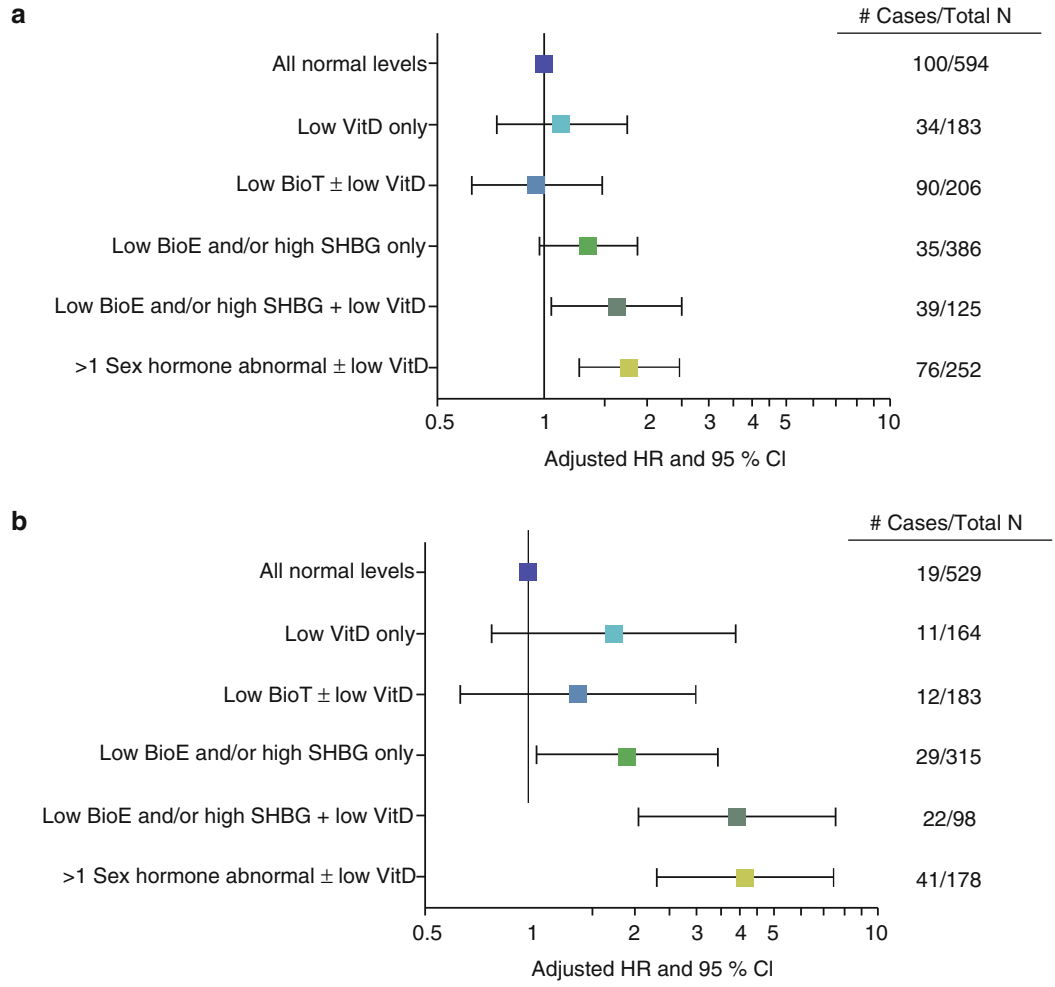


Fig. 5.5 (**a**) Risk of non-spine fracture and (**b**) major osteoporotic fracture by sex hormone/VitD groups: case-cohort sample. Adjusted for age, race, latitude of study site, season of blood draw, BMI, ever smoked, alcohol drinks per week, self-rated health condition, physical activity, kidney function (eGFR), and history of diabetes. *VitD* 25-hydroxyvitamin D, *BioE* bioavailable estradiol, *BioT* bioavailable testosterone, *SH* sex hormone. The proportion of men in each group was 34 % normal, 11 % low VitD only, 12 % low BioT ± low VitD, 22 % low BioE and/or high SHBG only, 7 % low BioE and/or high SHBG + low VitD, and 14 % >1 SH abnormality ± low VitD. Cutoffs for low VitD, <20 ng/ml; low BioE, <11 pg/ml; low BioT, <163 ng/dl and high SHBG, >59 nM (By permission of *Journal of Bone Mineral Research* [106])

References

1. Riggs BL, Khosla S, Melton 3rd LJ. A unitary model for involutional osteoporosis: estrogen deficiency causes both type I and type II osteoporosis in postmenopausal women and contributes to bone loss in aging men. J Bone Miner Res. 1998;13(5):763–73.
2. Sowers MR, Jannausch M, McConnell D, et al. Hormone predictors of bone mineral density changes during the menopausal transition. J Clin Endocrinol Metab. 2006;91(4):1261–7.
3. Lee JS, Ettinger B, Stanczyk FZ, et al. Comparison of methods to measure low serum estradiol levels in postmenopausal women. J Clin Endocrinol Metab. 2006;91(10):3791–7.
4. Thienpont LM, De Leenheer AP. Efforts by industry toward standardization of serum estradiol-17 beta measurements. Clin Chem. 1998;44(3):671–4.
5. Taieb J, Mathian B, Millot F, et al. Testosterone measured by 10 immunoassays and by isotope-dilution gas chromatography-mass spectrometry in sera from 116 men, women, and children. Clin Chem. 2003;49(8):1381–95.

6. Siekmann L. Determination of steroid hormones by the use of isotope dilution--mass spectrometry: a definitive method in clinical chemistry. J Steroid Biochem. 1979;11(1A):117–23.
7. Lawson AM, Gaskell SJ, Hjelm M. International Federation of Clinical Chemistry (IFCC), Office for Reference Methods and Materials (ORMM). Methodological aspects on quantitative mass spectrometry used for accuracy control in clinical chemistry. J Clin Chem Clin Biochem. 1985;23(7):433–41.
8. Khosla S, Amin S, Singh RJ, Atkinson EJ, Melton 3rd LJ, Riggs BL. Comparison of sex steroid measurements in men by immunoassay versus mass spectroscopy and relationships with cortical and trabecular volumetric bone mineral density. Osteoporos Int. 2008;19(10):1465–71.
9. Ohlsson C, Nilsson ME, Tivesten A, et al. Comparisons of immunoassay and mass spectrometry measurements of serum estradiol levels and their influence on clinical association studies in men. J Clin Endocrinol Metab. 2013;98(6):E1097–102.
10. Norman A, Litwack G. Steroid hormones: chemistry, biosynthesis, and metabolism. In: Hormones. 2nd ed. San Diego: Academic; 1997. p. 49–85.
11. Khosla S, Riggs BL, Robb RA, et al. Relationship of volumetric bone density and structural parameters at different skeletal sites to sex steroid levels in women. J Clin Endocrinol Metab. 2005;90(9):5096–103.
12. Khosla S, Melton 3rd LJ, Robb RA, et al. Relationship of volumetric BMD and structural parameters at different skeletal sites to sex steroid levels in men. J Bone Miner Res. 2005;20(5):730–40.
13. Orwoll E, Lambert LC, Marshall LM, et al. Testosterone and estradiol among older men. J Clin Endocrinol Metab. 2006;91(4):1336–44.
14. Cauley JA, Gutai JP, Sandler RB, LaPorte RE, Kuller LH, Sashin D. The relationship of endogenous estrogen to bone density and bone area in normal postmenopausal women. Am J Epidemiol. 1986;124(5):752–61.
15. Khosla S, Melton 3rd LJ, Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL. Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. J Clin Endocrinol Metab. 1998;83(7):2266–74.
16. Greendale GA, Edelstein S, Barrett-Connor E. Endogenous sex steroids and bone mineral density in older women and men: the Rancho Bernardo Study. J Bone Miner Res. 1997;12(11):1833–43.
17. Ettinger B, Pressman A, Sklarin P, Bauer DC, Cauley JA, Cummings SR. Associations between low levels of serum estradiol, bone density, and fractures among elderly women: the study of osteoporotic fractures. J Clin Endocrinol Metab. 1998;83(7):2239–43.
18. Murphy S, Khaw KT, Sneyd MJ, Compston JE. Endogenous sex hormones and bone mineral density among community-based postmenopausal women. Postgrad Med J. 1992;68(805):908–13.
19. Lambrinoudaki I, Christodoulakos G, Aravantinos L, et al. Endogenous sex steroids and bone mineral density in healthy Greek postmenopausal women. J Bone Miner Metab. 2006;24(1):65–71.
20. Tok EC, Ertunc D, Oz U, Camdeviren H, Ozdemir G, Dilek S. The effect of circulating androgens on bone mineral density in postmenopausal women. Maturitas. 2004;48(3):235–42.
21. Rapuri PB, Gallagher JC, Haynatzki G. Endogenous levels of serum estradiol and sex hormone binding globulin determine bone mineral density, bone remodeling, the rate of bone loss, and response to treatment with estrogen in elderly women. J Clin Endocrinol Metab. 2004;89(10):4954–62.
22. Bagur A, Oliveri B, Mautalen C, et al. Low levels of endogenous estradiol protect bone mineral density in young postmenopausal women. Climacteric. 2004;7(2):181–8.
23. Rogers A, Saleh G, Hannon RA, Greenfield D, Eastell R. Circulating estradiol and osteoprotegerin as determinants of bone turnover and bone density in postmenopausal women. J Clin Endocrinol Metab. 2002;87(10):4470–5.
24. Sowers MR, Zheng H, Jannausch ML, et al. Amount of bone loss in relation to time around the final menstrual period and follicle-stimulating hormone staging of the transmenopause. J Clin Endocrinol Metab. 2010;95(5):2155–62.
25. Greendale GA, Sowers MF, Han W, et al. Bone mineral density loss in relation to the final menstrual period in a multiethnic cohort: Results from the Study of Women's Health Across the Nation (SWAN). J Bone Miner Res. 2012;27(1):111–8.
26. Crandall CJ, Tseng CH, Karlamangla AS, et al. Serum sex steroid levels and longitudinal changes in bone density in relation to the final menstrual period. J Clin Endocrinol Metab. 2013;98(4):E654–63.
27. Recker R, Lappe J, Davies KM, Heaney R. Bone remodeling increases substantially in the years after menopause and remains increased in older osteoporosis patients. J Bone Miner Res. 2004;19(10):1628–33.
28. Sun L, Peng Y, Sharrow AC, et al. FSH directly regulates bone mass. Cell. 2006;125(2):247–60.
29. Gao J, Tiwari-Pandey R, Samadfam R, et al. Altered ovarian function affects skeletal homeostasis independent of the action of follicle-stimulating hormone. Endocrinology. 2007;148(6):2613–21.
30. Drake MT, McCready LK, Hoey KA, Atkinson EJ, Khosla S. Effects of suppression of follicle-stimulating hormone secretion on bone resorption markers in postmenopausal women. J Clin Endocrinol Metab. 2010;95(11):5063–8.
31. Slemenda C, Longcope C, Peacock M, Hui S, Johnston CC. Sex steroids, bone mass, and bone loss. A prospective study of pre-, peri-, and postmenopausal women. J Clin Invest. 1996;97(1):14–21.
32. Stone K, Bauer DC, Black DM, Sklarin P, Ensrud KE, Cummings SR. Hormonal predictors of bone loss in elderly women: a prospective study. The

Study of Osteoporotic Fractures Research Group. J Bone Miner Res. 1998;13(7):1167–74.
33. Yoshimura N, Kasamatsu T, Sakata K, Hashimoto T, Cooper C. The relationship between endogenous estrogen, sex hormone-binding globulin, and bone loss in female residents of a rural Japanese community: the Taiji Study. J Bone Miner Metab. 2002;20(5):303–10.
34. Guthrie JR, Lehert P, Dennerstein L, Burger HG, Ebeling PR, Wark JD. The relative effect of endogenous estradiol and androgens on menopausal bone loss: a longitudinal study. Osteoporos Int. 2004; 15(11):881–6.
35. Keen RW, Nguyen T, Sobnack R, Perry LA, Thompson PW, Spector TD. Can biochemical markers predict bone loss at the hip and spine?: a 4-year prospective study of 141 early postmenopausal women. Osteoporos Int. 1996;6(5):399–406.
36. Hui SL, Perkins AJ, Zhou L, et al. Bone loss at the femoral neck in premenopausal white women: effects of weight change and sex-hormone levels. J Clin Endocrinol Metab. 2002;87(4):1539–43.
37. Rannevik G, Jeppsson S, Johnell O, Bjerre B, Laurell-Borulf Y, Svanberg L. A longitudinal study of the perimenopausal transition: altered profiles of steroid and pituitary hormones, SHBG and bone mineral density. Maturitas. 1995;21(2):103–13.
38. Khosla S, Bilezikian JP. The role of estrogens in men and androgens in women. Endocrinol Metab Clin North Am. 2003;32(1):195–218.
39. Smith EP, Boyd J, Frank GR, et al. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. N Engl J Med. 1994;331(16):1056–61.
40. Morishima A, Grumbach MM, Simpson ER, Fisher C, Qin K. Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. J Clin Endocrinol Metab. 1995;80(12):3689–98.
41. Carani C, Qin K, Simoni M, et al. Effect of testosterone and estradiol in a man with aromatase deficiency. N Engl J Med. 1997;337(2):91–5.
42. Center JR, Nguyen TV, Sambrook PN, Eisman JA. Hormonal and biochemical parameters in the determination of osteoporosis in elderly men. J Clin Endocrinol Metab. 1999;84(10):3626–35.
43. Szulc P, Hofbauer LC, Heufelder AE, Roth S, Delmas PD. Osteoprotegerin serum levels in men: correlation with age, estrogen, and testosterone status. J Clin Endocrinol Metab. 2001;86(7):3162–5.
44. van den Beld AW, de Jong FH, Grobbee DE, Pols HA, Lamberts SW. Measures of bioavailable serum testosterone and estradiol and their relationships with muscle strength, bone density, and body composition in elderly men. J Clin Endocrinol Metab. 2000;85(9):3276–82.
45. Ravaglia G, Forti P, Maioli F, et al. Body composition, sex steroids, IGF-1, and bone mineral status in aging men. J Gerontol A Biol Sci Med Sci. 2000;55(9):M516–21.
46. Amin S, Zhang Y, Felson DT, et al. Estradiol, testosterone, and the risk for hip fractures in elderly men from the Framingham Study. Am J Med. 2006; 119(5):426–33.
47. Slemenda CW, Longcope C, Zhou L, Hui SL, Peacock M, Johnston CC. Sex steroids and bone mass in older men. Positive associations with serum estrogens and negative associations with androgens. J Clin Invest. 1997;100(7):1755–9.
48. Ackerman KE, Skrinar GS, Medvedova E, Misra M, Miller KK. Estradiol levels predict bone mineral density in male collegiate athletes: a pilot study. Clin Endocrinol (Oxf). 2012;76(3):339–45.
49. Martinez Diaz-Guerra G, Hawkins F, Rapado A, Ruiz Diaz MA, Diaz-Curiel M. Hormonal and anthropometric predictors of bone mass in healthy elderly men: major effect of sex hormone binding globulin, parathyroid hormone and body weight. Osteoporos Int. 2001;12(3):178–84.
50. Rapado A, Hawkins F, Sobrinho L, et al. Bone mineral density and androgen levels in elderly males. Calcif Tissue Int. 1999;65(6):417–21.
51. Fink HA, Ewing SK, Ensrud KE, et al. Association of testosterone and estradiol deficiency with osteoporosis and rapid bone loss in older men. J Clin Endocrinol Metab. 2006;91(10):3908–15.
52. Falahati-Nini A, Riggs BL, Atkinson EJ, O'Fallon WM, Eastell R, Khosla S. Relative contributions of testosterone and estrogen in regulating bone resorption and formation in normal elderly men. J Clin Invest. 2000;106(12):1553–60.
53. Araujo AB, Travison TG, Leder BZ, McKinlay JB. Correlations between serum testosterone, estradiol, and sex hormone-binding globulin and bone mineral density in a diverse sample of men. J Clin Endocrinol Metab. 2008;93(6):2135–41.
54. Paller CJ, Shiels MS, Rohrmann S, et al. Relationship of sex steroid hormones with bone mineral density (BMD) in a nationally representative sample of men. Clin Endocrinol (Oxf). 2009;70(1):26–34.
55. Khosla S, Melton 3rd LJ, Atkinson EJ, O'Fallon WM. Relationship of serum sex steroid levels to longitudinal changes in bone density in young versus elderly men. J Clin Endocrinol Metab. 2001; 86(8):3555–61.
56. Gennari L, Merlotti D, Martini G, et al. Longitudinal association between sex hormone levels, bone loss, and bone turnover in elderly men. J Clin Endocrinol Metab. 2003;88(11):5327–33.
57. Van Pottelbergh I, Goemaere S, Kaufman JM. Bioavailable estradiol and an aromatase gene polymorphism are determinants of bone mineral density changes in men over 70 years of age. J Clin Endocrinol Metab. 2003;88(7):3075–81.
58. Vanbillemont G, Lapauw B, Bogaert V, et al. Sex hormone-binding globulin as an independent determinant of cortical bone status in men at the age of peak bone mass. J Clin Endocrinol Metab. 2010; 95(4):1579–86.

59. Cauley JA, Ewing SK, Taylor BC, et al. Sex steroid hormones in older men: longitudinal associations with 4.5-year change in hip bone mineral density--the osteoporotic fractures in men study. J Clin Endocrinol Metab. 2010;95(9):4314–23.
60. Mellstrom D, Vandenput L, Mallmin H, et al. Older men with low serum estradiol and high serum SHBG have an increased risk of fractures. J Bone Miner Res. 2008;23(10):1552–60.
61. LeBlanc ES, Nielson CM, Marshall LM, et al. The effects of serum testosterone, estradiol, and sex hormone binding globulin levels on fracture risk in older men. J Clin Endocrinol Metab. 2009;94(9):3337–46.
62. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T. Capacity of endogenous sex steroids to predict bone loss in Japanese men: 10-year follow-up of the Taiji Cohort Study. J Bone Miner Metab. 2011;29(1):96–102.
63. Woo J, Kwok T, Leung JC, Ohlsson C, Vandenput L, Leung PC. Sex steroids and bone health in older Chinese men. Osteoporos Int. 2012;23(5):1553–62.
64. Khosla S, Melton 3rd LJ, Achenbach SJ, Oberg AL, Riggs BL. Hormonal and biochemical determinants of trabecular microstructure at the ultradistal radius in women and men. J Clin Endocrinol Metab. 2006;91(3):885–91.
65. Ahlborg HG, Johnell O, Turner CH, Rannevik G, Karlsson MK. Bone loss and bone size after menopause. N Engl J Med. 2003;349(4):327–34.
66. Zebaze RM, Ghasem-Zadeh A, Bohte A, et al. Intracortical remodelling and porosity in the distal radius and post-mortem femurs of women: a cross-sectional study. Lancet. 2010;375(9727):1729–36.
67. Vandenput L, Lorentzon M, Sundh D, et al. Serum estradiol levels are inversely associated with cortical porosity in older men. J Clin Endocrinol Metab. 2014;99(7):E1322–6.
68. Argoud T, Boutroy S, Claustrat B, Chapurlat R, Szulc P. Association between sex steroid levels and bone microarchitecture in men: the STRAMBO study. J Clin Endocrinol Metab. 2014;99(4):1400–10.
69. Travison TG, Araujo AB, Beck TJ, et al. Relation between serum testosterone, serum estradiol, sex hormone-binding globulin, and geometrical measures of adult male proximal femur strength. J Clin Endocrinol Metab. 2009;94(3):853–60.
70. Marshall DH, Crilly RG, Nordin BE. Plasma androstenedione and oestrone levels in normal and osteoporotic postmenopausal women. Br Med J. 1977; 2(6096):1177–9.
71. Longcope C, Baker RS, Hui SL, Johnston Jr CC. Androgen and estrogen dynamics in women with vertebral crush fractures. Maturitas. 1984;6(4):309–18.
72. Davidson BJ, Riggs BL, Wahner HW, Judd HL. Endogenous cortisol and sex steroids in patients with osteoporotic spinal fractures. Obstet Gynecol. 1983;61(3):275–8.
73. Riggs BL, Ryan RJ, Wahner HW, Jiang NS, Mattox VR. Serum concentrations of estrogen, testosterone, and gonadotropins in osteoporotic and nonosteoporotic postmenopausal women. J Clin Endocrinol Metab. 1973;36(6):1097–9.
74. Barrett-Connor E, Mueller JE, von Muhlen DG, Laughlin GA, Schneider DL, Sartoris DJ. Low levels of estradiol are associated with vertebral fractures in older men, but not women: the Rancho Bernardo Study. J Clin Endocrinol Metab. 2000;85(1):219–23.
75. Jassal SK, Barrett-Connor E, Edelstein SL. Low bioavailable testosterone levels predict future height loss in postmenopausal women. J Bone Miner Res. 1995;10(4):650–4.
76. Cummings SR, Browner WS, Bauer D, et al. Endogenous hormones and the risk of hip and vertebral fractures among older women. Study of Osteoporotic Fractures Research Group. N Engl J Med. 1998;339(11):733–8.
77. Garnero P, Sornay-Rendu E, Claustrat B, Delmas PD. Biochemical markers of bone turnover, endogenous hormones and the risk of fractures in postmenopausal women: the OFELY study. J Bone Miner Res. 2000;15(8):1526–36.
78. Chapurlat RD, Garnero P, Breart G, Meunier PJ, Delmas PD. Serum estradiol and sex hormone-binding globulin and the risk of hip fracture in elderly women: the EPIDOS study. J Bone Miner Res. 2000;15(9):1835–41.
79. Goderie-Plomp HW, van der Klift M, de Ronde W, Hofman A, de Jong FH, Pols HA. Endogenous sex hormones, sex hormone-binding globulin, and the risk of incident vertebral fractures in elderly men and women: the Rotterdam Study. J Clin Endocrinol Metab. 2004;89(7):3261–9.
80. Devine A, Dick IM, Dhaliwal SS, Naheed R, Beilby J, Prince RL. Prediction of incident osteoporotic fractures in elderly women using the free estradiol index. Osteoporos Int. 2005;16(2):216–21.
81. Sipila S, Heikkinen E, Cheng S, et al. Endogenous hormones, muscle strength, and risk of fall-related fractures in older women. J Gerontol A Biol Sci Med Sci. 2006;61(1):92–6.
82. Cauley JA, LaCroix AZ, Robbins JA, et al. Baseline serum estradiol and fracture reduction during treatment with hormone therapy: the Women's Health Initiative randomized trial. Osteoporos Int. 2010;21(1):167–77.
83. Finigan J, Gossiel F, Gluer CC, et al. Endogenous estradiol and the risk of incident fracture in postmenopausal women: the OPUS study. Calcif Tissue Int. 2012;91(1):59–68.
84. Prince RL, Dick IM, Beilby J, Dhaliwal SS, Devine A. A cohort study of the effect of endogenous estrogen on spine fracture risk and bone structure in elderly women and an assessment of its diagnostic usefulness. Bone. 2007;41(1):33–8.
85. Moberg L, Nilsson PM, Samsioe G, Borgfeldt C. Low androstenedione/sex hormone binding globulin ratio increases fracture risk in postmenopausal

women. The Women's Health in the Lund Area study. Maturitas. 2013;75(3):270–5.
86. Cauley JA, Chalhoub D, Kassem AM, Fuleihan GH. Geographic and ethnic disparities in osteoporotic fractures. Nat Rev Endocrinol. 2014;10(6):338–51.
87. Finkelstein JS, Sowers M, Greendale GA, et al. Ethnic variation in bone turnover in pre- and early perimenopausal women: effects of anthropometric and lifestyle factors. J Clin Endocrinol Metab. 2002;87(7):3051–6.
88. Stanley HL, Schmitt BP, Poses RM, Deiss WP. Does hypogonadism contribute to the occurrence of a minimal trauma hip fracture in elderly men? J Am Geriatr Soc. 1991;39(8):766–71.
89. Jackson JA, Riggs MW, Spiekerman AM. Testosterone deficiency as a risk factor for hip fractures in men: a case-control study. Am J Med Sci. 1992;304(1):4–8.
90. Gillberg P, Johansson AG, Ljunghall S. Decreased estradiol levels and free androgen index and elevated sex hormone-binding globulin levels in male idiopathic osteoporosis. Calcif Tissue Int. 1999; 64(3):209–13.
91. Pietschmann P, Kudlacek S, Grisar J, et al. Bone turnover markers and sex hormones in men with idiopathic osteoporosis. Eur J Clin Invest. 2001;31(5):444–51.
92. Legrand E, Hedde C, Gallois Y, et al. Osteoporosis in men: a potential role for the sex hormone binding globulin. Bone. 2001;29(1):90–5.
93. Evans SF, Davie MW. Low body size and elevated sex-hormone binding globulin distinguish men with idiopathic vertebral fracture. Calcif Tissue Int. 2002;70(1):9–15.
94. Nyquist F, Gardsell P, Sernbo I, Jeppsson JO, Johnell O. Assessment of sex hormones and bone mineral density in relation to occurrence of fracture in men: a prospective population-based study. Bone. 1998;22(2):147–51.
95. Center JR, Nguyen TV, Sambrook PN, Eisman JA. Hormonal and biochemical parameters and osteoporotic fractures in elderly men. J Bone Miner Res. 2000;15(7):1405–11.
96. Mellstrom D, Johnell O, Ljunggren O, et al. Free testosterone is an independent predictor of BMD and prevalent fractures in elderly men: MrOS Sweden. J Bone Miner Res. 2006;21(4):529–35.
97. Roddam AW, Appleby P, Neale R, et al. Association between endogenous plasma hormone concentrations and fracture risk in men and women: the EPIC-Oxford prospective cohort study. J Bone Miner Metab. 2009;27(4):485–93.
98. Kuchuk NO, van Schoor NM, Pluijm SM, Smit JH, de Ronde W, Lips P. The association of sex hormone levels with quantitative ultrasound, bone mineral density, bone turnover and osteoporotic fractures in older men and women. Clin Endocrinol (Oxf). 2007;67(2):295–303.
99. Meier C, Nguyen TV, Handelsman DJ, et al. Endogenous sex hormones and incident fracture risk in older men: the Dubbo Osteoporosis Epidemiology Study. Arch Intern Med. 2008;168(1):47–54.
100. Cauley JA, Parimi N, Ensrud KE, et al. Serum 25-hydroxyvitamin D and the risk of hip and non-spine fractures in older men. J Bone Miner Res. 2010;25(3):545–53.
101. Bjornerem A, Ahmed LA, Joakimsen RM, et al. A prospective study of sex steroids, sex hormone-binding globulin, and non-vertebral fractures in women and men: the Tromso Study. Eur J Endocrinol. 2007;157(1):119–25.
102. Hsu B, Cumming RG, Seibel MJ, et al. Reproductive Hormones and Longitudinal Change in Bone Mineral Density and Incident Fracture Risk in Older Men: The Concord Health and Ageing in Men Project. J Bone Miner Res. 2015.
103. Cawthon PM, Ensrud KE, Laughlin GA, et al. Sex hormones and frailty in older men: the osteoporotic fractures in men (MrOS) study. J Clin Endocrinol Metab. 2009;94(10):3806–15.
104. LeBlanc ES, Wang PY, Lee CG, et al. Higher testosterone levels are associated with less loss of lean body mass in older men. J Clin Endocrinol Metab. 2011;96(12):3855–63.
105. Ensrud KE, Taylor BC, Paudel ML, et al. Serum 25-hydroxyvitamin D levels and rate of hip bone loss in older men. J Clin Endocrinol Metab. 2009; 94(8):2773–80.
106. Barrett-Connor E, Laughlin GA, Li H, et al. The association of concurrent vitamin D and sex hormone deficiency with bone loss and fracture risk in older men: the osteoporotic fractures in men (MrOS) study. J Bone Miner Res. 2012;27(11):2306–13.

Animal Models for Aging Bone

6

Ken Watanabe and Gustavo Duque

Introduction

Age-related decline in bone mass is a universal phenomenon among laboratory mammals. Research on aging has been conducted using various models from yeast and nematode to mouse and non-human primates, and has rapidly progressed due to the recent development of forward and reverse genetics, as well as functional genomics. Some mouse models bearing artificially or naturally modified genes develop bone phenotypes with various pathologies. Among those mice, some are considered to be potent models for understanding the pathophysiology of age-related bone loss and osteoporosis in humans. Here, available models for the study of age-related bone loss and osteoporosis are introduced and discussed.

K. Watanabe, PhD (✉)
Department of Bone & Joint Disease, National Institute for Longevity Science (NILS), National Center for Geriatrics & Gerontology (NCGG), Obu, Aichi, Japan
e-mail: kwatanab@ncgg.go.jp

G. Duque, MD, PhD, FRACP
Australian Institute for Musculoskeletal Science, The University of Melbourne and Western Health, St. Albans, VIC 3021, Australia
e-mail: gduque@unimelb.edu.au

Normally Aged Animal Models

Besides mice and rats, studies of osteoporosis in guinea pigs, rabbits, cats, dogs, and pigs have been reported. And while, compared to mice and rats, some of those evaluated are considered to be better models relatively to humans in terms of similarity in estrus cycles or Haversian remodeling, the number of studies is quite limited. Studies in non-human primates, such as monkeys, have been considered to be the best and most relevant in terms of human skeletal structure and metabolism [1–6]. While breeding cost and ethical considerations are the highest among the animal models, therapeutic trials in non-human primate models are considered the most informative relative to humans. An age-dependent bone loss in these animals has also been well described. On the other hand, primary screening of candidate anti-osteoporotic compounds has been tested more often in rat than mouse models, probably because they have relatively more bone mass and an overall better response to ovariectomy (OVX). As observed in humans, decreased bone marrow cellularity and increased adiposity, as well as an age-related decline in bone mass, are apparent in rodent models of aging (Fig. 6.1). Laboratory mice usually live for 2–3 years and show a peak bone mass at 4–8 months of age followed by declining bone mass as they age.

A popular laboratory mouse strain, C57BL/6, develops a senile osteoporosis-like bone phenotype with decreased bone mass and quality [7–14]. Both

G. Duque, D.P. Kiel (eds.), *Osteoporosis in Older Persons: Advances in Pathophysiology and Therapeutic Approaches*, DOI 10.1007/978-3-319-25976-5_6

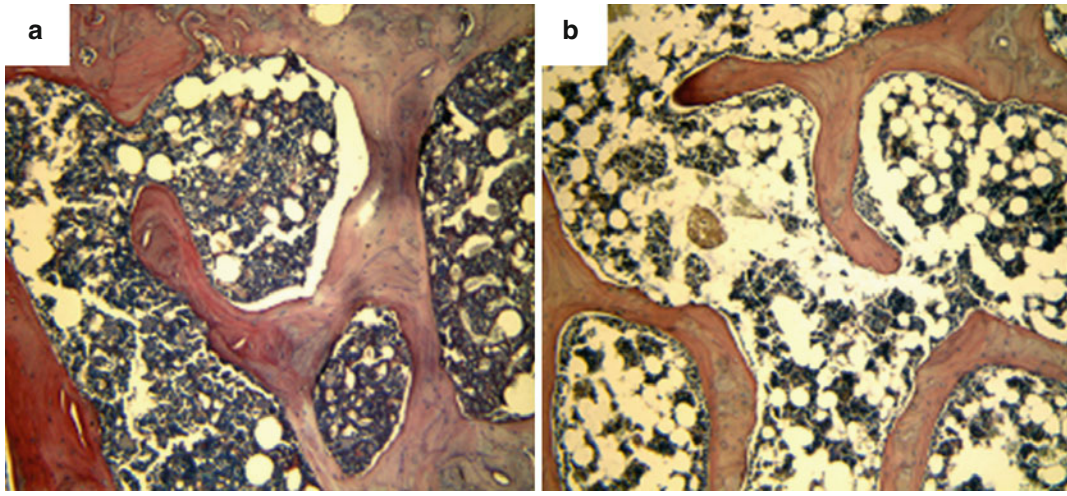


Fig. 6.1 A comparison of bone marrow between young and old rats. The figure shows remarkably higher levels of bone marrow fat (*white areas*) in a 24-month-old rat (**b**) as compared with a 4- month-old rat (**a**). In addition, the trabecular thickness is reduced in the old rat, as is the amount of hematopoietic tissue (Adapted from Duque [119])

trabecular and cortical bones suffer dynamic changes upon aging in these mice. Two studies [7, 8] have assessed the age-related changes in the bone of C57BL/6 J male mice. Mice were aged between 4 and 104 weeks. In young mice, rapid growth was marked by substantial increases in bone size, mineral mass, and mechanical properties. Maturity occurred between 12 and 42 weeks of age with the maintenance of bone mass and mechanical properties. From peak levels, mice aged for 104 weeks experienced decreased whole femur mass (12.1 and 18.6 % for dry and ash mass, respectively), percentage mineralization (7.4 %), diminished whole bone stiffness (29.2 %), energy to fracture (51.8 %), and decreased cortical thickness (20.1 %). Indices of surface-based formation decreased rapidly while the periosteal perimeter and, consequently, the cross-sectional moments of inertia continued to increase through 104 weeks, thus maintaining structural properties. This compensated for cortical thinning and increased brittleness due to decreased mineralization and stiffness. The shape of the mid-diaphysis became increasingly less elliptical in aged mice, and endocortical resorption and evidence of subsequent formation were present in 20–50 % of femurs aged $\geq$ 78 weeks. This, combined with the appearance of excessive endocortical resorption after 52 weeks, indicated a shift in normal mechanisms regulating bone shape and location, and was suggestive of remodeling. The authors concluded that the pattern of bone loss at the femoral mid-diaphysis was markedly similar to that seen in cortical bone in the human femoral neck in age-related osteoporosis.

Interestingly, expression of RANKL, also known as osteoclast differentiation factor, is increased upon aging and correlates with cancellous bone volume [9, 10]. On the other hand, bone marrow hematopoiesis is often affected by aging [11–14]. C57BL/6 is known to develop clonal B cell expansion and lymphoma frequently in this aging mouse strain [13, 14], suggesting that age-related, strain-specific hematopoietic disorganization, such as lymphoma, largely affects bone metabolism and bone resorption in particular. Furthermore, in another common strain, BALB/c, osteogenic stem cells from 24-month-old mice exhibit a decrease in proliferative potential upon aging [11]. It is suggested that the age-related bone loss in this model is caused by decreased osteogenic potential due to both quantitative and qualitative declines, especially in stem cell function (Figs. 6.2, 6.3, and 6.4).

In mature rats (from 8 to 36 months of age), the only change reported in bone structure is an increase in the cross-sectional moment of inertia (distribution of the bone around the central axis), due to the expansion of the outer diameter

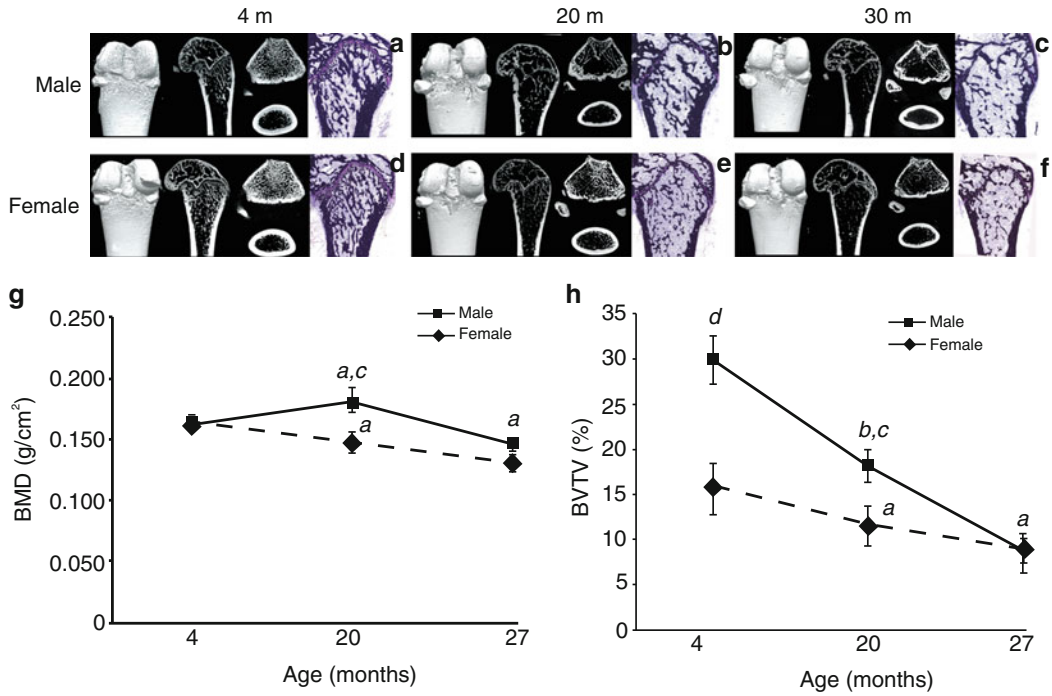


Fig. 6.2 MicroCT analysis (**a**–**f**) to evaluate bone structure and sections of undecalcified bone stained with von Kossa (**a**–**f**, *right panels*) (magnification × 10) to evaluate mineralized tissue (*black*) and fat volume (*white*). The figure shows three-dimensional images of the trabecular bone and coss-sectional images of the cortical bone from rats aged 4, 20 and 30 months (**a**–**f**). The loss in bone volume, the reduction in both trabecular bone and cortical thickness and the increasing cortical porosity with age are visually apparent. Age-related changes in bone mineral density (*BMD*) (**g**) and bone volume/trabecular volume (*BV/TV*) (**h**) showed a significant decline in both groups matching similar levels of bone mass and bone quality at 30 months of age. $^{a}p<0.01$, $^{b}p<0.001$ compared with 4 months, one-way ANOVA and Dunnett's test; $^{c}p<0.01$, $^{d}p<0.001$ males vs. females (From Duque et al. [19])

(periosteal deposition) of their bones, with a thinning of the cortical walls (endosteal resorption) [15]. Other study [16, 17], performed in trabecular bones in proximal tibias of 23-month-old and 5-month-old rats, found that mineral density, bone volume fraction, and trabecular number were significantly reduced in the aged rats compared with the younger rats. In addition, serum markers of bone formation were also reduced in the older rats [17, 18]. Interestingly, a model of "healthy-aging" rats known as LOU rats show the typical features of age-related osteoporosis – including high levels of bone marrow fat – despite their longer life span and low prevalence of diabetes and cancer [19].

Overall, the "normally aged" animal model of osteoporosis has the advantage of closely mimicking the age-related changes in bone. However, disadvantages include the high cost of maintaining a normally aging colony, the variability between different strains in terms of peak of bone mass and levels of bone turnover, and the fact that steroid hormones could play an important role in the levels of bone turnover during the post-menopausal months, which also vary from strain to strain.

Genetic Manipulation and Accelerated Aging

Development of genetic approaches to mimic osteoporosis is becoming a common practice worldwide. Genetic manipulation has been instrumental to our rapidly expanding knowledge of the molecular and cellular mechanisms underlying both normal and pathological bone biology. This methodology, which is more easily applied

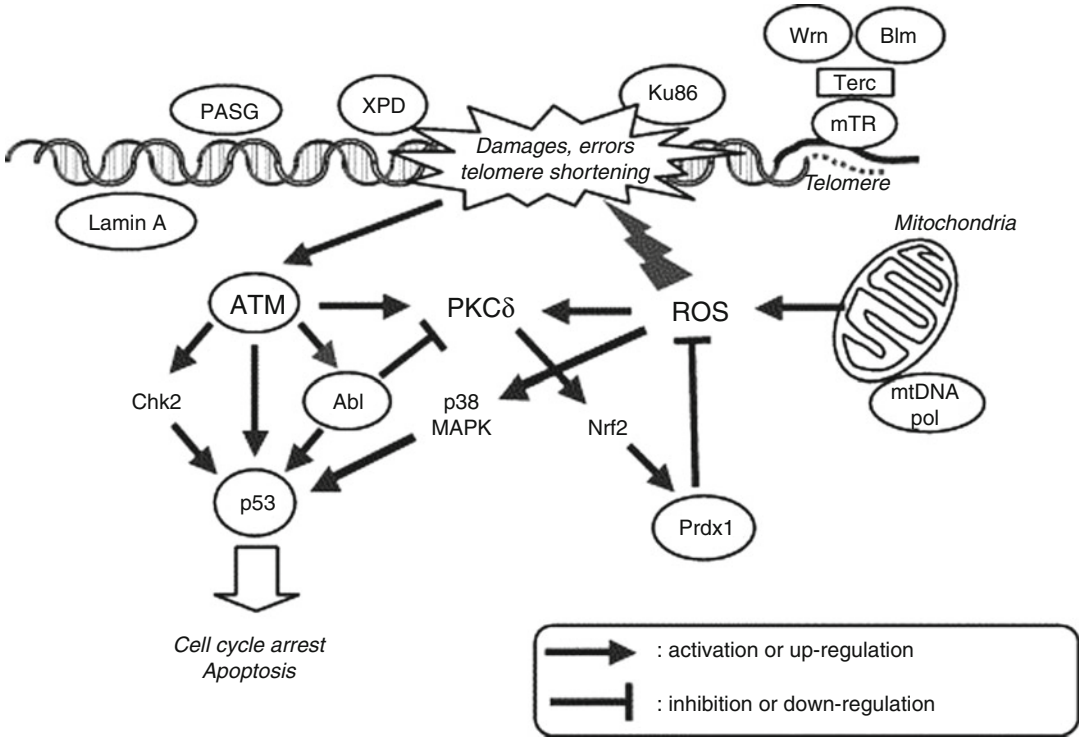


Fig. 6.3 Predicted pathways connecting the gene products responsible for the premature aging mutant phenotype. Most of the mouse models for premature aging described by now are caused by mutations in the genes involved in genomic integrity and subsequent cell cycle regulation. Errors and damage to the genome or telomere shortening, which also affects DNA integrity could, in theory, be detected and corrected. Mutations in the genes responsible for genomic stability cause accumulation of phenotypic abnormalities. Genomic disorganization activates cell cycle-regulating pathways involving checkpoint kinases and p53. Oxidative stress is among the triggers that elicit genomic instability via DNA damage. Elevation and excess of ROS affect downstream signaling, including PKCδ which subsequently stimulates the anti-ROS pathway, including transcriptional activation of Prdx1 (From Watanabe and Hishiya, Ref. [118]. With permission from Elsevier)

to mice, includes the targeted manipulation and ablation *in vivo* of one or several genes.

Some of the genetically modified mice recently developed by knockout or transgenic techniques show premature aging phenotypes. The clearest conclusion to be drawn from these models is that single gene mutations cause multiple aging phenotypes. This advantage is useful in defining the mechanisms regulating bone metabolism.

Amongst those mouse models, the senescence accelerated mice (SAM) have been established by Takeda et al., and accepted as suitable models for aging [20]. The SAM lines, derived from a mouse strain AKR/J, are divided into two classes; SAM-P lines exhibit an accelerated aging phenotype with shortened life-span, and SAM-R lines, which show a less accelerated phenotype than that of SAM-P. The aging phenotype of SAM-P lines becomes apparent at 6–8 months of age. Among the SAM lines, SAM-P6 has been demonstrated to be a correlative model for age-related osteoporosis in humans [21–24], and its bone phenotype has been well described. For example, Jilka et al. [21] demonstrated that the osteopenic phenotype in SAM-P6 is caused by reduced osteoblastogenesis and that their bone metabolism is resistant to gonadectomy. Furthermore, increased adipogenesis and myelopoiesis are observed in the bone marrow of these mice [23]. In addition, the long bones in SAM-P6 are longer but more fragile than controls [22]. This line is among the best studied as a model for age-related osteoporosis not only in terms of

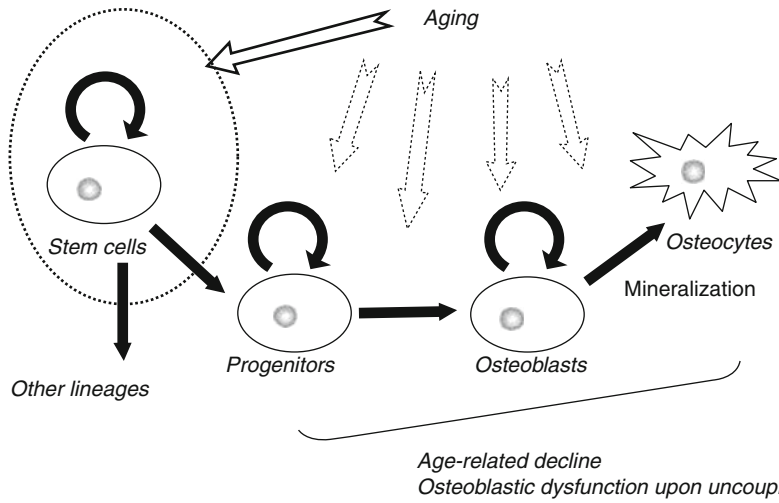


Fig. 6.4 Schematic presentation of osteogenesis and aging. Observations in naturally aged laboratory animals and mutant mice with aging phenotypes suggest that one of the keys to understanding aging and premature aging pathogenesis may be self-renewing stem cells. In these models, the pathway involving p53 (Fig. 6.3) upregulates the genes responsible for cell cycle arrest and/or apoptosis, lowering the regenerative potential necessary for homeostasis and tissue repair. While the mechanisms responsible for aging are largely unknown, the existing models suggest that there are common pathways, which may help in our understanding of the aging phenotype (From Watanabe and Hishiya, Ref. [118]. With permission from Elsevier)

skeletal morphology and pathology, but also in terms of its application for therapeutic-targeting experiments, such as drug testing and bone marrow transplantation [25–27]. Other numerous *in vivo* and *ex vivo* reports of SAM-P6 have been published whose observations are thought to be consistent between these aged mice and humans, but also include some controversial observations or interpretations, probably due to their complicated genetic backgrounds. Because the SAM strains are polygenic, the specific genetic factors accounting for their bone phenotype remain to be elucidated.

The observed differences in bone metabolism resulting from the various genetic backgrounds of these different mouse strains have been quantified by QTL analyzes. For example, whereas C57BL/6 mice have a relatively low bone mineral density (BMD) and reduced bone mass, C3H/HeJ have high BMD and are resistant to bone loss in response to OVX [28, 29]. These studies indicate that usage of wild-type inbred strains of mice, as well as rats, need to be well-characterized and given strong consideration in studies of bone metabolism and pathophysiology.

Other mouse models mimicking the human progeroid syndromes have been reported [30–35]. These genetically modified mice develop multiple aging phenotypes and exhibit a shortened life span (Table 6.1). For example, Werner syndrome is caused by a loss-of-function mutation in *WRN*, encoding the RecQ family DNA helicase, which plays a role in genome stability including telomere maintenance [36]. Unexpectedly, knockout mice for the Wrn gene are essentially normal and exhibit no characteristics of premature aging [37]. Mice have long telomeres and relatively high telomerase activity, suggesting that the aging phenotype is latent in these mice and results from residual activity surrounding telomere maintenance. Evidently, double knockout mice for Wrn and Terc, which encodes the RNA component of telomerase activity, show a Werner-like phenotype with osteoporosis [38, 39]. RecQ like-4 (Recql4) is a gene mutated in a subset of Rothmund-Thomson syndrome, recognized as a premature aging syndrome [40, 41]. Although Reql4 null mice are embryonic lethal, targeted deletion of exon 13 results in a form of aging phenotype that includes osteopenia [42]. Yang et al.

Table 6.1 Genetically modified mice with premature aging phenotype and/or short life span

Gene	Function	Modification	Bone phenotype	Characterization of bone	Related human case
Atm	Cell cycle checkpoint	K0	Osteopenia	MicroCT, histological analysis, *ex vivo* cell culture	Ataxia telangiectasia
BubR1	Spindle assembly checkpoint	Hypomorph	Normal (kyphosis)	DXA	
DNA-PKcs	DNA repair	K0	Osteopenia	X-ray analysis	
Klotho	Hormone /growth factor stimulating, mineral metabolism	K0	Osteopenia	SXA, microCT, histological analysis, *ex vivo* cell culture	
Ku86	DNA repair, transcription	K0	(Not indicated)		
Lmna	Nuclear architecture	Knock-in	Osteopenia	DXA	Hutchinson-Gilford progeria syndrome
mTR	Telomere maintenance	K0	Normal[a]	X-ray analysis, histological analysis	
PASG	DNA methylation	Hypomorph	Osteopenia	X-ray analysis, histological analysis	
PolgA	Mitochondrial DNA replication	Knock -in	Osteoporosis	X-ray analysis	
Recql4	DNA replication and repair	K0	Osteopenia	X-ray analysis, histological analysis	Rothmund-Thomson syndrome
Sirt6	DNA repair	K0	Osteopenia	X-ray analysis, DXA	
TRp53	Cell cycle checkpoint	Deletion mutant	Osteopenia	X-ray analysis, histological analysis	
		Mutant Tg	Ostopenia	X-ray analysis	
		Short isoform Tg	Osteopenia	X-ray analysis, histological analysis	
XPD	DNA replication and repair	Knock-in	Osteoporosis	X-ray analysis, DXA	Xeroderma pigmentosum
Wrn/Terc	Telomere maintenance	Double K0	Osteopenia	MicroCT	Werner syndrome

[a]The phenotype was observed in the 6th generation from mTR knockout mouse mattings

showed that osteoprogenitors are significantly decreased in heterozygous Recql4 (±) mice compared to wild-type controls [43]. In addition, mutated Recql4 has also been reported in Baller-Gerold syndrome, a rare autosomal recessive disorder with radial aplasia/hypoplasia and craniosynostosis [44].

Recently, a gene encoding lamin A has been identified to be responsible for human progeria, Hutchinson-Gilford syndrome [45, 46]. Mice carrying an autosomal recessive point mutation in the lamin A gene, corresponding to that identified in humans, also develop a progeria-like phenotype with osteoporotic symptoms [47]. Interestingly, expression of lamin A/C in osteoblasts and chondrocytes of C57BL/6 mice is decreased in an age-related manner [48]. In addition, recent studies have reported that lamin A-deficient mice are osteoporotic [49, 50], show a low anabolic response to exercise [51], and have high levels of fat infiltration in muscle and bone [52].

Furthermore, mice presenting with multiple aging phenotypes have also been reported. Null mutation of a gene, Ku86 (also known as Ku80), which plays roles in DNA repair and transcription exhibits a shortened life span and elicits a premature aging phenotype including osteopenia [53]. The aging phenotype has also been observed in mice lacking proliferation-associated SNF2-like gene (PASG), an SNF-like molecule that functions in DNA methylation [54]. Mutant mice show decreased BMD and a delay in the secondary ossification of the tibial epiphyses [54]. In addition to mutations in genes involved in genomic stability and nuclear organization, mice carrying mitochondrial DNA polymerase mutations that exclude a region responsible for its proofreading activity, also present the osteoporotic phenotype together with other premature aging symptoms [55]. A sir2/SIRT family of NAD-dependent histone deacetylases regulates life span. Knockout mice for Sirt6 exhibit genomic instability and an aging-like phenotype with osteopenia [56]; in particular decreased bone mass, now considered a hallmark of premature aging phenotypes. However, most observations of the skeletal phenotype were examined by X-ray analysis. The pathophysiology, including histology, of the bone phenotype in these models for premature aging, has not yet been fully described.

Errors in cell duplication, such as those miss programmed by the above-mentioned mutations can be detected and corrected by arresting the cell cycle. A system of cell cycle checkpoints has been shown to play a critical mechanistic role [57, 58]. Checkpoint kinase cascades are involved in DNA replication and other cell cycle events. ATM is a PI3K family kinase involved in DNA repair and oxidative response [59]. The gene encoding the protein kinase has been identified as a gene mutated in ataxia telangiectasia, recognized as one of the human premature aging syndromes [60]. Knockout mice for ATM exhibit a similar phenotype to the human disease, including hyper-radiosensitivity and ataxic defects [61–63]. It has been shown that the self- renewal capacity of hematopoietic stem cells in Atm knockout mice is significantly impaired with elevated reactive oxygen species (ROS), and that treatment with anti-oxidative agents rescues the bone marrow failure [64]. An osteopenic phenotype has also been observed in these knockout mice. Colony formation assays revealed that the phenotype was mainly caused by a proliferative defect in bone marrow mesenchymal stem cells or its progenitors [65].

Gain-of-function mutations in p53, a downstream effector of ATM kinase, also exhibit premature aging with an osteoporotic phenotype [66, 67]. Among them, p44 transgenic mice show a low progenitor turnover with significant decreases in osteoblast number and a slight reduction of osteoclasts [67]. Although further characterization of these models is required, these data suggest that the stem cell defect due to cell cycle arrest upon DNA damage or other cell cycle abnormalities, at least in part, may account for the decreased bone formation and subsequent osteopenia observed in these premature aging models.

In addition to stem cell defects in p53 and other checkpoint deficiencies, recent evidence indicates that p53 can directly regulate osteoblast differentiation [68]. Wang et al. [69] showed that mice lacking p53 exhibit increased bone mass due to accelerated osteoblast differentiation caused by elevated Osterix levels. Lengner et al. [68] examined osteoblast-specific ablation of Mdm2, a negative regulator of p53, and found reduced proliferation and decreased levels of Runx2 in the osteoblasts. Furthermore, they also described elevated Runx2 levels in p53-null osteoblasts, suggesting that p53 negatively regulates bone development and growth by inhibition of Runx2. Defects in osteoblast differentiation caused by dysregulation of Osterix was also recently reported in Atm knockout mice [70]. Thus, not only stem cell defects but also cell autonomous differentiation defects of osteoblasts are associated with the osteopenic phenotype in mouse models of premature aging.

Osteopenia Caused by Decrease in Bone Formation

Low turnover rates or uncoupling between bone resorption and formation in aged bones is often associated with a decline in osteoblast function [71]. Reduced bone formation is one of the features

observed in models for age-related osteoporosis. Some genes that play critical roles in bone formation have been described using genetically modified mice [72–75]. Several typical models are listed in Table 6.2. Sca1/Ly6A is a GPI-anchored membrane protein expressed in hematopoietic stem cells and a subset of bone marrow stromal cells [76, 77]. Whereas Sca1 knockout mice have normal bone development, the aged animals (15 months of age) show a significant bone loss [78]. Progenitor and differentiation assays of bone marrow cells in these mice reveal that decreased bone mass is caused by impaired self-renewal of mesenchymal progenitors. Stem cell defects in hematopoietic lineages have also been reported in Sca1 knockout mice [79]. Although multiple aging phenotypes in Sca1 knockout mice have been reported, this is a good model for age-related osteoporosis in humans, supporting the stem cell hypothesis in the pathogenesis of age-related osteoporosis [80].

In addition, IRS1 is a major substrate of insulin receptor (IR) and IGF-1 receptor (IGF1R) that transduces signals by interacting with signaling molecules in a phosphorylation-dependent manner, which is expressed in osteoblasts but not in osteoclasts. IRS1 knockout mice exhibit low bone mass compared to wild-type controls, and cultured osteoblasts from the knockout mice are impaired in IGF-induced proliferation and differentiation, whereas BMP-induction is not altered [73]. Reduced osteoclast formation is then the result of defective osteoblasts, resulting in low turnover osteopenia [81].

Wnt signaling regulates bone mass through the osteoblastic lineage. It has been revealed that an autosomal recessive disorder, osteoporosis-pseudoglioma syndrome (OPPG), is caused by mutations in the gene encoding LRP5, a cell surface co-receptor for Wnt [82]. It has also been independently shown that Val171 mutation of LRP5 causes high bone density in humans [83]. These correlative findings indicate a role for the Wnt pathway in bone development and remodeling. Kato et al. generated mice deficient in Lrp5, and showed that Lrp5 knockout mice also develop osteopenia caused by reduced osteoblast proliferation and function [84]. A significant decrease in the number of bone marrow stromal progenitor cell (CFU-F) colonies was observed in the knockout mice. Inhibition of GSK3, a negative regulator of Wnt/β-catenin signaling stimulates osteoblastic differentiation of the progenitors [85, 86]. The ligands, such as Wnt10b, specifically activate the canonical pathway, and constitutively activate β-catenin-stimulated osteoblast differentiation [87]. These findings support the idea that the canonical pathway via β-catenin signaling of Wnt plays a role in the regulation of osteoblasts. It should be noted that the canonical pathway also inhibits adipogenic differentiation of progenitor cells [88], suggesting that the pathway is also important in lineage commitment between osteoblastic and adipogenic fates. This observation may be associated with age-related alterations of bone marrow, resulting in decreased bone formation and increased adipogenesis to what is described as "fatty marrow".

On the other hand, some models presenting with osteopenia exhibit defects in osteoblast differentiation. Mice lacking a transcriptional cofactor, *four and a half LIM domains 2 (Fhl2)*, also

Table 6.2 Osteopenic mice with altered bone formation

Gene	Phenotype (knockout)	Osteoprogenitor (incl. stem cells)	Number of osteoblasts	Number of osteoclasts	Ex vivo osteoblast differentiation
Kl (klotho)	Osteopenia	⇓	⇓	⇓	⇓
ly6a (Seal)	Osteopenia	n.d.	⇓	⇓	⇔
lrs1	Osteopenia	⇓	⇓	⇓	–
lrp5	Osteopenia	⇓	⇓	⇔	⇔
Fhl2	Osteopenia	n.d.	⇔	⇔	⇓
Abl1 (Abl)	Osteopenia	⇓	⇓	⇔	⇓
Lmna	Osteopenia	⇓	⇓	⇓	⇓

n.d. not described

present with a significant decrease in bone mass [89]. Although numbers of osteoblasts and osteoclasts were comparable to littermate controls, bone formation rate was markedly reduced. Furthermore, transgenic mice overexpressing Fhl2 in osteoblasts exhibited enhanced bone formation and increased bone mass. Fhl2 interacts with Runx2 to increase its transcriptional activity and stimulates osteoblast maturation, suggesting that the Fhl2 knockout is a unique model for osteopenia caused by osteoblast activation deficiency [90].

Furthermore, c-Abl, a downstream protein kinase of ATM, functions in DNA repair and oxidative stress response [91]. Mice deficient for the Abl gene also develop osteopenia with reduced bone formation [92]. *Ex vivo* assays of osteoclastogenesis were not affected, and the number of osteoclasts in the Abl-deficient mice was similar to that of wild-type controls. Whereas the number of progenitors in bone marrow is significantly decreased, the differentiation of osteoblasts from Abl knockout mice is also impaired [92]. Using osteoblast culture, distinct roles in the oxidative stress response between c-Abl and ATM, have been proposed [93]. Although decreased expression of peroxiredoxin 1 (Prdx1) due to down-regulation of PKCδ was observed upon arsenate-induced oxidative stress in osteoblasts from Atm knockout mice, expression of the redox protein, through the upregulation of PKCδ, was increased in the cells derived from Abl knockouts. The opposite roles in the oxidative stress response may cause similar bone phenotypes in the knockout mice of Abl and Atm genes through distinct mechanisms. Life-span shortening and age-related defects have been reported in mice lacking Prdx1 or MsrA, which encodes methionine sulfoxide reductase [94, 95]. Both genes play important roles in the oxidative stress response through anti-ROS activity. Whereas the bone phenotype in these mutant mice has not yet been described, it will be interesting to see the potential pathogenic phenotype in bone from these mice. Oxidative stress, such as that caused by ROS, often causes damages in DNA, suggesting that the genomic stability and oxidative stress response may share some common pathways in the aging phenotype. As mentioned with Atm mice, an antioxidant also partially rescues the perinatal lethality observed in Ku86 knockout mice [96]. In addition to DNA damage, ROS is important in signal transduction and pathogenesis of diseases as well. For example, anti-oxidative agents reverse insulin resistance in diabetic models [97, 98]. Although it remains unclear whether ROS targets are part of the mechanistic pathways affected by aging, management of ROS may be significantly implicated in osteoblast function and aging.

The Aging Phenotype and Defects in Mineral Metabolism

Other models for accelerated aging phenotypes, where the responsible genes are apparently not directly involved in genomic integrity also exist. Mice carrying hypomorphic mutations of the gene Klotho show multiple aging phenotypes [99]. In Klotho mice (kl/kl), both bone formation and resorption are reduced, indicating a low turnover of bone metabolism resembling human osteoporosis [100]. Although neither osteoblasts nor osteoclasts express the kl gene, *ex vivo* cultures of osteoblastogenesis and osteoclastogenesis show reduced differentiation independently in both lineages. In contrast to the canonical progeroid models, this is a unique model for age-related osteoporosis in humans. Indeed, the molecular functions of KL protein have been reported. The protein, which is structurally similar to β-glucosidase, possesses β-glucuronidase activity [101]. KL protein acts as a co-receptor for IGF and is also required for FGF23 signaling through FGFR1 [102–107]. FGF23 has been identified as a gene responsible for autosomal dominant hypophosphatemic rickets and is suggested to play an important role in phosphate metabolism as a hormone, a candidate for phosphatonin [104]. FGF23 knockout mice also exhibit a premature aging-like phenotype [105]. Interestingly, the mice have elevated serum levels of vitamin D and hyperphosphatemia, and a part of the aging phenotype was rescued by lowering the vitamin D levels [105–107]. It is therefore suggested that control of the phosphate-regulating system by FGF23-KL is associated with the aging phenotype including

osteoporosis. Notably, PHEX (phosphate-regulating gene with homology to endopeptidases on the X chromosome) is highly expressed in osteocytes [108–111], and declines with age as well as with post-OVX and mechanical unloading [112–114]. Conceivably, osteocytes may be implicated in phosphate metabolism and age-related osteoporosis. In fact, FGF signaling coordinately regulates mineralization-related genes in the osteoblast lineage, and that ERK signaling is essential for Dmp1 expression and osteocyte differentiation in vivo [115].

What Mouse Models Teach

It has been recently described that mice deficient for molecular clock genes, such as Per1/2, Cry1/2, and BMAL1, exhibit increased bone mass with elevated bone formation [116]. The clock components inhibit osteoblast proliferation triggered by CREB activation responding to signals from sympathetic neurons. In contrast, it has also been reported that BMAL1 knockout mice have impaired circadian rhythms and display a premature aging phenotype including decreased bone mass [117]. Although these apparently opposite observations might be due to age differences (increased bone mass at 2 months; decreased at 40 weeks of age, compared to wild-type controls), bone phenotype is largely affected by many factors including mobility. Thus, the same mouse can tell different stories. Whereas decreased bone mass is a major indication of the aging phenotype as mentioned, age-related structural and functional alterations are seen not only in bone but also in other tissues and organs as well. Age-related osteoporosis has been recognized as due to a combination of age-related changes in bone caused by bone cell dysfunction, age-related decline in mineral metabolism or hormonal regulation, and neuronal and/or gonadal dysregulation. Nevertheless, these models inform us of the molecular mechanisms involved in bone biology, especially the molecular and cellular basis of bone pathophysiology, and include the possibility that cell autonomous bone defects may be implicated, at least in part, in the pathogenesis of age-related osteoporosis. Furthermore, the described genetically defined models can be useful for elucidation of the underlying mechanisms in pharmacological and other therapeutic-targeting studies.

References

1. Aufdemorte TB, Fox WC, Miller D, Buffum K, Holt GR, Carey KD. A non-human primate model for the study of osteoporosis and oral bone loss. Bone. 1993;14(3):581–6.
2. Champ JE, Binkley N, Havighurst T, Colman RJ, Kemnitz JW, Roecker EB. The effect of advancing age on bone mineral content of female rhesus monkeys. Bone. 1996;19(5):485–92.
3. Colman RJ, Kemnitz JW, Lane MA, Abbott DH, Binkley N. Skeletal effects of aging and menopausal status in female rhesus macaques. J Clin Endocrinol Metab. 1999;84(11):4144–8.
4. Colman RJ, Lane MA, Binkley N, Wegner FH, Kemnitz JW. Skeletal effects of aging in male rhesus monkeys. Bone. 1999;24(1):17–23.
5. Jayo MJ, Rankin SE, Weaver DS, Carlson CS, Clarkson TB. Accuracy and precision of lumbar bone mineral content by dual-energy X-ray absorptiometry in live female monkeys. Calcif Tissue Int. 1991;49(6):438–40.
6. Jayo MJ, Weaver DS, Rankin SE, Kaplan JR. Accuracy and reproducibility of lumbar bone mineral status determined by dual photon absorptiometry in live male cynomolgus macaques (Macaca fascicularis). Lab Anim Sci. 1990;40(3):266–9.
7. Halloran BP, Ferguson VL, Simske SJ, Burghardt A, Venton LL, Majumdar S. Changes in bone structure and mass with advancing age in the male C57BL/6 J mouse. J Bone Miner Res. 2002;17(6):1044–50.
8. Ferguson VL, Ayers RA, Bateman TA, Simske SJ. Bone development and age-related bone loss in male C57BL/6 J mice. Bone. 2003;33(3):387–98.
9. Perkins SL, Gibbons R, Kling S, Kahn AJ. Age-related bone loss in mice is associated with an increased osteoclast progenitor pool. Bone. 1994;15(1):65–72.
10. Cao J, Venton L, Sakata T, Halloran BP. Expression of RANKL and OPG correlates with age-related bone loss in male C57BL/6 mice. J Bone Miner Res. 2003;18(2):270–7.
11. Bergman RJ, Gazit D, Kahn AJ, Gruber H, McDougall S, Hahn TJ. Age-related changes in osteogenic stem cells in mice. J Bone Miner Res. 1996;11(5):568–77.
12. Morrison SJ, Wandycz AM, Akashi K, Globerson A, Weissman IL. The aging of hematopoietic stem cells. Nat Med. 1996;2(9):1011–6.
13. Ghia P, Melchers F, Rolink AG. Age-dependent changes in B lymphocyte development in man and mouse. Exp Gerontol. 2000;35(2):159–65.

14. LeMaoult J, Manavalan JS, Dyall R, Szabo P, Nikolic-Zugic J, Weksler ME. Cellular basis of B cell clonal populations in old mice. J Immunol. 1999;162(11):6384–91.
15. LaMothe JM, Hepple RT, Zernicke RF. Selected ontribution: bone adaptation with aging and long-term caloric restriction in Fischer 344 x Brown-Norway F1-hybrid rats. J Appl Physiol. 2003;95:1739–45.
16. Westerbeek ZW, Hepple RT, Zernicke RF. Effects of aging and caloric restriction on bone structure and mechanical properties. J Gerontol A Biol Sci Med Sci. 2008;63(11):1131–6.
17. Pietschmann P, Skalicky M, Kneissel M, Rauner M, Hofbauer G, Stupphann D, Viidik A. Bone structure and metabolism in a rodent model of male senile osteoporosis. Exp Gerontol. 2007;42(11):1099–108.
18. Ikeda T, Utsuyama M, Hirokawa K. Expression profiles of receptor activator of nuclear factor kappaB ligand, receptor activator of nuclear factor kappaB, and osteoprotegerin messenger RNA in aged and ovariectomized rat bones. J Bone Miner Res. 2001;16(8):1416–25. 12-.
19. Duque G, Rivas D, Li W, Li A, Henderson JE, Ferland G, Gaudreau P. Age-related bone loss in the LOU/c rat model of healthy ageing. Exp Gerontol. 2009;44(3):183–9.
20. Takeda T, Matsushita T, Kurozumi M, Takemura K, Higuchi K, Hosokawa M. Pathobiology of the senescence-accelerated mouse (SAM). Exp Gerontol. 1997;32(1-2):117–27.
21. Jilka RL, Weinstein RS, Takahashi K, Parfitt AM, Manolagas SC. Linkage of decreased bone mass with impaired osteoblastogenesis in a murine model of accelerated senescence. J Clin Invest. 1996;97(7):1732–40.
22. Silva MJ, Brodt MD, Ettner SL. Long bones from the senescence accelerated mouse SAMP6 have increased size but reduced whole-bone strength and resistance to fracture. J Bone Miner Res. 2002;17(9):1597–603.
23. Kajkenova O, Lecka-Czernik B, Gubrij I, et al. Increased adipogenesis and myelopoiesis in the bone marrow of SAMP6, a murine model of defective osteoblastogenesis and low turnover osteopenia. J Bone Miner Res. 1997;12(11):1772–9.
24. Matsushita M, Tsuboyama T, Kasai R, et al. Age-related changes in bone mass in the senescence-accelerated mouse (SAM). SAM-R/3 and SAM-P/6 as new murine models for senile osteoporosis. Am J Pathol. 1986;125(2):276–83.
25. Takada K, Inaba M, Ichioka N, et al. Treatment of senile osteoporosis in SAMP6 mice by intra-bone marrow injection of allogeneic bone marrow cells. Stem Cells. 2006;24(2):399–405.
26. Duque G, Macoritto M, Dion N, Ste-Marie LG, Kremer R. 1,25(OH)2D3 acts as a bone-forming agent in the hormone-independent senescence-accelerated mouse (SAM-P/6). Am J Physiol Endocrinol Metab. 2005;288(4):E723–30.
27. Ichioka N, Inaba M, Kushida T, et al. Prevention of senile osteoporosis in SAMP6 mice by intrabone marrow injection of allogeneic bone marrow cells. Stem Cells. 2002;20(6):542–51.
28. Li CY, Schaffler MB, Wolde-Semait HT, Hernandez CJ, Jepsen KJ. Genetic background influences cortical bone response to ovariectomy. J Bone Miner Res. 2005;20(12):2150–8.
29. Beamer WG, Shultz KL, Donahue LR, et al. Quantitative trait loci for femoral and lumbar vertebral bone mineral density in C57BL/6 J and C3H/HeJ inbred strains of mice. J Bone Miner Res. 2001;16(7):1195–206.
30. Hishiya A, Watanabe K. Progeroid syndrome as a model for impaired bone formation in senile osteoporosis. J Bone Miner Metab. 2004;22(5):399–403.
31. Warner HR, Sierra F. Models of accelerated ageing can be informative about the molecular mechanisms of ageing and/or age-related pathology. Mech Ageing Dev. 2003;124(5):581–7.
32. Hasty P, Vijg J. Accelerating aging by mouse reverse genetics: a rational approach to understanding longevity. Aging Cell. 2004;3(2):55–65.
33. Hasty P, Campisi J, Hoeijmakers J, van Steeg H, Vijg J. Aging and genome maintenance: lessons from the mouse? Science. 2003;299(5611):1355–9.
34. Kuro-o M. Disease model: human aging. Trends Mol Med. 2001;7(4):179–81.
35. Kipling D, Davis T, Ostler EL, Faragher RG. What can progeroid syndromes tell us about human aging? Science. 2004;305(5689):1426–31.
36. Yu CE, Oshima J, Fu YH, et al. Positional cloning of the Werner's syndrome gene. Science. 1996;272(5259):258–62.
37. Lombard DB, Beard C, Johnson B, et al. Mutations in the WRN gene in mice accelerate mortality in a p53-null background. Mol Cell Biol. 2000;20(9):3286–91.
38. Du X, Shen J, Kugan N, et al. Telomere shortening exposes functions for the mouse werner and bloom syndrome genes. Mol Cell Biol. 2004;24(19):8437–46.
39. Chang S, Multani AS, Cabrera NG, et al. Essential role of limiting telomeres in the pathogenesis of Werner syndrome. Nat Genet. 2004;36(8):877–82.
40. Mohaghegh P, Hickson ID. DNA helicase deficiencies associated with cancer predisposition and premature ageing disorders. Hum Mol Genet. 2001;10(7):741–6.
41. Kitao S, Shimamoto A, Goto M, et al. Mutations in RECQL4 cause a subset of cases of Rothmund-Thomson syndrome. Nat Genet. 1999;22(1):82–4.
42. Hoki Y, Araki R, Fujimori A, et al. Growth retardation and skin abnormalities of the Recql4-deficient mouse. Hum Mol Genet. 2003;12(18):2293–9.
43. Yang J, Murthy S, Winata T, et al. Recql4 haploinsufficiency in mice leads to defects in osteoblast progenitors: Implications for low bone mass phenotype. Biochem Biophys Res Commun. 2006;344(1):346–52.
44. Van Maldergem L, Siitonen HA, Jalkh N, et al. Revisiting the craniosynostosis-radial ray hypoplasia association: Baller-Gerold syndrome caused

by mutations in the RECQL4 gene. J Med Genet. 2006;43(2):148–52.
45. Eriksson M, Brown WT, Gordon LB, et al. Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. Nature. 2003;423(6937):293–8.
46. De Sandre-Giovannoli A, Bernard R, Cau P, et al. Lamin a truncation in Hutchinson-Gilford progeria. Science. 2003;300(5628):2055.
47. Mounkes LC, Kozlov S, Hernandez L, Sullivan T, Stewart CL. A progeroid syndrome in mice is caused by defects in A-type lamins. Nature. 2003;423(6937):298–301.
48. Duque G, Rivas D. Age-related changes in lamin A/C expression in the osteoarticular system: laminopathies as a potential new aging mechanism. Mech Ageing Dev. 2006;127(4):378–83.
49. Rivas D, Li W, Akter R, Henderson JE, Duque G. Accelerated features of age-related bone loss in zmpste24 metalloproteinase-deficient mice. J Gerontol A Biol Sci Med Sci. 2009;64(10):1015–24.
50. Li W, Yeo LS, Vidal C, McCorquodale T, Herrmann M, Fatkin D, Duque G. Decreased bone formation and osteopenia in lamin a/c-deficient mice. PLoS One. 2011;6(4), e19313.
51. Duque G, Li W, Yeo LS, Vidal C, Fatkin D. Attenuated anabolic response to exercise in lamin A/C haploinsufficient mice. Bone. 2011;49(3):412–8.
52. Tong J, Li W, Vidal C, Yeo LS, Fatkin D, Duque G. Lamin A/C deficiency is associated with fat infiltration of muscle and bone. Mech Ageing Dev. 2011;132(11-12):552–9.
53. Vogel H, Lim DS, Karsenty G, Finegold M, Hasty P. Deletion of Ku86 causes early onset of senescence in mice. Proc Natl Acad Sci U S A. 1999;96(19):10770–5.
54. Sun LQ, Lee DW, Zhang Q, et al. Growth retardation and premature aging phenotypes in mice with disruption of the SNF2-like gene. PASG Genes Dev. 2004;18(9):1035–46.
55. Trifunovic A, Wredenberg A, Falkenberg M, et al. Premature ageing in mice expressing defective mitochondrial DNA polymerase. Nature. 2004;429(6990):417–23.
56. Mostoslavsky R, Chua KF, Lombard DB, et al. Genomic instability and aging-like phenotype in the absence of mammalian SIRT6. Cell. 2006;124(2):315–29.
57. Hartwell L. Defects in a cell cycle checkpoint may be responsible for the genomic instability of cancer cells. Cell. 1992;71(4):543–6.
58. Nurse P. Checkpoint pathways come of age. Cell. 1997;91(7):865–7.
59. Rotman G, Shiloh Y. ATM: from gene to function. Hum Mol Genet. 1998;7(10):1555–63.
60. Lavin MF, Shiloh Y. The genetic defect in ataxia-telangiectasia. Annu Rev Immunol. 1997;15:177–202.
61. Barlow C, Hirotsune S, Paylor R, et al. Atm-deficient mice: a paradigm of ataxia telangiectasia. Cell. 1996;86(1):159–71.
62. Xu Y, Ashley T, Brainerd EE, Bronson RT, Meyn MS, Baltimore D. Targeted disruption of ATM leads to growth retardation, chromosomal fragmentation during meiosis, immune defects, and thymic lymphoma. Genes Dev. 1996;10(19):2411–22.
63. Elson A, Wang Y, Daugherty CJ, et al. Pleiotropic defects in ataxia-telangiectasia protein-deficient mice. Proc Natl Acad Sci U S A. 1996;93(23):13084–9.
64. Ito K, Hirao A, Arai F, et al. Regulation of oxidative stress by ATM is required for self-renewal of haematopoietic stem cells. Nature. 2004;431(7011):997–1002.
65. Hishiya A, Ito M, Aburatani H, Motoyama N, Ikeda K, Watanabe K. Ataxia telangiectasia mutated (Atm) knockout mice as a model of osteopenia due to impaired bone formation. Bone. 2005;37(4):497–503.
66. Tyner SD, Venkatachalam S, Choi J, et al. p53 mutant mice that display early ageing-associated phenotypes. Nature. 2002;415(6867):45–53.
67. Maier B, Gluba W, Bernier B, et al. Modulation of mammalian life span by the short isoform of p53. Genes Dev. 2004;18(3):306–19.
68. Lengner CJ, Steinman HA, Gagnon J, et al. Osteoblast differentiation and skeletal development are regulated by Mdm2-p53 signaling. J Cell Biol. 2006;172(6):909–21.
69. Wang X, Kua HY, Hu Y, et al. p53 functions as a negative regulator of osteoblastogenesis, osteoblast-dependent osteoclastogenesis, and bone remodeling. J Cell Biol. 2006;172(1):115–25.
70. Rasheed N, Wang X, Niu QT, Yeh J, Li B. Atm-deficient mice: an osteoporosis model with defective osteoblast differentiation and increased osteoclastogenesis. Hum Mol Genet. 2006;15(12):1938–48.
71. Manolagas SC, Jilka RL. Bone marrow, cytokines, and bone remodeling. Emerging insights into the pathophysiology of osteoporosis. N Engl J Med. 1995;332(5):305–11.
72. Davey RA, MacLean HE, McManus JF, Findlay DM, Zajac JD. Genetically modified animal models as tools for studying bone and mineral metabolism. J Bone Miner Res. 2004;19(6):882–92.
73. Chien KR, Karsenty G. Longevity and lineages: toward the integrative biology of degenerative diseases in heart, muscle, and bone. Cell. 2005;120(4):533–44.
74. Karsenty G. The complexities of skeletal biology. Nature. 2003;423(6937):316–8.
75. Karsenty G. The genetic transformation of bone biology. Genes Dev. 1999;13(23):3037–51.
76. Yeh ET, Reiser H, Benacerraf B, Rock KL. The expression, function, and ontogeny of a novel T cell-activating protein, TAP, in the thymus. J Immunol. 1986;137(4):1232–8.
77. Stanford WL, Haque S, Alexander R, et al. Altered proliferative response by T lymphocytes of Ly-6A (Sca-1) null mice. J Exp Med. 1997;186(5):705–17.
78. Bonyadi M, Waldman SD, Liu D, Aubin JE, Grynpas MD, Stanford WL. Mesenchymal progenitor self-renewal deficiency leads to age-dependent osteoporosis

in Sca-1/Ly-6A null mice. Proc Natl Acad Sci U S A. 2003;100(10):5840–5.
79. Ito CY, Li CY, Bernstein A, Dick JE, Stanford WL. Hematopoietic stem cell and progenitor defects in Sca-1/Ly-6A-null mice. Blood. 2003;101(2):517–23.
80. Duque G, Troen BR. Understanding the mechanisms of senile osteoporosis: new facts for a major geriatric syndrome. J Am Geriatr Soc. 2008;56(5):935–41.
81. Ogata N, Chikazu D, Kubota N, et al. Insulin receptor substrate-1 in osteoblast is indispensable for maintaining bone turnover. J Clin Invest. 2000;105(7):935–43.
82. Gong Y, Slee RB, Fukai N, et al. LDL receptor-related protein 5 (LRP5) affects bone accrual and eye development. Cell. 2001;107(4):513–23.
83. Boyden LM, Mao J, Belsky J, et al. High bone density due to a mutation in LDL-receptor-related protein 5. N Engl J Med. 2002;346(20):1513–21.
84. Kato M, Patel MS, Levasseur R, et al. Cbfa1-independent decrease in osteoblast proliferation, osteopenia, and persistent embryonic eye vascularization in mice deficient in Lrp5, a Wnt coreceptor. J Cell Biol. 2002;157(2):303–14.
85. Kulkarni NH, Onyia JE, Zeng Q, et al. Orally bioavailable GSK-3alpha/beta dual inhibitor increases markers of cellular differentiation in vitro and bone mass in vivo. J Bone Miner Res. 2006;21(6):910–20.
86. Clement-Lacroix P, Ai M, Morvan F, et al. Lrp5-independent activation of Wnt signaling by lithium chloride increases bone formation and bone mass in mice. Proc Natl Acad Sci U S A. 2005;102(48):17406–11.
87. Bennett CN, Longo KA, Wright WS, et al. Regulation of osteoblastogenesis and bone mass by Wnt10b. Proc Natl Acad Sci U S A. 2005;102(9):3324–9.
88. Ross SE, Hemati N, Longo KA, et al. Inhibition of adipogenesis by Wnt signaling. Science. 2000;289(5481):950–3.
89. Gunther T, Poli C, Muller JM, et al. Fhl2 deficiency results in osteopenia due to decreased activity of osteoblasts. Embo J. 2005;24(17):3049–56.
90. Kharbanda S, Yuan ZM, Weichselbaum R, Kufe D. Functional role for the c-Abl protein tyrosine kinase in the cellular response to genotoxic stress. Biochim Biophys Acta. 1997;1333(2):O1–7.
91. Hantschel O, Superti-Furga G. Regulation of the c-Abl and Bcr-Abl tyrosine kinases. Nat Rev Mol Cell Biol. 2004;5(1):33–44.
92. Li B, Boast S. de los Santos K, et al. Mice deficient in Abl are osteoporotic and have defects in osteoblast maturation. Nat Genet. 2000;24(3):304–8.
93. Li B, Wang X, Rasheed N, et al. Distinct roles of c-Abl and Atm in oxidative stress response are mediated by protein kinase C delta. Genes Dev. 2004;18(15):1824–37.
94. Moskovitz J, Bar-Noy S, Williams WM, Requena J, Berlett BS, Stadtman ER. Methionine sulfoxide reductase (MsrA) is a regulator of antioxidant defense and lifespan in mammals. Proc Natl Acad Sci U S A. 2001;98(23):12920–5.
95. Neumann CA, Krause DS, Carman CV, et al. Essential role for the peroxiredoxin Prdx1 in erythrocyte antioxidant defence and tumour suppression. Nature. 2003;424(6948):561–5.
96. Reliene R, Goad ME, Schiestl RH. Developmental cell death in the liver and newborn lethality of Ku86 deficient mice suppressed by antioxidant N-acetylcysteine. DNA Repair (Amst). 2006.
97. Furukawa S, Fujita T, Shimabukuro M, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest. 2004;114(12):1752–61.
98. Houstis N, Rosen ED, Lander ES. Reactive oxygen species have a causal role in multiple forms of insulin resistance. Nature. 2006;440(7086):944–8.
99. Kuro-o M, Matsumura Y, Aizawa H, et al. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. Nature. 1997;390(6655):45–51.
100. Kawaguchi H, Manabe N, Miyaura C, Chikuda H, Nakamura K, Kuro-o M. Independent impairment of osteoblast and osteoclast differentiation in klotho mouse exhibiting low-turnover osteopenia. J Clin Invest. 1999;104(3):229–37.
101. Tohyama O, Imura A, Iwano A, et al. Klotho is a novel beta-glucuronidase capable of hydrolyzing steroid beta-glucuronides. J Biol Chem. 2004;279(11):9777–84.
102. Kurosu H, Ogawa Y, Miyoshi M, et al. Regulation of fibroblast growth factor-23 signaling by klotho. J Biol Chem. 2006;281(10):6120–3.
103. Kurosu H, Yamamoto M, Clark JD, et al. Suppression of aging in mice by the hormone Klotho. Science. 2005;309(5742):1829–33.
104. ADHR-Consortium. Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. Nat Genet. 2000;26(3):345–8.
105. Razzaque MS, Sitara D, Taguchi T, St-Arnaud R, Lanske B. Premature aging-like phenotype in fibroblast growth factor 23 null mice is a vitamin D-mediated process. Faseb J. 2006;20:720–2.
106. Tsujikawa H, Kurotaki Y, Fujimori T, Fukuda K, Nabeshima Y. Klotho, a gene related to a syndrome resembling human premature aging, functions in a negative regulatory circuit of vitamin D endocrine system. Mol Endocrinol. 2003;17(12):2393–403.
107. Yoshida T, Fujimori T, Nabeshima Y. Mediation of unusually high concentrations of 1,25-dihydroxyvitamin D in homozygous klotho mutant mice by increased expression of renal 1alpha-hydroxylase gene. Endocrinology. 2002;143(2):683–9.
108. Liu S, Zhou J, Tang W, Jiang X, Rowe DW, Quarles LD. Pathogenic role of Fgf23 in Hyp mice. Am J Physiol Endocrinol Metab. 2006;291(1):E38–49.
109. Thompson DL, Sabbagh Y, Tenenhouse HS, et al. Ontogeny of Phex/PHEX protein expression in mouse embryo and subcellular localization in osteoblasts. J Bone Miner Res. 2002;17(2):311–20.
110. Westbroek I, De Rooij KE, Nijweide PJ. Osteocyte-specific monoclonal antibody MAb OB7.3 is directed against Phex protein. J Bone Miner Res. 2002;17(5):845–53.

111. Miao D, Bai X, Panda D, McKee M, Karaplis A, Goltzman D. Osteomalacia in hyp mice is associated with abnormal phex expression and with altered bone matrix protein expression and deposition. Endocrinology. 2001;142(2):926–39.
112. Aguirre JI, Plotkin LI, Stewart SA, et al. Osteocyte apoptosis is induced by weightlessness in mice and precedes osteoclast recruitment and bone loss. J Bone Miner Res. 2006;21(4):605–15.
113. Jilka RL, Weinstein RS, Bellido T, Roberson P, Parfitt AM, Manolagas SC. Increased bone formation by prevention of osteoblast apoptosis with parathyroid hormone. J Clin Invest. 1999;104(4):439–46.
114. Tomkinson A, Gevers EF, Wit JM, Reeve J, Noble BS. The role of estrogen in the control of rat osteocyte apoptosis. J Bone Miner Res. 1998;13(8):1243–50.
115. Kyono A, Avishai N, Ouyang Z, Landreth GE, Murakami S. FGF and ERK signaling coordinately regulate mineralization-related genes and play essential roles in osteocyte differentiation. J Bone Miner Metab. 2012;30(1):19–30.
116. Fu L, Patel MS, Bradley A, Wagner EF, Karsenty G. The molecular clock mediates leptin-regulated bone formation. Cell. 2005;122(5):803–15.
117. Kondratov RV, Kondratova AA, Gorbacheva VY, Vykhovanets OV, Antoch MP. Early aging and age-related pathologies in mice deficient in BMAL1, the core component of the circadian clock. Genes Dev. 2006;20(14):1868–73.
118. Watanabe K, Hishiya A. Mouse models of senile osteoporosis. Mol Aspects Med. 2005;26(3):221–31.
119. Duque G. As a matter of fat: new perspectives on the understanding of age-related bone loss. BoneKEy-Osteovision. 2007;4(4):129–40.

Osteoporosis as a Geriatric Syndrome

7

Cathleen S. Colón-Emeric

Introduction

An osteoporotic fracture in an older adult can be a devastating event that sets off a cascade of consequences resulting in functional decline, impaired quality of life, and sometimes death. Identifying interventions to prevent osteoporotic fractures or disrupt the negative cascade that follows them has therefore been a priority for clinicians, researchers, patients and families. Many of the advances in the field over the last decade have resulted from viewing osteoporosis as a disease state characterized by abnormal bone mass, architecture, and strength; understanding the pathogenesis of this disease has led to new targets for pharmacologic therapy that improve bone properties and reduce fracture rates.

However, it is increasingly evident that multiple factors outside of bone contribute to the development and consequences of osteoporotic fractures. Moreover, even when the broken bone heals promptly patients may still experience the downward spiral of functional decline and disability. The traditional disease model of osteoporosis has difficulty explaining how these interacting pathogenetic pathways in different organ systems result in fractures and their negative sequelae. A model which considers the multifactorial, complex, and interacting nature of these pathways may lead to new understandings and interventions to improve outcomes.

In this chapter, we make the case for conceptualizing osteoporotic fracture as a geriatric syndrome. We define geriatric syndromes, and compare them to disease models and traditional medical syndrome models. We describe how conceptualizing osteoporotic fractures as a geriatric syndrome has implications for screening, treatment, research, and policy.

What is a Geriatric Syndrome?

A geriatric syndrome has been defined as symptoms that arise not solely from a discreet disease, but also from accumulated impairments in multiple systems. Geriatric syndromes develop when the accumulated effects of impairments in multiple domains compromise compensatory ability, resulting in a united manifestation [1]. Figure 7.1 compares models of disease states, traditional medical syndromes, and geriatric syndromes [2]. In a disease model, a known etiology (e.g., influenza virus) leads to a defined pathogenetic pathway (innate and adaptive immune responses) which result in a known, but variable set of symptoms (fever, myalgias, anorexia). More often,

C.S. Colón-Emeric, MD, MHS
Division of Geriatrics, Duke University Medical Center, Durham, NC 27710, USA
e-mail: Cathleen.colonemeric@dm.duke.edu

G. Duque, D.P. Kiel (eds.), *Osteoporosis in Older Persons: Advances in Pathophysiology and Therapeutic Approaches*, DOI 10.1007/978-3-319-25976-5_7

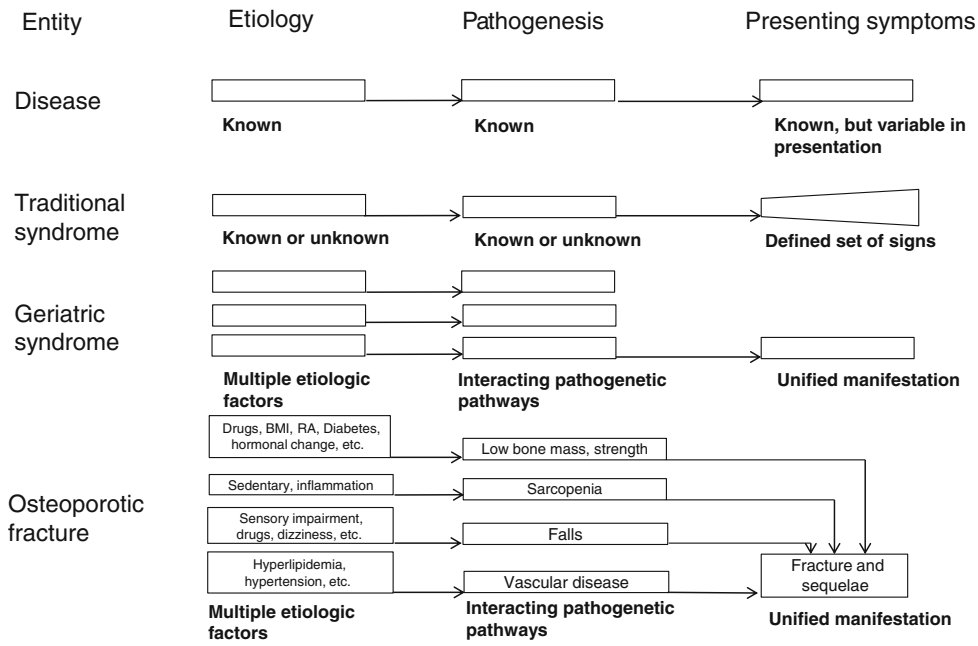


Fig. 7.1 Models for discrete disease, traditional syndromes, and geriatric syndromes (Adapted from *Journal of the American Geriatrics Society* – with permission from Wiley 55(5):780–91, 11 APR 2007 DOI: 10.1111/j.1532-5415.2007.01156.x http://onlinelibrary.wiley.com/doi/10.1111/j.1532-5415.2007.01156.x/full#f1)

conditions of older adults fall into the traditional medical syndrome model in which a known or unknown etiology triggers a pathogenetic pathway resulting in a defined set of symptoms. For example, an unknown etiology causes destruction of dopaminergic neurons in the substantia nigra resulting in the resting tremor, shuffling gait, masked facies, and rigidity of Parkinson's Disease. In contrast, geriatric syndromes such as delirium have multiple and variable etiologic factors (electrolyte imbalance, medications, sensory impairment, pain, hypoxia, infection) producing interacting pathogenetic pathways (changes in inflammatory markers, hormones, neurotransmitters) resulting in a common manifestation (confusion, inattention, altered level of consciousness).

Why has it been useful to conceptualize conditions such as delirium, falls, and pressure ulcers as geriatric syndromes rather than diseases or traditional medical syndromes? First, identifying individuals at risk for the syndrome requires an assessment for multiple etiologic factors and an understanding of how risk factors interact with each other. Second, prevention and treatment strategies for these conditions have been most effective when they address multiple risk factors or pathways, rather than a single target. Third, research to understand the interaction between pathogenetic pathways in multiple organ systems has led to new understandings and potential treatment targets, including pleiotropic agents that have an effect on more than one pathway and syndrome. Finally, clearly defining geriatric syndromes to stakeholders has led to practice and policy reforms which have made comprehensive models of care available to more patients, such as in the case of fall prevention [3].

The Case for Osteoporotic Fractures as a Geriatric Syndrome

One criterion for a geriatric syndrome is that it must have the greatest prevalence and impact in older adults. Certainly this is true of osteoporotic

fractures. As discussed in more detail elsewhere in the book, the rates of osteoporotic fractures increase exponentially with age; for example the incidence of hip fracture in U.S. women rises from 1/1000 per year at age 60–64 years, to 26/1000 per year at age 85–89 years [4]. Geriatric syndromes typically have a major impact on functional status and quality of life; osteoporotic fractures are the 5th greatest cause of disability adjusted life years in the Americas and Europe, and hip fractures are estimated to cause an excess 740,000 deaths annually. After a fracture of any type, 7 % of patients experience permanent disability and 8 % require long-term care, with rates substantially higher for hip and vertebral fractures [5]. Geriatric syndromes impose a large burden on the healthcare system; the worldwide cost of hip fractures is estimated to exceed 35 billion U.S. dollars annually [5].

But beyond their high prevalence and burden in older adults, geriatric syndromes are characterized by having multiple etiologic factors in multiple organ systems that interact and contribute to the presenting symptoms and resultant disability [1, 2, 6]. In osteoporosis research, changes in bone density, microarchitecture, macro architecture, and mineralization have been the primary focus of attention; the etiology of these changes is clearly multifactorial with risk factors including hormone changes, inflammation, medications, mechanical loading, and genetics [7, 8]. Outside of bone tissue, muscle-bone interactions have been recognized as an important mediator of bone material quality and architecture [9], in part through mechanical loading (the "mechanostat") and in part through secretion of osteogenic myokines such as IGF-1 and FGF-2. Adipose tissue exerts an important influence on bone in the microenvironment, where osteogenic and adipogenic lineages compete during bone marrow stem cell differentiation, as well as at the whole-body level as evidenced by the increased risk for fracture in patients with diabetes, perhaps mediated by leptin and adiponectin [10]. A link between bone and the cardiovascular system is slowly being untangled; it has long been known that patients with low bone density have a higher than expected prevalence of cardiovascular disease after controlling for multiple confounders [11], and conversely patients with heart failure have a higher than expected rate of osteopenia and fractures [12]. While the mechanisms for the association are not fully understood, evidence suggests that parathyroid hormone [13], rank ligand inhibitor [14], and circulating calcifying cells [15] may link the cardiovascular and skeletal systems. Thus, at least three other organ systems interact directly or indirectly with bone strength.

But osteoporosis is not symptomatic until a fracture develops, and 90 % of fractures occur after a fall [16]. Falls are themselves a prototypical geriatric syndrome, with multiple risk factors including sarcopenia, cognitive impairment, medications, orthostatic hypotension, vestibular dysfunction, sensory impairment, gait disorders, and vitamin D deficiency [17]. Osteoporotic fractures commonly result in high levels of circulating cytokines and other inflammatory markers [18], which have been implicated in the high rates of myocardial infarction [19], thromboembolism [19], delirium [20], and muscle atrophy [21] which follow. A characteristic of a geriatric syndrome is that it shares common risk factors with other geriatric syndromes (Fig. 7.2) [2, 22], and that patients with one geriatric syndrome are at higher risk for others. Note that an osteoporotic fracture, especially a hip or vertebral fracture, is associated with higher risk of falls, delirium, depression [23], pressure ulcers [24], and weight loss [25]. Shared risk factors for osteoporosis and other geriatric syndromes, even after accounting for the mediating risk of falls, include mood disorders, poor physical performance, malnutrition, and cognitive impairment.

In summary, osteoporotic fractures have many features that are more consistent with a geriatric syndrome than a traditional medical syndrome or disease. The development of impaired bone strength and fractures is multifactorial, involves interacting pathways in multiple organ systems, and overlaps with the other common geriatric syndromes. In the sections that follow, we discuss the implications of conceptualizing osteoporotic fractures as a geriatric syndrome on screening, treatment, research and policy.

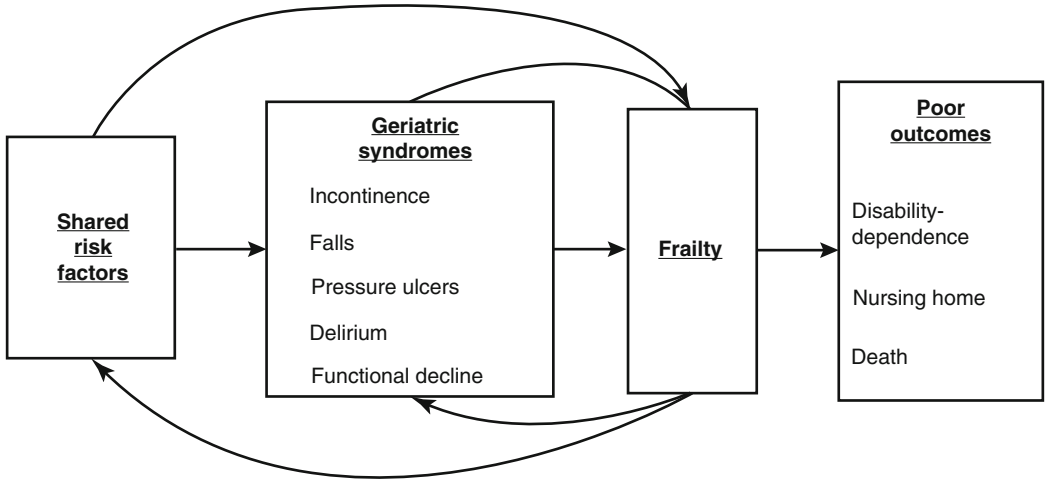


Fig. 7.2 Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept (*Journal of the American Geriatrics Society*. 55(5):780–91, 11 APR 2007 DOI: 10.1111/j.1532-5415.2007.01156.x. http://onlinelibrary.wiley.com/doi/10.1111/j.1532-5415.2007.01156.x/full#f2)

Implications for Screening

Because the etiology of geriatric syndromes is by definition multifactorial, identification of persons at highest risk requires consideration of multiple risk factors. It has long been recognized that BMD explains only part of the fracture risk, and that most fractures occur in patients with "osteopenic" levels of BMD rather than those with T scores ≤ -2.5 [26]. Multifactorial risk assessment tools such as FRAX [27], QFracture [28] and the Garvan nomogram [29] have been developed in an attempt to incorporate other risk factors into screening and treatment decisions. However, which risk factors should be considered is a matter of some controversy, and indeed, which risk factors are most important likely varies with advancing age. For example, because age is such a powerful predictor of fractures in tools such as FRAX, a large proportion of women over age 80 years meet current treatment thresholds [30] even without other risk factors. A study of long-term care residents suggested that FRAX with BMD selected over 80 % of the population for treatment and FRAX without BMD (incorporating BMI) selects 98 % [31]. On the other hand, FRAX does not incorporate fall history, Parkinson's Disease, stroke, chronic kidney disease, or other important risk factors for osteoporotic fracture in the very elderly. Thus, while multifactorial fracture risk assessment tools are useful in younger populations (who contributed most of the data in the predictive models), they have limitations in the oldest patients who are at highest risk. Clinicians need to consider the patient's functional status, fall risk, other comorbidities, and goals and preferences in making treatment decisions. Refining tools to provide more rational risk stratification in patients over 80 years is a research priority.

Because of the overlap among geriatric syndromes, an optimal screening program should identify not just risk factors related to bone quality, but also consider related geriatric syndromes. Certainly a fall history is important for risk stratification, and identification of a patient at risk should prompt appropriate fall evaluation and interventions to reduce risk of additional falls and fractures [16]. Urinary incontinence has been associated with a higher risk of osteoporotic fractures in women [32], especially urge incontinence [33] which may lead to hurried trips to the bathroom. Late life depression is associated with more falls in older adults [34], and the commonly used selective serotonin reuptake inhibitors are associated with higher risk of fractures [35]. Conversely, a high rate of major depression is observed following a hip or vertebral fracture

[36], which may contribute in part to the high risk of subsequent fractures [37]. Frailty, characterized by muscle weakness, slow gait speed, exhaustion, and declines in physical performance and function, has been described as a unifying pathway for the interaction among geriatric syndromes (Fig. 7.2) [2]. High rates of frailty have been described in patients with osteoporosis [38], and in the Women's Health and Aging Study, sarcopenia and severe osteopenia/osteoporosis were synergistically associated with presence of frailty [39]. Following a hip fracture, high rates of delirium are observed; such patients are at higher risk of poor functional recovery [20], subsequent dementia [40], and likely more falls and fractures. Thus, identification of patients at high risk for osteoporosis or with recent osteoporotic fracture should prompt screening for related geriatric syndromes as well.

Implications for Prevention and Treatment

Conceptualizing osteoporotic fracture as a geriatric syndrome strongly implies a need for a multi-modal approach to prevention and treatment, since "optimal clinical care cannot be based entirely on a biological framework" [2] but must address multiple etiology and pathogenetic pathways. Clinicians are accustomed to considering multiple pathways to improve bone strength, including providing calcium and vitamin D supplements, identifying and treating secondary causes of osteoporosis, minimizing corticosteroids or antiepileptic medications, prescribing osteoporosis pharmacotherapies, and counseling about smoking, alcohol use, and physical activity.

Increasingly, clinical practice guidelines also recommend interventions to reduce fall risk [41]. Because falls are themselves multifactorial, this may be best accomplished in a dedicated fall clinic or prevention program, which are described in greater detail elsewhere in this book. Weight bearing exercise has been widely studied as a means to improve both muscle strength and bone density [42] although studies are heterogeneous and compliance rates generally low [43]. Advocacy efforts around fall prevention have led to more widespread availability of balance and exercise classes such as Tai Chi or Otago for older adults in the U.S., and such classes are generally covered by Medicare through the Silver Sneakers program [44]. As noted above, addressing other related geriatric syndromes identified during screening such as incontinence and depression may have both direct and indirect effects on bone strength and fall risk; comprehensive geriatric assessment programs may be helpful in managing these overlapping geriatric syndromes.

A multi-factorial approach is also required to prevent post-fracture complications and their resulting spiral of decline. Multi-component prevention strategies have been shown to reduce the incidence of post-fracture delirium by one third, and are likely cost effective [45]. Nutritional supplements have not been found to improve mortality or disability, but show a trend toward reduction in a composite outcome of mortality or medical complications after hip fracture and deserve additional study [46]. Extended physical therapy to improve muscle strength, improve physical function, and reduce falls has been demonstrated to be effective after an osteoporotic fracture [47, 48], but frequently is not covered by payers.

Treatment decisions are also influenced by the fact that osteoporotic fractures have the greatest impact in older adults who commonly have other geriatric syndromes, multiple medical co-morbidities, frailty, and limited life expectancy. The decision to prescribe a bone active medication may be relatively straightforward in an otherwise healthy postmenopausal woman, but becomes much more challenging in a frail older adult who already takes an average of eight medications [49] and has an average of five chronic conditions [50]. For example, a hypothetical patient with co-morbid osteoporosis, osteoarthritis, diabetes, hypertension and COPD who is treated according to clinical practice guidelines would be taking 19 doses of 12 unique medications a day, requiring five different administration times, at a cost of more than $400 per month [51]. Moreover, frail older patients may have

limited life expectancy which impacts the effectiveness of osteoporosis medications; in fact for patients with incident hip, vertebral or forearm fracture, the 5-year mortality risk exceeds the 5-year fracture risk by about 40 % [52].

Nevertheless, it is clear across multiple healthcare settings and countries that older adults are substantially under-treated for osteoporosis, particularly after a fracture, and this under treatment is worsening over time [53]. Despite the competing mortality risk, the numbers of patients needed to treat to prevent one additional fracture after an osteoporotic fracture are still low (8–46 patients treated) [52], and treatment is cost savings or highly cost effective even for women at age 90 years in the lowest quartile of life expectancy [54]. Withholding osteoporosis treatment is therefore not justified based solely on advanced age or multi-morbidity, but clinicians do need to be mindful about their patients' other medical conditions and goals of care. Strategies to minimize the burden of osteoporosis treatment, such as using monthly or yearly dosing schedules, are helpful. Focusing on treatments that influence more than one condition of importance to patients makes the most sense in this population; for example, providing exercise interventions that favorably impact bone quality, falls, mood, and sarcopenia.

Implications for Research and Policy

Research in geriatric syndromes can be particularly challenging. As Inouye and colleagues describe, "a decision to focus all efforts on a single risk factor may lack geriatric relevance, because it addresses only a small portion of the overall risk and fails to consider other risk factors. By contrast, any research attempt to address all relevant risk factors runs the risk of being unfocused." [2] It cannot be denied that the traditional disease-focused translational research model has resulted in a growing range of effective pharmacotherapies targeting multiple pathways in bone. However, conceptualizing osteoporotic fractures as a geriatric syndrome implies that additional gains can be made by modifying the research paradigm to consider the multiple, interacting pathways involved.

First, it is imperative that frail older patients are included in osteoporosis research despite the complexity that they add to the study design, execution, and interpretation. This will provide better evidence to support claims of safety and efficacy in real world practice, and provide crucial information about how treatments interact with co-morbidities that is currently lacking [55]. Second, examining interactive synergisms between risk factors, the pathways by which each risk factor contributes to osteoporotic fractures, and how they biologically interact may lead to new physiologic insights and identify new targets for intervention. For example, research examining how cardiovascular disease and osteoporosis interact, described briefly above, has the potential to lead to important new information about both conditions.

Next, the overlap between multiple geriatric syndromes implies that there may be interventions with pleiotropic effects on multiple outcomes including osteoporotic fractures. Several such pleiotropic interventions have been examined, with variable success to date. As described above, exercise is an example of a successful pleiotropic intervention, while the data for protein supplements less robust. Pharmacologic agents with pleiotropic effects have also been examined and found to reduce fracture, but as typified by the case of estrogen supplements, the balance of benefits and harms across multiple organs and systems must be carefully weighed [56]. Testosterone supplementation in older men has a favorable impact on bone density and muscle mass [57] though long-term studies with more clinically relevant outcomes and safety data are needed before these can be recommended for this indication. Growth hormone secretagogues have favorable impact on muscle mass, bone density and physical performance [58], however clinical trials were stopped early due to insufficient impact on the primary outcome of lean body mass. Cox-2

anti-inflammatory use is associated with higher BMD [59], but long-term cardiac and gastrointestinal safety have limited their clinical use. Myostatin inhibitors are currently in clinical trials to reduce muscle atrophy, improve physical performance, and reduce falls after hip fracture [60]. While the idea of developing interventions with favorable impact on several systems is appealing, this field is still evolving and will likely always require careful evaluation of the balance of benefits and harms.

Beyond translational research, health services research is needed to develop, refine, and disseminate models of care for preventing or treating osteoporotic fractures. Ortho-geriatric services [61], fall and fracture clinics [62], and fracture liaison services [63] are three examples of such models of care that have been found to be effective in at least some settings. Such models invariably use a multi-disciplinary and multifactorial intervention approach concordant with treating osteoporotic fracture as a geriatric syndrome. A challenge in this research is that it is nearly impossible to identify which of the multiple components of the intervention are most effective, and translating it to other settings requires modifications to the program which may impact its efficacy.

Finally, conceptualizing osteoporosis as a geriatric syndrome has implications for clinical practice guideline development and healthcare policy. A framework for considering multimorbidity during the development of clinical practice guidelines has been developed [64], but has not been widely incorporated into osteoporosis clinical practice guidelines to date. Such guidelines might include explicit descriptions of the trade-offs of benefits and harms at different ages or with different co-morbidities. In addition, guidelines should include recommendations for evidence-based models of care which address the multifactorial nature of osteoporotic fracture, such as fracture liaison services or ortho-geriatric services. This type of guideline could provide the foundation for advocacy efforts to make such services more widely available to patients through practice incentives and payment reform.

Conclusion

Osteoporotic fractures have a major impact on older adults, result from multiple interacting pathogenetic pathways, and overlap with other common geriatric syndromes such as falls, sarcopenia, delirium, incontinence, and depression. Thus, they are best viewed as a geriatric syndrome in their own right. Using this model to conceptualize osteoporotic fractures may drive further research advances, help clinicians to consider multiple risk factors and treatment strategies, and lead policy makers to implement more comprehensive and appropriate models of care.

References

1. Flacker JM. What is a geriatric syndrome anyway? J Am Geriatr Soc. 2003;51(4):574–6.
2. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. J Am Geriatr Soc. 2007;55(5):780–91.
3. Tinetti ME, Baker DI, King M, Gottschalk M, Murphy TE, Acampora D, Carlin BP, Leo-Summers L, Allore HG. Effect of dissemination of evidence in reducing injuries from falls. N Engl J Med. 2008;359(3):252–61.
4. Ettinger B, Black DM, Dawson-Hughes B, Pressman AR, Melton III LJ. Updated fracture incidence rates for the US version of FRAX®. Osteoporos Int. 2010;21(1):25–33.
5. Harvey N, Dennison E, Cooper C. Osteoporosis: impact on health and economics. Nat Rev Rheumatol. 2010;6(2):99–105.
6. Cruz-Jentoft AJ, Landi F, Topinková E, Michel J-P. Understanding sarcopenia as a geriatric syndrome. Curr Opin Clin Nutr Metab Care. 2010;13(1):1–7. doi:10.1097/MCO.1090b1013e328333c328331c328331.
7. Kanis J, Borgstrom F, De Laet C, Johansson H, Johnell O, Jonsson B, Oden A, Zethraeus N, Pfleger B, Khaltaev N. Assessment of fracture risk. Osteoporos Int. 2005;16(6):581–9.
8. Duque G, Troen BR. Understanding the mechanisms of senile osteoporosis: new facts for a major geriatric syndrome. J Am Geriatr Soc. 2008;56(5):935–41.
9. Ferretti JL, Cointry GR, Capozza RF, Frost HM. Bone mass, bone strength, muscle–bone interactions, osteopenias and osteoporoses. Mech Ageing Dev. 2003;124(3):269–79.
10. Gimble JM, Nuttall ME. The relationship between adipose tissue and bone metabolism. Clin Biochem. 2012;45(12):874–9.

11. Ness J, Aronow WS. Comparison of prevalence of atherosclerotic vascular disease in postmenopausal women with osteoporosis or osteopenia versus without osteoporosis or osteopenia. Am J Cardiol. 2006;97(10):1427–8.
12. Majumdar SR, Ezekowitz JA, Lix LM, Leslie WD. Heart failure is a clinically and densitometrically independent risk factor for osteoporotic fractures: population-based cohort study of 45,509 subjects. J Clin Endocrinol Metab. 2012;97(4):1179–86.
13. Goettsch C, Iwata H, Aikawa E. Parathyroid hormone: critical bridge between bone metabolism and cardiovascular disease. Arterioscler Thromb Vasc Biol. 2014;34(7):1333–5.
14. Leistner DM, Seeger FH, Fischer A, Röxe T, Klotsche J, Iekushi K, Seeger T, Assmus B, Honold J, Karakas M, et al. Elevated levels of the mediator of catabolic bone remodeling RANKL in the bone marrow environment link chronic heart failure with osteoporosis. Circ Heart Fail. 2012;5(6):769–77.
15. Fadini GP, Rattazzi M, Matsumoto T, Asahara T, Khosla S. Emerging role of circulating calcifying cells in the bone-vascular axis. Circulation. 2012;125(22):2772–81.
16. Bischoff-Ferrari H. The role of falls in fracture prediction. Curr Osteoporos Rep. 2011;9(3):116–21.
17. Tinetti ME. Preventing falls in elderly persons. N Engl J Med. 2003;348(1):42–9.
18. Beloosesky Y, Hendel D, Weiss A, Hershkovitz A, Grinblat J, Pirotsky A, Barak V. Cytokines and C-reactive protein production in hip-fracture-operated elderly patients. J Gerontol A Biol Sci Med Sci. 2007;62(4):420–6.
19. Wood M, Mantilla CB, Horlocker TT, Schroeder DR, Berry DJ, Brown DL. Frequency of myocardial infarction, pulmonary embolism, deep venous thrombosis, and death following primary hip or knee arthroplasty. Anesthesiology. 2002;96(5):1140–6.
20. Marcantonio E, Ta T, Duthie E, Resnick NM. Delirium severity and psychomotor types: their relationship with outcomes after hip fracture repair. J Am Geriatr Soc. 2002;50(5):850–7.
21. Visser M, Harris TB, Fox KM, Hawkes W, Hebel JR, YuYahiro J, Michael R, Zimmerman SI, Magaziner J. Change in muscle mass and muscle strength after a hip fracture: relationship to mobility recovery. J Gerontol A Biol Sci Med Sci. 2000;55(8):M434–40.
22. Tinetti ME, Inouye SK, Gill TM, Doucette JT. Shared risk factors for falls, incontinence, and functional dependence: unifying the approach to geriatric syndromes. JAMA. 1995;273(17):1348–53.
23. Zimmerman SI, Smith HD, Gruber-Baldini A, Fox KM, Hebel JR, Kenzora J, Felsenthal G, Magaziner J. Short-term persistent depression following hip fracture: a risk factor and target to increase resilience in elderly people. Soc Work Res. 1999;23(3):187–96.
24. Baumgarten M, Rich SE, Shardell MD, Hawkes WG, Margolis DJ, Langenberg P, Orwig DL, Palmer MH, Jones PS, Sterling R, et al. Care-related risk factors for hospital-acquired pressure ulcers in elderly adults with hip fracture. J Am Geriatr Soc. 2012;60(2):277–83.
25. Reider L, Hawkes W, Hebel JR, D'Adamo C, Magaziner J, Miller R, Orwig D, Alley DE. The association between body mass index, weight loss and physical function in the year following a hip fracture. J Nutr Health Aging. 2013;17(1):91–5.
26. Johnell O, Kanis J. Epidemiology of osteoporotic fractures. Osteoporos Int. 2005;16(2):S3–7.
27. Kanis JA, McCloskey EV, Johansson H, Oden A, Ström O, Borgström F. Development and use of FRAX® in osteoporosis. Osteoporos Int. 2010;21(2):407–13.
28. Hippisley-Cox J, Coupland C. Derivation and validation of updated QFracture algorithm to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study. BMJ. 2012;344, e3427. http://www.bmj.com/content/344/bmj.e3427.short.
29. Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV. Development of a nomogram for individualizing hip fracture risk in men and women. Osteoporos Int. 2007;18(8):1109–17.
30. Hillier TA, Cauley JA, Rizzo JH, Pedula KL, Ensrud KE, Bauer DC, Lui L-Y, Vesco KK, Black DM, Donaldson MG, et al. WHO absolute fracture risk models (FRAX): do clinical risk factors improve fracture prediction in older women without osteoporosis? J Bone Miner Res. 2011;26(8):1774–82.
31. Greenspan SL, Perera S, Nace D, Zukowski KS, Ferchak MA, Lee CJ, Nayak S, Resnick NM. FRAX or fiction: determining optimal screening strategies for treatment of osteoporosis in residents in long-term care facilities. J Am Geriatr Soc. 2012;60(4):684–90.
32. Brown J, Vittinghoff E, Wyman J, Stone K, Nevitt M, Ensrud K, Grady D. Urinary incontinence: does it increase risk for falls and fractures? Study of Osteoporotic Fractures Research Group. J Am Geriatr Soc. 2000;48(7):721–5.
33. Chiarelli PE, Mackenzie LA, Osmotherly PG. Urinary incontinence is associated with an increase in falls: a systematic review. Aust J Physiother. 2009;55(2):89–95.
34. Korpelainen R, Korpelainen J, Heikkinen J, Väänänen K, Keinänen-Kiukaanniemi S. Lifelong risk factors for osteoporosis and fractures in elderly women with low body mass index—a population-based study. Bone. 2006;39(2):385–91.
35. Rabenda V, Bruyère O, Reginster J-Y. Risk of nonvertebral fractures among elderly postmenopausal women using antidepressants. Bone. 2012;51(4):674–9.
36. Lenze EJ, Munin MC, Skidmore ER, Amanda Dew M, Rogers JC, Whyte EM, Quear T, Begley A, Reynolds CF. Onset of depression in elderly persons after hip fracture: implications for prevention and early intervention of late-life depression. J Am Geriatr Soc. 2007;55(1):81–6.
37. Colón-Emeric C, Kuchibhatla M, Pieper C, Hawkes W, Fredman L, Magaziner J, Zimmerman S, Lyles K. The contribution of hip fracture to risk of subse-

quent fractures: data from two longitudinal studies. Osteoporos Int. 2003;14(11):879–83.
38. Ensrud KE, Ewing SK, Taylor BC, Fink HA, Stone KL, Cauley JA, Tracy JK, Hochberg MC, Rodondi N, Cawthon PM, et al. Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. J Gerontol A Biol Sci Med Sci. 2007;62(7):744–51.
39. Frisoli Jr A, Chaves PH, Ingham SJM, Fried LP. Severe osteopenia and osteoporosis, sarcopenia, and frailty status in community-dwelling older women: results from the Women's Health and Aging Study (WHAS) II. Bone. 2011;48(4):952–7.
40. Lundström M, Edlund A, Bucht G, Karlsson S, Gustafson Y. Dementia after delirium in patients with femoral neck fractures. J Am Geriatr Soc. 2003;51(7):1002–6.
41. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of postmenopausal osteoporosis. http://www.guideline.gov/content.aspx?id=34968&search=treatment+osteoporosis.
42. Hagen K, Dagfinrud H, Moe R, Osteras N, Kjeken I, Grotle M, Smedslund G. Exercise therapy for bone and muscle health: an overview of systematic reviews. BMC Med. 2012;10(1):167.
43. Nikander R, Sievanen H, Heinonen A, Daly R, Uusi-Rasi K, Kannus P. Targeted exercise against osteoporosis: a systematic review and meta-analysis for optimising bone strength throughout life. BMC Med. 2010;8(1):47.
44. Hamar B, Coberley CR, Pope JE, Rula EY. Impact of a senior fitness program on measures of physical and emotional health and functioning. Popul Health Manag. 2013;16(6):364–72.
45. Akunne A, Davis S, Westby M, Young J. The cost-effectiveness of multi-component interventions to prevent delirium in older people undergoing surgical repair of hip fracture. Eur J Orthop Surg Traumatol. 2014;24(2):187–95.
46. Avenell A, Handoll H. Nutritional supplementation for hip fracture aftercare in older people. Cochrane Database of Syst Rev. 2006;(4):CD001880.
47. Auais M, Eilayyan O, Mayo NE. Extended exercise rehabilitation after hip fracture improves patients' physical function: a systematic review and meta-analysis. Phys Ther. 2012;92:1437–51.
48. Dusdal K, Grundmanis J, Luttin K, Ritchie P, Rompre C, Sidhu R, Harris SR. Effects of therapeutic exercise for persons with osteoporotic vertebral fractures: a systematic review. Osteoporos Int. 2011;22(3):755–69.
49. Lai S-W, Liao K-F, Liao C-C, Muo C-H, Liu C-S, Sung F-C. Polypharmacy correlates with increased risk for hip fracture in the elderly: a population-based study. Medicine. 2010;89(5):295–9. doi:10.1097/MD.1090b1013e3181f1015efc.
50. van den Bussche H, Koller D, Kolonko T, Hansen H, Wegscheider K, Glaeske G, von Leitner E-C, Schafer I, Schon G. Which chronic diseases and disease combinations are specific to multimorbidity in the elderly? Results of a claims data based cross-sectional study in Germany. BMC Public Health. 2011;11(1):101.
51. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. JAMA. 2005;294(6):716–24.
52. Curtis JR, Arora T, Matthews RS, Taylor A, Becker DJ, Colon-Emeric C, Kilgore ML, Morrisey MA, Saag KG, Safford MM, et al. Is withholding osteoporosis medication after fracture sometimes rational? A comparison of the risk for second fracture versus death. J Am Med Dir Assoc. 2010;11(8):584–91.
53. Kanis JA, Svedbom A, Harvey N, McCloskey EV. The osteoporosis treatment gap. J Bone Miner Res. 2014;29(9):1926–8.
54. Pham AN, Datta SK, Weber TJ, Walter LC, Colón-Emeric CS. Cost-effectiveness of oral bisphosphonates for osteoporosis at different ages and levels of life expectancy. J Am Geriatr Soc. 2011;59(9):1642–9.
55. Lee RH, Colón-Emeric C. Effectiveness of osteoporosis therapy among frail, older adults: should we carry out more trials? Aging Health. 2012;8(5):461–70.
56. Writing Group for the Women's Health Initiative I. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. JAMA. 2002;288(3):321–33.
57. Kenny AM, Kleppinger A, Annis K, Rathier M, Browner B, Judge JO, McGee D. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels, low bone mass, and physical frailty. J Am Geriatr Soc. 2010;58(6):1134–43.
58. White HK, Petrie CD, Landschulz W, MacLean D, Taylor A, Lyles K, Wei JY, Hoffman AR, Salvatori R, Ettinger MP, Morey MC, Blackman MR, Merriam GR, Capromorelin Study Group. Effects of an oral growth hormone secretagogue in older adults. J Clin Endocrinol Metab. 2009;94(4):1198–206.
59. Carbone LD, Tylavsky FA, Cauley JA, Harris TB, Lang TF, Bauer DC, Barrow KD, Kritchevsky SB. Association between bone mineral density and the use of nonsteroidal anti-inflammatory drugs and aspirin: impact of cyclooxygenase selectivity. J Bone Miner Res. 2003;18(10):1795–802.
60. Grossmann M. Myostatin inhibition: a new treatment for androgen deprivation-induced sarcopenia? J Clin Endocrinol Metab. 2014;99(10):3625–8.
61. Kammerlander C, Roth T, Friedman SM, Suhm N, Luger TJ, Kammerlander-Knauer U, Krappinger D, Blauth M. Ortho-geriatric service—a literature review comparing different models. Osteoporos Int. 2010;21(4):637–46.
62. Gomez F, Curcio C, Suriyaarachchi P, Demontiero O, Duque G. Differing approaches to falls and

fracture prevention between Australia and Colombia. Dovepress. 2013;8:61–7.
63. Ganda K, Puech M, Chen JS, Speerin R, Bleasel J, Center JR, Eisman JA, March L, Seibel MJ. Models of care for the secondary prevention of osteoporotic fractures: a systematic review and meta-analysis. Osteoporos Int. 2013;24(2):393–406.
64. Uhlig K, Leff B, Kent D, Dy S, Brunnhuber K, Burgers J, Greenfield S, Guyatt G, High K, Leipzig R, et al. A framework for crafting clinical practice guidelines that are relevant to the care and management of people with multimorbidity. J Gen Intern Med. 2014;29(4):670–9.

Genetics of Osteoporosis in Older Age

8

David Karasik and Douglas P. Kiel

Generalized osteoporosis is the most common form of the disease, affecting the majority of the bones in a skeleton. Osteoporosis results from a failure to acquire optimal peak bone mass during growth and/or failure to maintain bone homeostasis in later years. The prevalence and severity of osteoporosis is especially high in older persons (so called involutional osteoporosis), in both men and women [1, 2]. Women additionally experience a rapid phase of bone loss after the menopause, as a result of estrogen withdrawal [3, 4]. With aging, the skeleton is susceptible to osteoporotic fractures, which seem to be dependent on genetic factors (heritable). The genetic contribution to involutional osteoporosis is substantial and its heritability has been extensively studied. With recent advances in the elucidation of the mechanisms involved in osteoporosis, there is recognition that there are genetic contributions to fractures and related bone traits, in particular in elderly persons, which may or may not be shared with genetic mechanisms of bone maintenance in younger individuals.

The susceptibility to fractures depends on many factors, including non-skeletal ones, such as propensity to fall, diminished soft tissue cushion etc. Nevertheless, the most reliable predictor of fracture is bone mineral density (BMD), also a trait highly susceptible to genetic alterations. The importance of bone mass to fracture risk is also evident in the WHO's definition of osteoporosis ("low bone mass leading to structural fragility" [5]). Better understanding of the genetic contribution to BMD offers the opportunity to learn more about the biology of bone fragility. In order to identify and quantify the genetic contributions to a complex disease, such as osteoporosis, there is a need to identify and validate an "endophenotype". Endophenotypes are defined as intermediate components of a phenotype of interest, in contrast to a final ("visible") exophenotype. This distinction is especially challenging in the case of osteoporosis, where the phenotype of interest is clinically occult until the "structural fragility" ultimately manifests as a fracture [6].

In many complex diseases, an "upstream" intermediate measurable phenotype between genotype and disease, is chosen as an endophenotype, and serves as a target for gene mapping. These are usually well-known risk factors with pathophysiological importance and biological meanings, which are measurable before the onset of disease [7]; by definition, endophenotypes are thus putatively closer to the effect of genes. In

D. Karasik, PhD (✉)
Institute for Aging Research, Hebrew SeniorLife, Boston, MA 02131, USA
e-mail: karasik@hsl.harvard.edu

D.P. Kiel, MD, MPH
Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

Director Musculoskeletal Research Center, Institute for Aging Research, Hebrew SeniorLife, Boston, MA, USA
e-mail: kiel@hsl.harvard.edu

G. Duque, D.P. Kiel (eds.), *Osteoporosis in Older Persons: Advances in Pathophysiology and Therapeutic Approaches*, DOI 10.1007/978-3-319-25976-5_8

osteoporosis, BMD is routinely investigated in clinical practice with dual-energy X-ray absorptiometry (DXA) at the lumbar spine and hip, because this endophenotype constitutes one of the strongest predictors of future fracture.

BMD was always considered as a proxy for osteoporotic fracture risk. Many traditional biochemical and endocrine measures (e.g., serum cholesterol for heart disease creatinine for chronic kidney disease, insulin for diabetes, etc.) fit into this category [7]. However, biochemical and endocrine markers are rarely used in osteoporosis genetics [8, 9], despite advanced understanding of pathophysiologic pathways they are involved in.

Most of the controversy surrounding the choice of BMD as the best bone phenotype was due to an observation that genes contributing to variation in BMD evidently do not always contribute to osteoporotic fractures [6]. For these reasons, the 'endpoint disease', e.g., osteoporotic fracture *per se*, was still considered to be a valuable exophenotype for genetic studies of osteoporosis. Traditional studies suggested that bone density and fractures have a different genetic milieu. Variance component analysis suggested that less than 1 % of additive genetic variance is shared between BMD and osteoporotic fractures at the hip [10]. Studies of many candidate genes in the pre-GWAS era (such as *ESR1* [11], *COL1A1* [12], *IGF-1* [13, 14]) confirmed this early observation.

Much has changed in the last 7 years since our previous review of the field. In the terms of quantitative genetics and genomics, these 7 years equate to a lifetime. One revolutionary development was the technology of genotyping arrays that made it possible to study genes at a genome scale, using a genome-wide association study (GWAS) technique. To date, the GWAS approach has been proven productive in uncovering multiple genes responsible for complex diseases [15]. Micro-array-based GWAS relies on the principle of linkage disequilibrium (LD), whereby the SNPs found to be associated with a phenotype like BMD may not necessarily be the true causal variants or even map to the correct causative gene because it cannot be established which of the SNPs in high LD are causal. Advances in bioinformatics and genotyping technology support the approach of using even denser genotype data achieved through imputation of un-genotyped SNPs. We refer the interested reader to the excellent reviews of the technique and the achievements of GWAS [16, 17].

Multiple GWAS have been performed in children and young adults, which suggests a genetic role in peak bone mass accrual, which may impact the risk of osteoporosis later in life; (we however focus this overview on the studies that deal with older ages). Recent GWAS studied the risk of forearm fracture in younger adults [18] and peak bone mass in premenopausal women [19]. These studies clearly identify genetic loci associated with BMD and fracture at younger ages.

Based on the principle of reverse genetics (i.e., what phenotype can be affected by changes in a gene), GWAS can be brought up to serve as an arbiter in the dispute on what is a phenotype of choice for osteoporosis. If for example BMD is indeed an "endophenotype" (closer to the effect of genes than fracture), then the effects of changes in genes for osteoporosis would be more visible than for the "exophenotype", fracture. We know that genetic correlations among quantitative traits predict how many associated SNPs are shared between these traits [20], this may also be true for a commonality between the quantitative phenotype such as BMD and a dichotomous trait, such as osteoporotic fracture, in regard to GWAS loci.

Indeed, many of the BMD-associated variants discovered by GWAS have some effect on fracture. Thus, in the most recent and largest GWAS meta-analysis for BMD to date, with measurements from >80,000 individuals, 56 loci were associated with BMD at genome-wide significant levels [21]. Fourteen of these BMD loci were also found to be associated with the risk for osteoporotic fracture, of which six (including *FAM210A, SLC25A13, LRP5, MEPE/IBSP, SPTBN1* and *DKK1*, see also Table 8.1) attained genome-wide significance levels ($P < 5 \times 10^{-8}$) [21]. Of note, the fractures used in these analyses were quite heterogeneous, and included hip, spine, and wrist, as well as other types of fractures.

In their recent review in 2013, Liu et al. [27] summarized the putative osteoporotic fracture genes identified in GWASs. Since then, several

Table 8.1 Chromosomal loci found to be associated with osteoporotic fractures and their associations to BMD and related phenotypes

Chr	Locus	Gene(s) – symbol	Alias	Fracture phenotype	Reference (fracture)	OR	95 % CI	P-value (fracture)	P-value (FN BMD)	P-value (LS BMD)	Reference (BMD)	Other associated bone phenotypes (reference)	
1	1p36.23-p35.1	*WNT4*	Wingless-related MMTV integration site 4	Any type	[21]	1.09	1.06–1.13	1.40×10^{-7}	2.85×10^{-9}	9.66×10^{-11}	[21]		
2	2p16.2	*SPTBN1*	Spectrin, beta, nonerythrocytic, 1	Any type	[21]	1.06	1.04–1.08	2.60×10^{-8}	5.9×10^{-6}	2.25×10^{-18}	[21]	4.24×10^{-13} (heel ultrasound)	[22]
3	3p22.1	*CTNNB1*	Catenin (cadherin-associated protein), beta 1	Any type	[21]	1.06	1.07–1.08	2.90×10^{-7}	4.41×10^{-25}	1.54×10^{-18}	[21]		
3	3q26.2	*MECOM*	MDS1 and EVI1 complex locus	Osteoporotic fracture	[23]	1.37	1.23–1.53	1.05×10^{-8}					
4	4q22.1	*MEPE/ IBSP/SPP1*	Matrix, extracellular, phosphoglycoprotein	Any type	[21]	1.06	1.04–1.08	1.62×10^{-9}		1.7×10^{-8}	[21]		
5	5q31	*ALDH7A1*	Aldehyde dehydrogenase 7 family, member A1	Hip osteoporotic fracture	[24]	2.25	1.72–2.94	2.08×10^{-9}	6.39×10^{-6}		[24]		
6	6q22.33	*RSPO3*	R-spondin-3	Osteoporotic fracture	Oei, L, 2014, unpublished	1.07	1.05–1.09	3.73×10^{-12}	8.03×10^{-12}		Oei, L, 2014, unpublished	9.26×10^{-13} (heel ultrasound), 4.11×10^{-13} (heel BMD)	[22]
6	6q25.1	*ESR1/ C6orf97*	Estrogen receptor 1; Chromosome 6 Open Reading Frame 97	Vertebral fractures	[25]	1.93	1.23–3.05	0.005	4.15×10^{-18}	3.95×10^{-35}	[21]		
7	7q21.3	*SLC25A13/ SHFM1*	Solute carrier family 25 (citrin), member 1	Any type	[21]	1.07	1.05–1.10	1.04×10^{-12}	8.10×10^{-48}	2.13×10^{-35}	[21]		

(continued)

Table 8.1 (continued)

Chr	Locus	Gene(s) – symbol	Alias	Fracture phenotype	Reference (fracture)	OR	95 % CI	P-value (fracture)	P-value (FN BMD)	P-value (LS BMD)	Reference (BMD)	Other associated bone phenotypes (reference)	
7	7q31	*WNT16*	Wingless-related MMTV integration site 16	Any type	[21]	1.06	1.04–1.08	2.7×10^{-7}	5.02×10^{-40}	3.17×10^{-51}	[21]	2.3×10^{-12} forearm BMD; 2.6×10^{-31} (TB BMD); $P=1.9\times10^{-16}$ (skull BMD) 4.3×10^{-35} to 1.6×10^{-59} (heel ultrasound)	[18, 22, 26]
10	10q21.1	*MBL2/ DKK1*	Lectin, mannose-binding, soluble, 2	Any type	[21]	1.09	1.06–1.13	9.00×10^{-9}	1.45×10^{-8}	1.56×10^{-12}	[21]	(heel ultrasound)	[22]
11	11p14.1	*DCDC5*	Doublecortin domain containing 5	Any type	[21]	1.05	1.03–1.07	3.30×10^{-5}	2.06×10^{-8}	2.19×10^{-11}	[21]		
11	11q13.2	*LRP5*	Low density lipoprotein receptor-related protein	Any type	[21]	1.09	1.06–1.13	1.40×10^{-8}	4.83×10^{-11}	2.08×10^{-26}	[21]		
17	17q21.31	*C17orf53*	Chromosome 17 open reading frame 53	Any type	[21]	1.05	1.03–1.07	4.10×10^{-5}	2.56×10^{-24}	9.92×10^{-10}	[21]		
17	17q21.31	*SOST*	Sclerostin	Any type	[21]	1.07	1.05–1.09	3.13×10^{-13}	1.95×10^{-11}	9.43×10^{-10}	[21]		
18	18p11.21	*FAM210A/ RNMT*	Family With Sequence Similarity 210, Member A; RNA (Guanine-7-) Methyltransferase	Any type	[21]	1.09	1.06–1.10	8.80×10^{-13}	4.85×10^{-8}		[21]		
21	21q22.2	*ETS2*	V-Ets Avian Erythroblastosis Virus E2 Oncogene Homolog 2	Osteoporotic fracture	Oei, L, 2014, unpublished	1.07	1.05–1.10	2.77×10^{-10}					

Blank: no association ($p>5\times10^{-3}$)

Abbreviations:

Chr chromosome; *OR* odds ratio; *CI* confidence interval; *FN BMD* femoral neck BMD; *LS BMD* lumbar spine BMD

notable GWAS's of fractures were performed, mostly within the GEFOS ("Genetic Factors for Osteoporosis") Consortium The shear number of genetic loci discovered by GWAS for osteoporosis-related (quantitative) traits since 2007 (almost 100) speaks for its success as a revolutionary tool. However, a GWAS for fractures was not completed until recently.

GWAS for vertebral fractures identified one genome-wide significant signal in the discovery phase, which was not convincingly replicated in 15 studies world-wide [28]. The GWAS discovery was based on the Rotterdam Study and comprised 329 cases and 2666 controls with radiographic scoring of vertebral fracture (McCloskey–Kanis or Genant semi-quantitative definitions) and genetic data. A SNP (rs11645938) on chromosome 16q24 was associated with the risk for vertebral fractures at $p=4.6\times10^{-8}$. Replication of this SNP was pursued by de-novo genotyping of 15 independent studies across Europe, the United States, and Australia and one Asian study, combining 5720 cases and 21,791 controls. Association of this SNP with fracture was characterized by a high degree of heterogeneity ($p=0.0006$) [28]; notably, the SNP maps to a region previously found to be associated with LS BMD by the GEFOS consortium [21].

Oei et al. [29] also performed a genome-wide analysis of copy number variants (CNV) in 5178 individuals from the Netherlands, including 809 fracture cases; the Discovery was followed by *in silico* lookups and *de novo* replication in several independent samples. A 210 kb deletion located on 6p25.1 was associated with the risk of fracture, in in-silico meta-analyses of four studies (odds ratio [OR] 3.11, 95 % confidence interval [CI] from 1.01 to 8.22; $p=0.02$). The prevalence of this deletion showed heterogeneity, mostly due to geographic diversity (some European samples could not identify such a CNV because of its rarity (population prevalence = 0.14 %)).

Most recently, the largest GWAS meta-analysis for the fracture phenotype to date (n = 102,873, 19,414 fractures) from 24 cohorts, was performed with fractures confirmed by medical, radiological or questionnaire reports (Oei et al., 2014, unpublished). When possible, fractures of the fingers, toes and skull, and high-energy traffic accidents or falls from greater than standing height were excluded from analyses. The sex-pooled meta-analysis comprised statistics from up to 2,768,948 SNPs across 24 studies (female-only meta-analysis included participants from 22 studies, and the male-only meta-analysis, from 18 studies). The Discovery GWAS was followed-up by a replication phase that included 35 SNPs from 27 loci, in 163,292 participants (38,021 cases and 125,271 controls). Ten loci replicated at genome-wide significance levels, with small to moderate effect on fracture risk (OR 1.06–1.18); many of these loci were those previously found to be associated with BMD levels as well, of which several seem to be involved in Wnt signaling. A signal at 21q22.2, which had not been previously reported in either fracture or BMD GWASs, maps upstream of the gene *ETS2* that encodes a protein which has a role in skeletal development [30]. Although this is not a previously known BMD locus, its association with fracture risk still might involve BMD, as the SNP was nominally associated with DXA-derived BMD in the GEFOS study ($P=0.00014$ for LSBMD) [21]. Notably, in this largest study of fracture risk (Oei et al., 2014, unpublished), genome-wide analysis of sex-chromosomes has not been performed. Table 8.1 summarizes the chromosomal loci found to date being associated with osteoporotic fractures. It is also apparent that the majority of these "fracture genes" are associated to BMD and related proxy phenotypes.

This large GWAS meta-analysis for the fracture phenotype is not without its limitations. First, "cases" included individuals starting at the age of 18 years, in whom skeletal fragility factors may be different than those occurring at later ages. For example, fractures at younger ages may be due to more severe trauma (e.g., during sports events) or due to different skeletal function such as the *modeling* that occurs up until the time of peak bone mass, which is in contrast to the *remodeling* that influences fracture risk at later ages. Second, as said above, fractures of the fingers, toes and skull are routinely excluded. However, they might share some genetic etiology with the "mainstream" long bones (hip, tibia) and complex bones (vertebra). For BMD, several loci display skeletal-site specific effects [21], and for fracture risk,

site-specific genetic effects have been proposed as well [31]. If genetic risk factors exert site-specific effects, focusing on specific fracture types (e.g., long bone fractures of the extremity or only vertebral fractures) may be worthwhile in future studies. However, so far these approaches have been challenging, and the field has not solved the problem of genetic and non-genetic etiological heterogeneity underlying different types of fractures. Empirically, analyzing the non-vertebral fracture and vertebral fracture in addition to all-type of fracture has not produced any additional signals [21]. Furthermore, not all studies in the meta-analysis verified self-report of fractures, which may have resulted in some misclassification between cases and controls.

In addition to site-specificity, there are problems with a phenotype definition and sample size making its study a challenge at present. Exploring age-specific effects would require even larger samples; the same can be expected for the SNP-by-age (or SNP-by-sex) interaction [32]. Large biobanks such as the ones in the U.K., Germany, Estonia, Iceland, and the Netherlands, and studies using medical records linked to genotype in large populations, hold future promise for the study of fracture phenotypes. Of note there has been some attempt to combine a fracture occurrence and BMD measures as an osteoporosis phenotype [33] or to use a clinical diagnosis of osteoporosis as a phenotype, in a case-control study [34].

What Has Been Achieved to Date: The Therapeutic Promises of Genomics

The ultimate goal of genetic discovery is to define the molecular mechanisms that underlie the genotype-phenotype association, and to determine the potential for additional ways to treat human diseases (identify drug targets). Many loci emerging from GWAS discoveries seem to be actively involved in bone development and homeostasis, as well as systemic factors. Targeted functional studies using molecular techniques (e.g., animal experiments and cell line work) are necessary to increase our knowledge about the function of newly-discovered genes. Therefore, the fracture phenotype poses additional challenges for use of animal models: existing lab models of bone fracture are usually not too "physiological", since rodent fragility is an artifact. Similarly, fractures are a challenge for the pharmacogenetics of the drug targets, since fracture prevention requires very large sample sizes in the conduct of clinical trials.

In addition to GWAS holding the potential to discover new pathways affecting the skeleton, some had hoped that genetic risk assessment could be added to traditional lifestyle risk score to better predict fractures. Recently, only a limited clinical utility has been shown for a genetic risk score (GRS) to predict fracture risk in elderly persons [35]. As mentioned above, meta-analysis by Estrada et al. identified 63 autosomal SNPs associated with BMD, of which 16 were also associated with fracture risk. Based on these findings two genetic risk scores (GRS63 and GRS16) were calculated and applied to 2 male (MrOS-US and MrOS-Sweden) and one female (SOF) large prospective cohorts of older subjects, with radiographically and/or medically confirmed incident fractures (8067 persons, 2185 incident non-vertebral or vertebral fractures). Both GRS63 and GRS16 were associated with fractures, however, after adjustment for BMD, the effect sizes for these associations were substantially reduced. Net reclassification improvements were modest and substantially attenuated with the addition of the GRSs to a base BMD-adjusted models [35]. The clinical utility of the two GRSs for fracture prediction is limited in elderly subjects if their BMD is known. Knowing a genetic risk score at very young ages could motivate an individual to optimize bone health behaviors before reaching the age of increased skeletal fragility and fracture risk.

Along with the DXA-derived BMD, there is a potential value of using other proxies, such as pQCT, bone geometry measures or even biomarkers (OPG, osteocalcin etc.).

High resolution peripheral quantitative computed tomography (HR-pQCT) analysis has the advantage of revealing additional information about some structural bone traits, such as cortical porosity and trabecular bone architecture, and

of volumetric BMD in 3-D rendering. Paternoster et al. [36] published the first GWAS to identify genetic loci associated with cortical and trabecular bone structural parameters in Europeans using standard peripheral computed tomography. Their GWAS meta-analysis for cortical vBMD (Discovery n=5878, followed by replication, n=1052) identified genetic variants in four separate loci (*RANKL, LOC285735, OPG(TNFRSF11B)* and *ESR1/C6orf97*). The trabecular vBMD meta-analysis (Discovery n=2500; replication, n=1022) identified one locus reaching genome-wide significance (*FMN2/GREM2*). The genetic variant in the *FMN2/GREM2* locus was also associated with fracture risk in older men from the Sweden cohort and with GREM2 expression in human osteoblasts.

Utility of Genetic Markers in Osteoporosis and Fracture Prediction

Osteoporosis genetic research was expected to provide a set of variants that could predict risk of future fracture. This in turn would allow preventive therapy or life-style intervention to be applied early on. Since many alleles have been and have continued to be identified by GWAS and sequencing efforts (see below), a weighted allele score approach had been implemented, by counting the number of deleterious alleles per person and weighting each allele by its effect size, so that higher risk score points out an individual with more deleterious alleles [37]. Thus, using alleles of 63 autosomal SNPs from the GEFOS-2 GWAS, the consortium was able to capture a difference between the highest risk group and lowest risk group of approximately ~0.86 standard deviations [21]. Similar to [35], only minor improvements in the area-under-curve (AUC) for fractures were seen by GEFOS-2 when the alleles were added to a base model (age, sex and weight), thus to date it seems that generally-measured clinical risk factors, such as age, sex, and body size, outperform an allelic risk score.

Most genetic variants claimed to be associated with a disease have small effects and only a tiny fraction of the genetic variance has been captured [38]. In their influential review, Richards et al. [37] predicted that many more common variants would be needed to capture the variance in BMD or fracture. They further predicted this may be improved by identifying less common variants that have a large effect on the risk of fracture and/or BMD. However, increase in the number of risk alleles comes at the expense of decreasing effect size for each subsequent allele. Furthermore, in addition to the highly polygenic allelic architecture of BMD and osteoporotic fracture, gene-gene and allele-by-environment interactions make additive genetic risk scores somewhat limited. Environment interacts with the genetic background, and this interaction affects predisposition to diseases, including propensity to break bones [39]. Studies of gene-by-environment interactions had only begun quite recently, but in the future may afford prognostication of osteoporosis and will make personalized prevention efforts feasible.

Next-Generation Sequencing

Since the publication of the previous edition of this book, new and efficient methods of DNA sequencing have become available. As was true for single-SNP association studies, the advent of sequencing in the field of skeletal genetics started with the candidate genes for BMD and fractures. Thus, the *LRP5* gene – its 23 exons and exon–intron boundaries – were sequenced in fracture-prone Finnish children [40]; 15 novel missense or silent coding variants were found. McGuigan et al. [41] sequenced the osteocalcin gene in a cohort of 996 women (all aged 75 years). More recently, GWAS-identified genes were studied: Koromila et al. sequenced the entire *DKK1* gene in 607 postmenopausal women [42]. In 128 young Danish men with extreme t-scores for whole-body BMD, the gene *WNT16* was sequenced [43]. In the latter study, 10 known SNPs were re-discovered, including rs55710688, insertion –/CCCA (so called "Kozak sequence"). Importantly, Hendrickx et al. also performed a functional evaluation of that sequence by luciferase reporter assay and in-vitro translation assay.

Affordable next-generation sequencing (NGS) approaches led to the identification of hundreds of genes causing Mendelian disorders, including some for skeletal diseases. The majority of discovered mutations alter the coding regions of genes, which makes selective sequencing of protein-coding regions – the exons – a most cost-effective approach for the discovery of new mutations. NGS approaches can be applied to analyze the exome of even a single individual with a Mendelian disease. Thus, for a patient with severe osteogenesis imperfecta (OI), a truncating mutation in gene *SERPINF1* was discovered [44]. In several patients with the same *SERPINF1* mutation, fractures of long bones and severe vertebral deformities were observed as early as the first year of life. In a similar study, in a 6-year-old boy with vertebral compression fractures and low trabecular BMD, whole-exome sequencing (WES) implicated a mutation in *LRP5* gene [45]. The boy had a history of seven low-energy long-bone fractures starting at 19 months of age and multiple radiographic vertebral compression fractures. WES revealed a heterozygous insertion of a nucleotide in exon 12 of *LRP5*, which corresponds to a loss-of-function mutation [45]. This mutation had previously been reported in another juvenile osteoporotic patient, again confirming a role of *LRP5* in bone fragility early of life. Another example of successful WES's application comes from a gnathodiaphyseal dysplasia (GDD), a rare autosomal dominant condition characterized by bone fragility, irregular BMD, and fibro-osseous lesions in the skull and jaw [46]. A whole exome capture and massive parallel sequencing of two affected individuals (a mother and son) and the mother's unaffected parents, identified a mutation in the C-propeptide cleavage site of *COL1A1,* – another osteoporosis candidate gene.

Obviously, for a complex disease such as osteoporosis and phenotypes of fracture and BMD, although the NGS approach can be applied, sample size requirements are several orders of magnitude larger, and issues such as a possible misclassification have arisen. Thus, whole-genome sequencing of Icelandic individuals was undertaken. In the discovery analysis, cases (n = 4931) were defined as those with adjusted BMD levels <1 S.D. from the mean at the total hip, lumbar spine, or whole body, whereas the control group comprised 69,034 individuals who either had BMD above −1 S.D. and, for increased power, those who had no BMD information available at all [47]. The investigators found a rare nonsense mutation within the leucine rich repeat-containing G-protein-coupled receptor 4 (LGR4) gene (C376T) that was strongly associated with low BMD and osteoporotic fractures. This is a rare nonsense mutation, which terminates *LGR4* and completely disrupts the function of the protein. This mutation is also Iceland-specific, since it wasn't found in other Europeans [47].

More recently, Friedman et al. [48] performed a WES for the stress fracture (SF) phenotype. Although SF is believed to be a specific disease entity, genetic factors contributing to its pathogenesis may be shared with osteoporotic fractures. The authors thus performed an exome sequence capture followed by massive parallel sequencing of two pooled DNA samples from Israeli combat soldiers: cases with high grade SF (N = 34) and healthy controls (N = 60). The resulting sequence variants were genotyped in the same individuals and then validated in a second cohort of cases and controls (N = 136 SF cases and 127 controls). Of a total of 1174 discovered variants with >600 reads/variant, 146 (in 127 genes) exhibited different rates between SF cases and controls (statistically significant at $P < 0.05$ after multiple comparisons correction). Subsequent verification of these sequence variants using the Sequenom™ platform validated 20 of the 146 variants with significantly different rates in SF cases compared with controls. Notably, the list of implicated exons/genes did not overlap with those known for osteoporotic fracture or its proxy phenotypes, which might be a reflection of modest discovery sample size, thus had to be taken with a "pinch of salt".

Atypical fracture is another newly-recognized skeletal disease entity. Those are usually subtrochanteric fractures in mostly female patients with long-term use of bisphosphonates. These fractures have a distinct etiology from the osteoporotic fractures, however, it is not clear yet whether they share pathophysiology with osteoporotic or stress fractures. Having a large, well-powered (or

smaller, but homogenous) sample of patients for genome sequencing might provide an answer. Reverse genetics could then inform us, whether or not these atypical fractures have a common genetics with early-life stress or late-life osteoporotic fractures.

NGS-based approaches had been pursued for the BMD and fracture phenotypes. Zheng et al. [49] tested genome-wide significant variants associated with BMD for their effect on risk of fracture in 10,459 cases and 27,581 controls, and identified a variant rs11692564 near *WNT16* associated with fracture risk [49]. The observed effect size at rs11692564 was fourfold larger than the mean for DXA BMD (~0.05 S.D. per effect allele) and double the largest previously reported effect (0.1 S.D.) Along with finding larger effect sizes, this study also taught us several important lessons. First, gene-based collapsing methods did not identify any convincing novel associations which were not genome-wide significant through single-SNP associations. This included collapsing variants below 1 and 5 % MAF thresholds, or including all variants, only selecting evolutionarily conserved variants, or those from protein-coding regions. Second, some significant rare variants were identified only from few cohorts. As shown above, there are population-specific mutations [47], therefore replication in other cohorts might not be achievable. Finally, despite large sample size, rare variants, especially singletons, cannot be adequately captured for the collapsing tests due to poor imputation [49].

In summary, while whole exome and whole genome sequencing might be of use in diagnosis of rare disorders and syndromes for which early intervention may modify the clinical decision process, utility of these methods for complex disease such as osteoporosis and related fractures has yet to be established.

Genetics of Falls

Not much is known about genetic factors contributing to the risk of falling, although it is such an important geriatric syndrome and risk factor for osteoporotic fractures. According to an earlier report [50], this phenotype has evidence of moderate heritability. Thus, in a study of 99 monozygotic (MZ) and 114 dizygotic (DZ) Finnish female twin pairs aged 63–76, "familial influences" accounted for susceptibility to at least one fall (30 % attributed to heritability), and for recurrent falls this estimate was 40 %. This study hinted also at the problems with the phenotype of falling, namely, it relies on self-report (the participants of cohort studies usually record their falls on a calendar; those incidents have to be verified via telephone interview, and circumstances, causes, and consequences of the fall should be asked about to prevent phenocopies).

Since vitamin D has been implicated as playing a role in multiple organ systems in older persons, it has been suggested that vitamin D supplementation may reduce the incidence of falls by reducing body sway and increasing muscle power [51]. Furthermore, vitamin D receptor (VDR) genotypes have been associated with cognitive status, depressive symptoms, BMD, and sarcopenia, all of which are related to falling. Thus, it is not surprising that this gene was studied for its relationship with falls in a study of 259 Italian participants (mean age 85.0 ± 4.5 (SD) years; 172 (66.4 %) were women [52]. Restriction enzyme's polymorphisms Fok-1 and BsmI were analyzed. After adjusting for potential confounders, compared with participants with the BB genotype, those with the bb genotype had a significantly lower OR for falls: 0.14 (95 % CI, 0.03–0.66), while rate of falls did not differ significantly across FokI genotypes (FF: 14.4 %, Ff: 11.9 %, ff: 9.1 %; $p = 0.43$) [52].

This indication of association between vitamin D receptor gene polymorphisms and falls, was tested in two additional independent population cohorts of postmenopausal women. Five polymorphisms of the *VDR* gene were analyzed (Cdx-2, Fok-1, BsmI, Taq1 and Apa1) in the Aberdeen cohort from UK. Carriers of the Bsm1 B allele showed an increased risk for both multiple falls ($p = 0.047$) and for recurrent falls ($p = 0.043$). Similar results were found in the "OPUS" cohort for falls ($p = 0.025$) and multiple falls ($p = 0.015$). Bsm1 polymorphisms were also associated with balance and muscle power measurements. Results found in the APOSS cohort

were then validated in an independent cohort (the five European cities based OPUS study). These studies demonstrate an association between the *VDR* Bsm1 polymorphism and risk of falling.

The genetic influence on such a multifactorial phenotype as falls might be either due to accumulation of sensory difficulties, autonomic nervous system, postural balance, or weak muscles. Current studies tended to look "under the lamp post" – for the genetic and non-genetic factors that are easily available. The time may be right for performing a GWAS study for propensity to fall, since it holds a promise to bring to light new genomic loci.

Genetic Predisposition to Fracture Non-union

Once a fracture occurs and the bones are re-aligned, a healing process begins. Fracture healing is a complex process; in some cases the fracture healing is ineffective, leading to non-unions, more often in long bones. Fracture non-unions, while multifactorial in origin, include a component of genetic predisposition. One pilot study performed an analysis of SNPs in a genetic pathway known to regulate fracture healing, the Bone Morphogenetic Protein pathway [53]. SNPs in 4 genes (*BMP2, BMP7, NOGGIN* and *SMAD6*) were examined in 62 patients with atrophic non-union compared to 47 patients with uneventful fracture union. As expected, this analysis revealed patient's age to be an important covariate in the development of atrophic non-union. Also, two SNPs, rs1372857 located in *NOGGIN* and rs2053423, located in *SMAD6*, were found to be associated with a greater risk of fracture non-union, after adjustment for age. One might thus consider an existence of a potential genetically predetermined impairment within the BMP signaling cascade, above and beyond effect of the patient's age [53].

Another similar study tested 16 SNPs within five genes involved in bone repair (*FAM5C*, *BMP4*, *FGF3*, *FGF10*, and *FGFR1*) in 167 patients with long bone fractures (101 with uneventful healing vs. 66 with aseptic non-unions) [54]. A significant association of variants in *BMP4* ($p=0.01$) and *FGFR1* ($p=0.005$) with non-union was observed, while uneventful healing showed association with *FAM5C* rs1342913 ($p=0.04$). Based on these early candidate-gene studies, polymorphisms in certain genetic pathways, such as growth factors, can be involved in delayed bone healing. Similarly, a comparison of the transcriptome of mouse callus tissues across a period of fracture healing showed that about one-third of the expressed genes are mouse homologues of the genes induced in human embryonic stem cells, such as members of BMPs, Wnt and homeobox pathways. Many of the genes that control appendicular limb development also show increased expression during fracture healing. Fracture healing might be seen as reminiscent of the post-natal developmental process (see an influential paper of Gerstenfeld et al. [55]), therefore bone's diminished ability to regenerate with advanced age can be attributed to the aging paradigm. There is a need to bridge between the studies in human patient cohorts and animal models, to dissect the mechanism underlying the influence of specific gene loci on the processes of fracture repair, as well as the contribution of aging, to be translated into personalized treatment options [56].

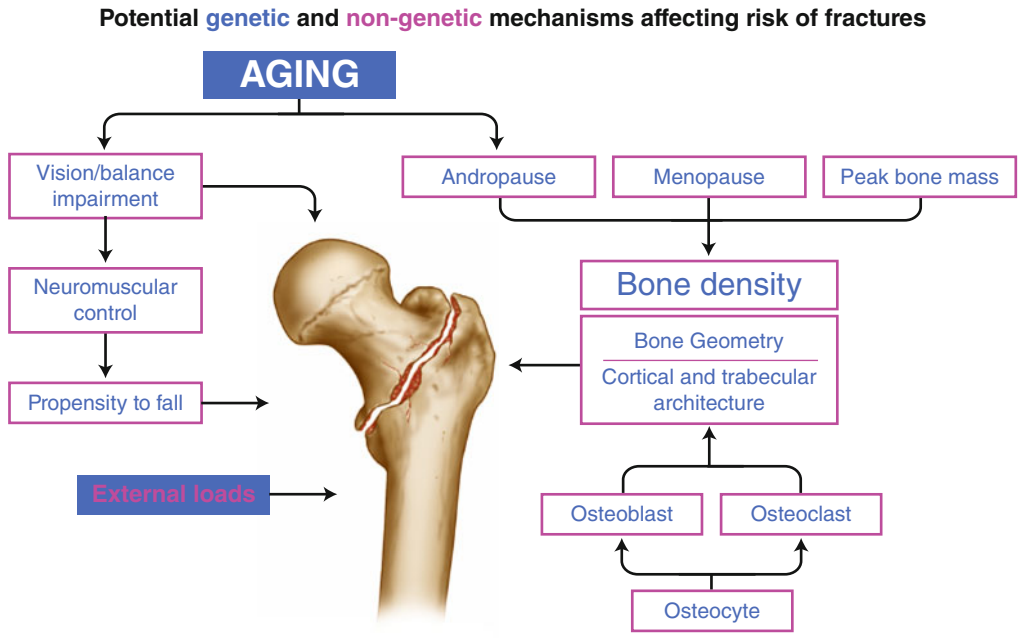
Concluding Remarks

Identification of significant genetic variants underlying the phenotypes of bone aging is now possible more than ever due to rapidly developing advanced genomic technologies. Contemporaneous growth of molecular and cellular, human and animal data, and our ability to model biological processes in-vitro and in-vivo, is unparalleled. The revolutionary changes at a time of explosive growth in whole genome sequencing and bioinformatics, present both tremendous opportunities and great challenges to the field of human genetics [57].

Any statistically-identified genetic variation has to be substantiated in a real biological context [38]. The use of animal modeling experiments can guide hypothesis-driven human studies and to validate their results. However, animal models do not fully recapitulate the phenotype of human fracture, therefore human genetic studies of the

aging skeleton need to continue into new domains. Since fractures are multifactorial, contributing factors, including non-skeletal ones, should always be considered even in genetic studies. New sophisticated endophenotypes, such as ultra-fine bone imaging techniques, should be explored.

Continuous success in advancing the field will depend on collaborations across cohesive multi-disciplinary groups [57]. We must effectively combine the genomic tools in our possession, bioinformatic data and advanced phenotypes, to inform our search for disease mechanisms. Since aging also brings changes to the epigenome and to post-translational modification of proteins, future research will undoubtedly leverage the synergy of genomics, epigenetics, statistical modeling, bioinformatics, and experimentation to provide advances in the study of genetic contributions to osteoporotic fracture and its proxy phenotypes [57]. If successful, these studies will have chance to bring genetics into practical use in medicine for common diseases [38].



References

1. Burger H, de Laet CE, van Daele PL, Weel AE, Witteman JC, Hofman A, Pols HA. Risk factors for increased bone loss in an elderly population: the Rotterdam Study. Am J Epidemiol. 1998;147:871–9.
2. Hannan MT, Felson DT, Dawson-Hughes B, Tucker KL, Cupples LA, Wilson PW, Kiel DP. Risk factors for longitudinal bone loss in elderly men and women: the Framingham Osteoporosis Study. J Bone Miner Res. 2000;15:710–20.
3. Melton 3rd LJ, Atkinson EJ, O'Connor MK, O'Fallon WM, Riggs BL. Determinants of bone loss from the femoral neck in women of different ages. J Bone Miner Res. 2000;15:24–31.
4. Riggs BL, Khosla S, Melton LJ. A unitary model for involutional osteoporosis: estrogen deficiency causes both type I and type II osteoporosis in postmenopausal women and contributes to bone loss in aging men. J Bone Miner Res. 1998;13:763–73.
5. U.S. Department of Health and Human Services. Bone health and osteoporosis: a report of the surgeon general. Rockville: U.S. Department of Health and Human Services, Office of the Surgeon General; 2004.
6. Schulze TG, McMahon FJ. Defining the phenotype in human genetic studies: forward genetics and reverse phenotyping. Hum Hered. 2004;58:131–8.
7. Pan WH, Lynn KS, Chen CH, Wu YL, Lin CY, Chang HY. Using endophenotypes for pathway clusters to map complex disease genes. Genet Epidemiol. 2006;30:143–54.
8. Kwan JS, Hsu YH, Cheung CL, Dupuis J, Saint-Pierre A, Eriksson J, Handelman SK, Aragaki A, Karasik D, Pramstaller PP, Kooperberg C, Lacroix AZ, Larson

MG, Lau KS, Lorentzon M, Pichler I, Sham PC, Taliun D, Vandenput L, Kiel DP, Hicks AA, Jackson RD, Ohlsson C, Benjamin EJ, Kung AW. Meta-analysis of genome-wide association studies identifies two loci associated with circulating osteoprotegerin levels. Hum Mol Genet. 2014;23(24):6684–93.

9. Livshits G, Yakovenko C, Kobyliansky E. Quantitative genetic analysis of circulating levels of biochemical markers of bone formation. Am J Med Genet. 2000; 94:324–31.
10. Deng HW, Mahaney MC, Williams JT, Li J, Conway T, Davies KM, Li JL, Deng H, Recker RR. Relevance of the genes for bone mass variation to susceptibility to osteoporotic fractures and its implications to gene search for complex human diseases. Genet Epidemiol. 2002;22:12–25.
11. Ioannidis JP, Stavrou I, Trikalinos TA, Zois C, Brandi ML, Gennari L, Albagha O, Ralston SH, Tsatsoulis A. Association of polymorphisms of the estrogen receptor alpha gene with bone mineral density and fracture risk in women: a meta-analysis. J Bone Miner Res. 2002;17:2048–60.
12. Mann V, Hobson EE, Li B, Stewart TL, Grant SF, Robins SP, Aspden RM, Ralston SH. A COL1A1 Sp1 binding site polymorphism predisposes to osteoporotic fracture by affecting bone density and quality. J Clin Invest. 2001;107:899–907.
13. Rivadeneira F, Houwing-Duistermaat JJ, Beck TJ, Janssen JA, Hofman A, Pols HA, Van Duijn CM, Uitterlinden AG. The influence of an insulin-like growth factor I gene promoter polymorphism on hip bone geometry and the risk of nonvertebral fracture in the elderly: the Rotterdam study. J Bone Miner Res. 2004;19:1280–90.
14. Rivadeneira F, Houwing-Duistermaat JJ, Vaessen N, Vergeer-Drop JM, Hofman A, Pols HA, Van Duijn CM, Uitterlinden AG. Association between an insulin-like growth factor I gene promoter polymorphism and bone mineral density in the elderly: the Rotterdam Study. J Clin Endocrinol Metab. 2003;88:3878–84.
15. Hindorff LA, Sethupathy P, Junkins HA, Ramos EM, Mehta JP, Collins FS, Manolio TA. Potential etiologic and functional implications of genome-wide association loci for human diseases and traits. Proc Natl Acad Sci U S A. 2009;106:9362–7.
16. Sivakumaran S, Agakov F, Theodoratou E, Prendergast JG, Zgaga L, Manolio T, Rudan I, McKeigue P, Wilson JF, Campbell H. Abundant pleiotropy in human complex diseases and traits. Am J Hum Genet. 2011;89:607–18.
17. Welter D, MacArthur J, Morales J, Burdett T, Hall P, Junkins H, Klemm A, Flicek P, Manolio T, Hindorff L, Parkinson H. The NHGRI GWAS Catalog, a curated resource of SNP-trait associations. Nucleic Acids Res. 2014;42:D1001–6.
18. Zheng HF, Tobias JH, Duncan E, Evans DM, Eriksson J, Paternoster L, Yerges-Armstrong LM, Lehtimaki T, Bergstrom U, Kahonen M, Leo PJ, Raitakari O, Laaksonen M, Nicholson GC, Viikari J, Ladouceur M, Lyytikainen LP, Medina-Gomez C, Rivadeneira F, Prince RL, Sievanen H, Leslie WD, Mellstrom D, Eisman JA, Moverare-Skrtic S, Goltzman D, Hanley DA, Jones G, St Pourcain B, Xiao Y, Timpson NJ, Smith GD, Reid IR, Ring SM, Sambrook PN, Karlsson M, Dennison EM, Kemp JP, Danoy P, Sayers A, Wilson SG, Nethander M, McCloskey E, Vandenput L, Eastell R, Liu J, Spector T, Mitchell BD, Streeten EA, Brommage R, Pettersson-Kymmer U, Brown MA, Ohlsson C, Richards JB, Lorentzon M. WNT16 influences bone mineral density, cortical bone thickness, bone strength, and osteoporotic fracture risk. PLoS Genet. 2012;8:e1002745.
19. Koller DL, Zheng HF, Karasik D, Yerges-Armstrong L, Liu CT, McGuigan F, Kemp JP, Giroux S, Lai D, Edenberg HJ, Peacock M, Czerwinski SA, Choh AC, McMahon G, St Pourcain B, Timpson NJ, Lawlor DA, Evans DM, Towne B, Blangero J, Carless MA, Kammerer C, Goltzman D, Kovacs CS, Prior JC, Spector TD, Rousseau F, Tobias JH, Akesson K, Econs MJ, Mitchell BD, Richards JB, Kiel DP, Foroud T. Meta-analysis of genome-wide studies identifies WNT16 and ESR1 SNPs associated with bone mineral density in premenopausal women. J Bone Miner Res. 2013;28:547–58.
20. Karasik D, Hsu YH, Zhou Y, Cupples LA, Kiel DP, Demissie S. Genome-wide pleiotropy of osteoporosis-related phenotypes: the Framingham study. J Bone Miner Res. 2010;25:1555–63.
21. Estrada K, Styrkarsdottir U, Evangelou E, Hsu YH, Duncan EL, Ntzani EE, Oei L, Albagha OM, Amin N, Kemp JP, Koller DL, Li G, Liu CT, Minster RL, Moayyeri A, Vandenput L, Willner D, Xiao SM, Yerges-Armstrong LM, Zheng HF, Alonso N, Eriksson J, Kammerer CM, Kaptoge SK, Leo PJ, Thorleifsson G, Wilson SG, Wilson JF, Aalto V, Alen M, Aragaki AK, Aspelund T, Center JR, Dailiana Z, Duggan DJ, Garcia M, Garcia-Giralt N, Giroux S, Hallmans G, Hocking LJ, Husted LB, Jameson KA, Khusainova R, Kim GS, Kooperberg C, Koromila T, Kruk M, Laaksonen M, Lacroix AZ, Lee SH, Leung PC, Lewis JR, Masi L, Mencej-Bedrac S, Nguyen TV, Nogues X, Patel MS, Prezelj J, Rose LM, Scollen S, Siggeirsdottir K, Smith AV, Svensson O, Trompet S, Trummer O, van Schoor NM, Woo J, Zhu K, Balcells S, Brandi ML, Buckley BM, Cheng S, Christiansen C, Cooper C, Dedoussis G, Ford I, Frost M, Goltzman D, Gonzalez-Macias J, Kahonen M, Karlsson M, Khusnutdinova E, Koh JM, Kollia P, Langdahl BL, Leslie WD, Lips P, Ljunggren O, Lorenc RS, Marc J, Mellstrom D, Obermayer-Pietsch B, Olmos JM, Pettersson-Kymmer U, Reid DM, Riancho JA, Ridker PM, Rousseau F, Lagboom PE, Tang NL, et al. Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture. Nat Genet. 2012;44:491–501.

22. Moayyeri A, Hsu YH, Karasik D, Estrada K, Xiao SM, Nielson C, Srikanth P, Giroux S, Wilson SG, Zheng HF, Smith AV, Pye SR, Leo PJ, Teumer A, Hwang JY, Ohlsson C, McGuigan F, Minster RL, Hayward C, Olmos JM, Lyytikainen LP, Lewis JR, Swart KM, Masi L, Oldmeadow C, Holliday EG, Cheng S, van Schoor NM, Harvey NC, Kruk M, del Greco MF, Igl W, Trummer O, Grigoriou E, Luben R, Liu CT, Zhou Y, Oei L, Medina-Gomez C, Zmuda J, Tranah G, Brown SJ, Williams FM, Soranzo N, Jakobsdottir J, Siggeirsdottir K, Holliday KL, Hannemann A, Go MJ, Garcia M, Polasek O, Laaksonen M, Zhu K, Enneman AW, McEvoy M, Peel R, Sham PC, Jaworski M, Johansson A, Hicks AA, Pludowski P, Scott R, Dhonukshe-Rutten RA, van der Velde N, Kahonen M, Viikari JS, Sievanen H, Raitakari OT, Gonzalez-Macias J, Hernandez JL, Mellstrom D, Ljunggren O, Cho YS, Volker U, Nauck M, Homuth G, Volzke H, Haring R, Brown MA, McCloskey E, Nicholson GC, Eastell R, Eisman JA, Jones G, Reid IR, Dennison EM, Wark J, Boonen S, Vanderschueren D, Wu FC, Aspelund T, Richards JB, Bauer D, Hofman A, Khaw KT, Dedoussis G, Obermayer-Pietsch B, Gyllensten U, Pramstaller PP, Lorenc RS, et al. Genetic determinants of heel bone properties: genome-wide association meta-analysis and replication in the GEFOS/GENOMOS consortium. Hum Mol Genet. 2014;23:3054–68.
23. Hwang JY, Lee SH, Go MJ, Kim BJ, Kou I, Ikegawa S, Guo Y, Deng HW, Raychaudhuri S, Kim YJ, Oh JH, Kim Y, Moon S, Kim DJ, Koo H, Cha MJ, Lee MH, Yun JY, Yoo HS, Kang YA, Cho EH, Kim SW, Oh KW, Kang MI, Son HY, Kim SY, Kim GS, Han BG, Cho YS, Cho MC, Lee JY, Koh JM. Meta-analysis identifies a MECOM gene as a novel predisposing factor of osteoporotic fracture. J Med Genet. 2013;50:212–9.
24. Guo Y, Tan LJ, Lei SF, Yang TL, Chen XD, Zhang F, Chen Y, Pan F, Yan H, Liu X, Tian Q, Zhang ZX, Zhou Q, Qiu C, Dong SS, Xu XH, Guo YF, Zhu XZ, Liu SL, Wang XL, Li X, Luo Y, Zhang LS, Li M, Wang JT, Wen T, Drees B, Hamilton J, Papasian CJ, Recker RR, Song XP, Cheng J, Deng HW. Genome-wide association study identifies ALDH7A1 as a novel susceptibility gene for osteoporosis. PLoS Genet. 2010;6:e1000806.
25. Luo L, Xia W, Nie M, Sun Y, Jiang Y, Zhao J, He S, Xu L. Association of ESR1 and C6orf97 gene polymorphism with osteoporosis in postmenopausal women. Mol Biol Rep. 2014;41:3235–43.
26. Medina-Gomez C, Kemp JP, Estrada K, Eriksson J, Liu J, Reppe S, Evans DM, Heppe DH, Vandenput L, Herrera L, Ring SM, Kruithof CJ, Timpson NJ, Zillikens MC, Olstad OK, Zheng HF, Richards JB, St Pourcain B, Hofman A, Jaddoe VW, Smith GD, Lorentzon M, Gautvik KM, Uitterlinden AG, Brommage R, Ohlsson C, Tobias JH, Rivadeneira F. Meta-analysis of genome-wide scans for total body BMD in children and adults reveals allelic heterogeneity and age-specific effects at the WNT16 locus. PLoS Genet. 2012;8:e1002718.
27. Liu YJ, Zhang L, Papasian CJ, Deng HW. Genome-wide association studies for osteoporosis: a 2013 update. J Bone Metab. 2014;21:99–116.
28. Oei L, Estrada K, Duncan EL, Christiansen C, Liu CT, Langdahl BL, Obermayer-Pietsch B, Riancho JA, Prince RL, van Schoor NM, McCloskey E, Hsu YH, Evangelou E, Ntzani E, Evans DM, Alonso N, Husted LB, Valero C, Hernandez JL, Lewis JR, Kaptoge SK, Zhu K, Cupples LA, Medina-Gomez C, Vandenput L, Kim GS, Hun Lee S, Castano-Betancourt MC, Oei EH, Martinez J, Daroszewska A, van der Klift M, Mellstrom D, Herrera L, Karlsson MK, Hofman A, Ljunggren O, Pols HA, Stolk L, van Meurs JB, Ioannidis JP, Zillikens MC, Lips P, Karasik D, Uitterlinden AG, Styrkarsdottir U, Brown MA, Koh JM, Richards JB, Reeve J, Ohlsson C, Ralston SH, Kiel DP, Rivadeneira F. Genome-wide association study for radiographic vertebral fractures: a potential role for the 16q24 BMD locus. Bone. 2014;59:20–7.
29. Oei L, Hsu YH, Styrkarsdottir U, Eussen BH, de Klein A, Peters MJ, Halldorsson B, Liu CT, Alonso N, Kaptoge SK, Thorleifsson G, Hallmans G, Hocking LJ, Husted LB, Jameson KA, Kruk M, Lewis JR, Patel MS, Scollen S, Svensson O, Trompet S, van Schoor NM, Zhu K, Buckley BM, Cooper C, Ford I, Goltzman D, Gonzalez-Macias J, Langdahl BL, Leslie WD, Lips P, Lorenc RS, Olmos JM, Pettersson-Kymmer U, Reid DM, Riancho JA, Slagboom PE, Garcia-Ibarbia C, Ingvarsson T, Johannsdottir H, Luben R, Medina-Gomez C, Arp P, Nandakumar K, Palsson ST, Sigurdsson G, van Meurs JB, Zhou Y, Hofman A, Jukema JW, Pols HA, Prince RL, Cupples LA, Marshall CR, Pinto D, Sato D, Scherer SW, Reeve J, Thorsteinsdottir U, Karasik D, Richards JB, Stefansson K, Uitterlinden AG, Ralston SH, Ioannidis JP, Kiel DP, Rivadeneira F, Estrada K. A genome-wide copy number association study of osteoporotic fractures points to the 6p25.1 locus. J Med Genet. 2014;51:122–31.
30. Hill CA, Sussan TE, Reeves RH, Richtsmeier JT. Complex contributions of Ets2 to craniofacial and thymus phenotypes of trisomic "Down syndrome" mice. Am J Med Genet A. 2009;149A:2158–65.
31. Fox KM, Cummings SR, Powell-Threets K, Stone K. Family history and risk of osteoporotic fracture. Study of Osteoporotic Fractures Research Group. Osteoporos Int. 1998;8:557–62.
32. Liu CT, Estrada K, Yerges-Armstrong LM, Amin N, Evangelou E, Li G, Minster RL, Carless MA, Kammerer CM, Oei L, Zhou Y, Alonso N, Dailiana Z, Eriksson J, Garcia-Giralt N, Giroux S, Husted LB, Khusainova RI, Koromila T, Kung AW, Lewis JR, Masi L, Mencej-Bedrac S, Nogues X, Patel MS, Prezelj J, Richards JB, Sham PC, Spector T, Vandenput L, Xiao SM, Zheng HF, Zhu K, Balcells S, Brandi ML, Frost M, Goltzman D, Gonzalez-Macias J, Karlsson M, Khusnutdinova EK, Kollia P, Langdahl

BL, Ljunggren O, Lorentzon M, Marc J, Mellstrom D, Ohlsson C, Olmos JM, Ralston SH, Riancho JA, Rousseau F, Urreizti R, Van Hul W, Zarrabeitia MT, Castano-Betancourt M, Demissie S, Grundberg E, Herrera L, Kwan T, Medina-Gomez C, Pastinen T, Sigurdsson G, Thorleifsson G, Vanmeurs JB, Blangero J, Hofman A, Liu Y, Mitchell BD, O'Connell JR, Oostra BA, Rotter JI, Stefansson K, Streeten EA, Styrkarsdottir U, Thorsteinsdottir U, Tylavsky FA, Uitterlinden A, Cauley JA, Harris TB, Ioannidis JP, Psaty BM, Robbins JA, Zillikens MC, Vanduijn CM, Prince RL, Karasik D, Rivadeneira F, Kiel DP, Cupples LA, Hsu YH. Assessment of gene-by-sex interaction effect on bone mineral density. J Bone Miner Res. 2012;27:2051–64.

33. Styrkarsdottir U, Cazier JB, Kong A, Rolfsson O, Larsen H, Bjarnadottir E, Johannsdottir VD, Sigurdardottir MS, Bagger Y, Christiansen C, Reynisdottir I, Grant SF, Jonasson K, Frigge ML, Gulcher JR, Sigurdsson G, Stefansson K. Linkage of osteoporosis to chromosome 20p12 and association to BMP2. PLoS Biol. 2003;1:E69.
34. Sonoda T, Takada J, Iba K, Asakura S, Yamashita T, Mori M. Interaction between ESRalpha polymorphisms and environmental factors in osteoporosis. J Orthop Res. 2012;30:1529–34.
35. Eriksson J, Evans DS, Nielson CM, Shen J, Srikanth P, Hochberg M, McWeeney S, Cawthon PM, Wilmot B, Zmuda J, Tranah G, Mirel DB, Challa S, Mooney M, Crenshaw A, Karlsson M, Mellstrom D, Vandenput L, Orwoll E, Ohlsson C. Limited clinical utility of a genetic risk score for the prediction of fracture risk in elderly subjects. J Bone Miner Res. 2014;30(1):184–94.
36. Paternoster L, Lorentzon M, Lehtimaki T, Eriksson J, Kahonen M, Raitakari O, Laaksonen M, Sievanen H, Viikari J, Lyytikainen LP, Mellstrom D, Karlsson M, Ljunggren O, Grundberg E, Kemp JP, Sayers A, Nethander M, Evans DM, Vandenput L, Tobias JH, Ohlsson C. Genetic determinants of trabecular and cortical volumetric bone mineral densities and bone microstructure. PLoS Genet. 2013;9:e1003247.
37. Richards JB, Zheng HF, Spector TD. Genetics of osteoporosis from genome-wide association studies: advances and challenges. Nat Rev Genet. 2012;13:576–88.
38. Fenger M. Next generation genetics. Front Genet. 2014;5:322.
39. Ackert-Bicknell CL, Karasik D. Impact of the environment on the skeleton: is it modulated by genetic factors? Curr Osteoporos Rep. 2013;11(3):219–28.
40. Saarinen A, Mayranpaa MK, Lehesjoki AE, Makitie O. Low-density lipoprotein receptor-related protein 5 (LRP5) variation in fracture prone children. Bone. 2010;46:940–5.
41. McGuigan F, Kumar J, Ivaska KK, Obrant KJ, Gerdhem P, Akesson K. Osteocalcin gene polymorphisms influence concentration of serum osteocalcin and enhance fracture identification. J Bone Miner Res. 2010;25:1392–9.
42. Koromila T, Georgoulias P, Dailiana Z, Ntzani EE, Samara S, Chassanidis C, Aleporou-Marinou V, Kollia P. CER1 gene variations associated with bone mineral density, bone markers, and early menopause in postmenopausal women. Hum Genomics. 2013;7:21.
43. Hendrickx G, Boudin E, Fijałkowski I, Nielsen TL, Andersen M, Brixen K, Van Hul W. Variation in the Kozak sequence of WNT16 results in an increased translation and is associated with osteoporosis related parameters. Bone. 2014;59:57–65.
44. Becker J, Semler O, Gilissen C, Li Y, Bolz HJ, Giunta C, Bergmann C, Rohrbach M, Koerber F, Zimmermann K, de Vries P, Wirth B, Schoenau E, Wollnik B, Veltman JA, Hoischen A, Netzer C. Exome sequencing identifies truncating mutations in human SERPINF1 in autosomal-recessive osteogenesis imperfecta. Am J Hum Genet. 2011;88:362–71.
45. Fahiminiya S, Majewski J, Roughley P, Roschger P, Klaushofer K, Rauch F. Whole-exome sequencing reveals a heterozygous LRP5 mutation in a 6-year-old boy with vertebral compression fractures and low trabecular bone density. Bone. 2013;57:41–6.
46. McInerney-Leo AM, Duncan EL, Leo PJ, Gardiner B, Bradbury LA, Harris JE, Clark GR, Brown MA, Zankl A. COL1A1 C-propeptide cleavage site mutation causes high bone mass, bone fragility and jaw lesions: a new cause of gnathodiaphyseal dysplasia? Clin Genet. 2014;88(1):49–55.
47. Styrkarsdottir U, Thorleifsson G, Sulem P, Gudbjartsson DF, Sigurdsson A, Jonasdottir A, Oddsson A, Helgason A, Magnusson OT, Walters GB, Frigge ML, Helgadottir HT, Johannsdottir H, Bergsteinsdottir K, Ogmundsdottir MH, Center JR, Nguyen TV, Eisman JA, Christiansen C, Steingrimsson E, Jonasson JG, Tryggvadottir L, Eyjolfsson GI, Theodors A, Jonsson T, Ingvarsson T, Olafsson I, Rafnar T, Kong A, Sigurdsson G, Masson G, Thorsteinsdottir U, Stefansson K. Nonsense mutation in the LGR4 gene is associated with several human diseases and other traits. Nature. 2013;497:517–20.
48. Friedman E, Moran DS, Ben-Avraham D, Yanovich R, Atzmon G. Novel candidate genes putatively involved in stress fracture predisposition detected by whole-exome sequencing. Genet Res (Camb). 2014;96:e004.
49. Zheng HF, Forgetta V, Hsu YH, Estrada K, Rosello-Diez A, Leo PJ, Dahia CL, Park-Min KH, Tobias JH, Kooperberg C, Kleinman A, Styrkarsdottir U, Liu CT, Uggla C, Evans DS, Nielson CM, Walter K, Pettersson-Kymmer U, Mccarthy S, Eriksson J, Kwan T, Jhamai M, Trajanoska K, Memari Y, Min J, Huang J, Danecek P, Wilmot B, Li R, Chou WC, Moayyeri A, Mokry LE, Claussnitzer M, Cheung W, Cheng CH, Medina-Gomez C, Ge B, Chen SH, Choi K, Oei L, Fraser J, Kraaij R, Gregson CL, Hibbs MA, Paquette D, Hofman A, Wibom C, Marshall M, Tranah GJ, Gardiner BB, Cremin K, Auer P, Hsu L, Ring S, Tung JY, Thorleifsson G, Enneman AW, De Groot LC, Van Schoor NM, Van Der Velde N, Melin B, Kemp JP,

Christiansen C, Sayers A, Zhou Y, Calderari S, Van Rooij J, Carlson C, Peters U, Berlivet S, Dostie J, Uitterlinden AG, Williams SR, Farber C, Grinberg D, Haessler J, Lacroix AZ, Chasman DI, Giulianini F, Rose LM, Eisman JA, Ridker PM, Nguyen TV, Nogues X, Center JR, Garcia-Giralt N, Gudnason V, Launer LL, Mellstrom D, Vandenput L, Amin N, Karlsson MK, Van Duijn CM, Ljunggren O, Svensson O, Hallmans G, Rousseau F, Giroux S, Bussiere J, Arp PP, et al. Whole-genome sequencing identifies EN1 as a determinant of bone density and fracture. Nature. 2015;526(7571):112–7.

50. Pajala S, Era P, Koskenvuo M, Kaprio J, Viljanen A, Rantanen T. Genetic factors and susceptibility to falls in older women. J Am Geriatr Soc. 2006;54:613–8.
51. Barr R, Macdonald H, Stewart A, McGuigan F, Rogers A, Eastell R, Felsenberg D, Gluer C, Roux C, Reid DM. Association between vitamin D receptor gene polymorphisms, falls, balance and muscle power: results from two independent studies (APOSS and OPUS). Osteoporos Int. 2010;21:457–66.
52. Onder G, Capoluongo E, Danese P, Settanni S, Russo A, Concolino P, Bernabei R, Landi F. Vitamin D receptor polymorphisms and falls among older adults living in the community: results from the ilSIRENTE study. J Bone Miner Res. 2008;23:1031–6.
53. Dimitriou R, Carr IM, West RM, Markham AF, Giannoudis PV. Genetic predisposition to fracture non-union: a case control study of a preliminary single nucleotide polymorphisms analysis of the BMP pathway. BMC Musculoskelet Disord. 2011;12:44.
54. Guimarães JM, Guimarães ICDV, Duarte MEL, Vieira T, Vianna VF, Fernandes MBC, Vieira AR, Casado PL. Polymorphisms in BMP4 and FGFR1 genes are associated with fracture non-union. J Orthop Res. 2013;31:1971–9.
55. Gerstenfeld LC, Cullinane DM, Barnes GL, Graves DT, Einhorn TA. Fracture healing as a post-natal developmental process: molecular, spatial, and temporal aspects of its regulation. J Cell Biochem. 2003; 88:873–84.
56. Drissi H, Paglia DN, Alaee F, Yoshida R. Constructing the toolbox: patient-specific genetic factors of altered fracture healing. Genes Dis. 2014;1:140–8.
57. Cushman SA. Grand challenges in evolutionary and population genetics: the importance of integrating epigenetics, genomics, modeling, and experimentation. Front Genet. 2014;5:197.

Fracture Epidemiology Among Individuals 75+

9

Heike A. Bischoff-Ferrari

Introduction

Fractures contribute significantly to morbidity and mortality of older individuals. Approximately 75 % of all osteoporotic fractures occur among seniors age 65 and older [1], and 1 in 2 women and 1 in 5 men age 50 are expected to sustain a fracture in their remaining life time [2].

After age 75, hip fractures are the most frequent fracture and up to 50 % of older individuals suffering a hip fracture will have permanent functional disability [3–6]. Most critical is the first year after hip fracture with 21–30 % of patients being re-admitted to acute care for any reason [6, 7], 5–8 % fracturing their other hip [6, 8], 15–34 % requiring long-term nursing home care [3–6], and up to 20 % loosing their life [3–6]. The exponential increase in hip fractures after age 75 translates into an estimated 1 in 3 women, and 1 in 6 men who will have sustained a hip fracture by their 90th decade [9]. Consequently, hip fracture account for substantial and increasing health care expenses with annual costs in the United States projected to increase from 7.2 billion in 1990 to 16 billion in 2020 [10].

This chapter reviews epidemiologic data on the rates of hip and other common fractures among older individuals. In addition, future projections, geographic, and seasonal patterns of hip and other common fractures will be summarized.

Critical for the understanding of fractures at later age is their close relationship with muscle weakness [11] and falling [6, 12, 13]. Thus, at the beginning of this chapter, the epidemiology of falls, and their importance in regard to fracture risk among older individuals is being reviewed.

Falls and Why They Need to be Addressed for Optimal Fracture Prevention Among Older Individuals

With a focus on fractures at age 70+ in this chapter, falling is essential to take into consideration [13]. The primary risk factor for a hip fracture is a fall, and over 90 % of all fractures occur after a fall [11]. Recurrent fallers may have close to a four-fold increased odds of sustaining a fall-related fracture compared to individuals with a single fall [14]. As the number of seniors aged 65 and older is predicted to increase from 25 to 40 % by 2030 [15–19], the number of fall related fractures will increase substantially. Fall rates increase 10 % per decade, and over 30 % of all community-dwelling and 50 % of all institutionalized men and women aged 65 fall once a year [20]. Serious injuries occur with 10–15 % of

H.A. Bischoff-Ferrari, MD, DrPH
Department of Geriatrics and Aging Research, University Hospital Zurich and University of Zurich, Zurich, Switzerland
e-mail: Heike.Bischoff@usz.ch

G. Duque, D.P. Kiel (eds.), *Osteoporosis in Older Persons: Advances in Pathophysiology and Therapeutic Approaches*, DOI 10.1007/978-3-319-25976-5_9

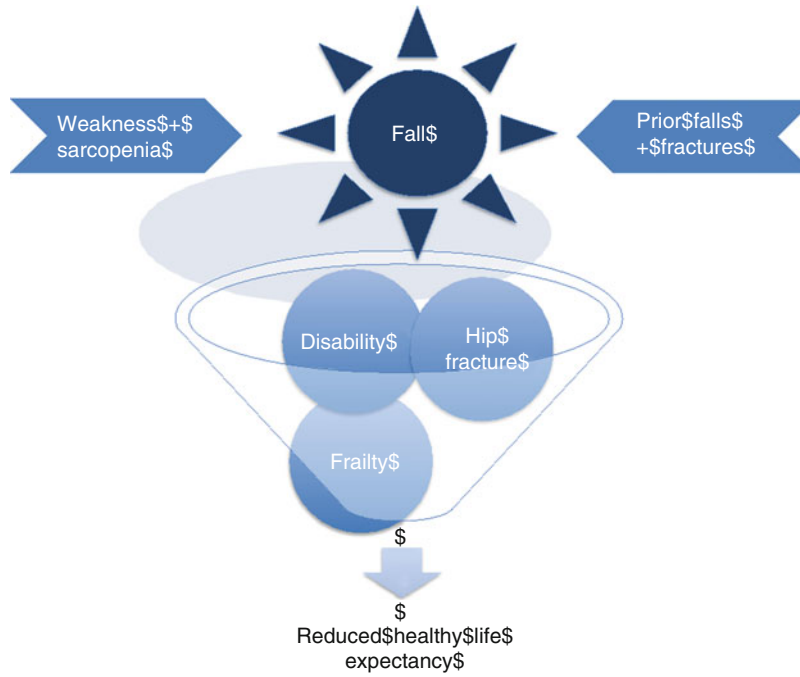
falls [12], resulting in fractures in 5 % and hip fracture in 1–2 %.

Falls are multi-factorial [13, 20, 21], however, key contributors to the risk of falling and their consequences are muscle weakness and sarcopenia [22], as well as prior falls and fractures [23]. As an independent determinant of functional decline and disability [24] and primary risk factor of hip fractures [11], falls are a hallmark of frailty, lead to 40 % of all nursing home admissions (loss of autonomy) [4] and thereby reduce healthy life expectancy (see Graph 9.1).

Because of the increasing proportion of older individuals, annual costs from all fall-related injuries in the United States in persons 65 years or older are projected to increase from $20.3 billion in 1994 to $32.4 billion in 2020 [25]. Thus interventions that reduce the risk and thereby consequences of falls, such as fractures, may have substantial public health value.

Mechanistically, the circumstances [26] and the direction [27] of a fall determine the type of fracture, whereas bone density and factors that attenuate a fall, such as better strength or better padding, critically determine whether a fracture will take place when the faller lands on a certain bone [28]. Consistent with the understanding that factors unrelated to bone are at play in fracture epidemiology, the circumstances of different fractures are strikingly different. Hip fractures tend to occur in less active individuals falling indoors from a standing height with little forward momentum, and they tend to fall sideways or straight down on their hip [29–31]. On the other hand, other non-vertebral fractures, such as distal forearm or humerus fractures tend to occur among more active older individuals who are correspondingly more likely to be outdoors and have a greater forward momentum when they fall [32–34].

Even if bone is the primary target, falling may indirectly affect bone density through increased immobility from self-restriction of activities [35]. It is well known that falls may lead to psychological trauma known as fear of falling [36]. In a recent survey among community-dwelling older persons, 13 % of men and 21 % of women aged 66–70 years old are reported to be moderately or very fearful of falling [36]. After their first fall, about 30 % of persons develop fear of falling [35]



Graph 9.1 Relevance of falls

resulting in self-restriction of activities [35], increasing immobility, and decreased quality of life [36]. Challenging for the assessment of falls is that falls tend to be forgotten if not associated with significant injury [37], requiring short periods of follow-up.

Thus, for optimal fracture prevention, both muscle and bone health need attention [6, 28, 38, 39]. Notably, the world wide promotion of fracture liason services for the secondary prevention of fractures build on fall prevention as a key component [40].

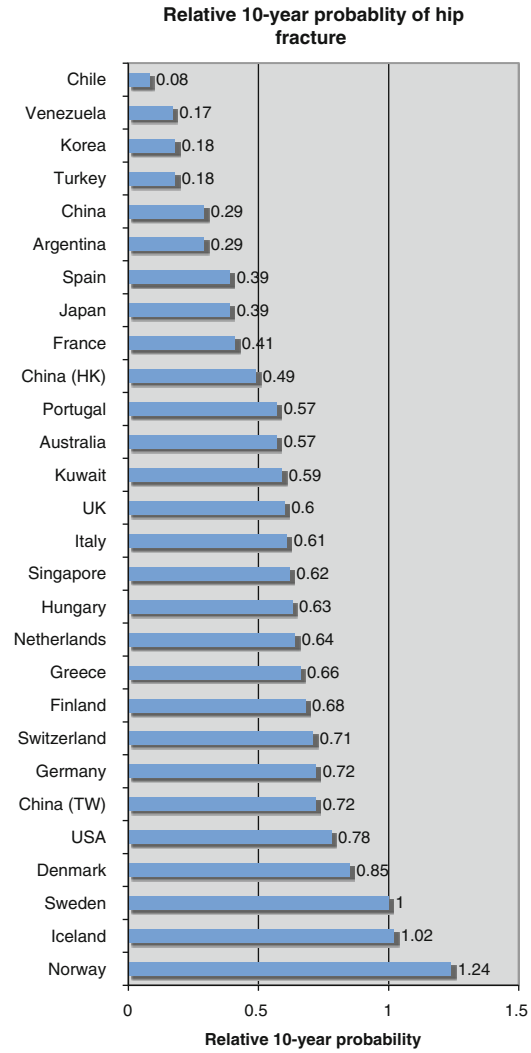
Site-Specific Fracture Epidemiology Among Older Individuals

Hip Fractures

Hip fractures are the most common fractures among white and black individuals age 75 and older [41, 42]. Future projections indicate that hip fractures increase in many countries [43]. By 2050 the worldwide incidence in hip fractures is expected to increase by 240 % among women and 310 % among men [43].

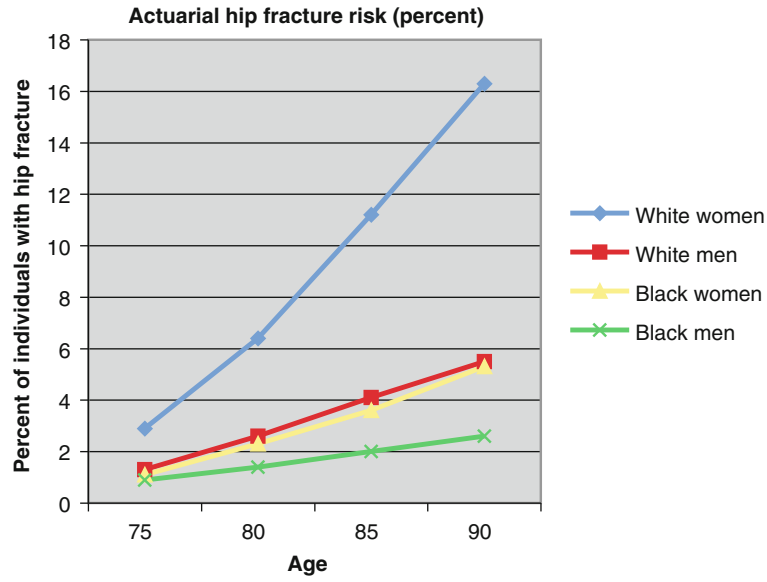
Assuming no change in the age- and sex-specific incidence, the number of hip fractures are estimated to double by the year of 2025, and more than triple by the year 2050. Most pronounced increases are expected for Asia, where in 1990 26 % of all hip fractures occurred. In 2025 it has been predicted that 37 % of all hip fractures occur in Asia, with a further increase in 2050 with 45 %. 10-Year hip fracture probability varies world-wide and is shown in Graph 9.2 according to Kanis JA et al. [44]. This is in part explained by increased life expectancy plus the expected demographic changes with a significant rise of the oldest and frailest segment of the population [16].

Within different countries and race/ethnicity groups hip fracture risk increases exponentially with age. Graph 9.3 gives US population-based data on the actuarial risk of hip fracture among individuals with age 65 (Medicare recipients) according to Barrett et al [41]. In addition, hip fracture rates vary considerably by gender and



Graph 9.2 World-wide comparison of hip fracture probability standardized to Sweden (Adapted from Kanis et al. (© American Society of Bone and Mineral Research) [44]) Standardized to Swedish hip fracture data, within Europe the highest 10-year hip fracture probability is observed in Norway, followed by Iceland

type of dwelling [45] and based on selection criteria from randomized controlled trials. The highest hip fracture rates were observed in the placebo group of vitamin D trials among nursing home residents. Table 9.1 shows calculated hip fracture rates among older individuals per 10,000 person-years based on different cohort studies, as well as the placebo groups from several large bisphosphonate and vitamin D trials. Based on this



Graph 9.3 Actuarial risk of hip fracture in percent of a 65 year old individual (Data is adapted from Barrett et al. [41]) More than 16 % of 65-year old white women and 5.5 % of white men, as well as 5.3 % of black women and 2.6 % of black men can expect to sustain a hip fracture by age 90. The actuarial risk takes into consideration that after age 75 death rates become substantial and reduce the number of individuals at risk for a fracture

comparison, vitamin D trial included participants at higher risk of fracture, and thereby more representative of the population at risk of hip fracture. Table 9.2 shows risk factors for hip fracture among women age 65 and older. Risk factors for hip fractures among older men include falls [38], low estradiol and low testosterone levels [61], prior fracture, and low hip bone density [27].

Other Common Non-vertebral Fractures

Apart from hip fractures, **the other two most common fractures at non-vertebral sites** are distal forearm and proximal humerus fractures, and similar to hip fractures, distal forearm (Graph 9.4) and proximal humerus fractures (Graph 9.5) show a steep increase with age [41], which is most pronounced in white women. Notably, however, the circumstances of these fractures are strikingly different compared with hip fractures. Hip fractures tend to occur in less active seniors falling indoors from a standing height with little forward momentum, and they tend to fall sideways or straight down on their hip [29–31]. On the other hand, distal forearm or humerus fractures tend to occur among more active seniors who are correspondingly more likely to be outdoors and have a greater forward momentum when they fall [32–34]. This may also explain why hip fracture incidence shows little to no seasonal change, while the winter/summer seasonal swing is pronounced in distal forearm and humerus fractures, and more so in men than in women [62] (see section on seasonality and fracture risk in this chapter).

Ankle fractures are less common than hip, forearm and humerus fractures, an their increase with age is less pronounced (see Graph 9.6).

Vertebral Fractures

Vertebral fractures cause disability, back pain [63], and decreased quality of life among older individuals [64]. Women with a first vertebral fracture, have a more than 19 % risk of developing a second vertebral fracture in the subsequent year [65], a 2.5-fold increased risk for any subsequent fracture [23], and a 2.8-fold increased mortality rate within the following 10 years [66].

Compared with hip fractures, the epidemiology of vertebral fractures is challenging with less than 30 % of vertebral fractures coming to clinical attention [42]. Based on data from Cooper and

Table 9.1 Hip fracture rates from cohort studies and clinical trials

Data source	Age	Hip fracture rates per 10,000 person-years
Cohort data		
NHANES I – men [46]	70+	37
NHANES I – women	70+	87
Framingham – men [47]		
	75–79	3.2
	80–84	6.6
	85–89	18.8
	90–94	30.6
	95+	45.5
Framingham – women		
	75–79	7.8
	80–84	15
	85–89	28.4
	90–94	43.5
	95+	70.2
Dubbo – men [48]	85+	119
Dubbo – women	85+	260
Trial data – primary prevention (all women)		
FREEDOM trial for denosumab [49] (**bone mineral density T score of less than −2.5 at the lumbar spine or total hip**)	72 (60–90)	37
HORIZON trial for zolendronate [50] (**T-score ≤ −2.5 or ≤ −1.5 with prevalent vertebral fracture**)	73 (65–89)	76
HIP trial for residronate (**T-score of < − 4.0 or T-score < − 3.0 plus a nonskeletal risk factor for hip fracture**) [51]	74 (SD ± 3)	101
HIP trial for residronate (**at least one nonskeletal risk factor for hip fracture or low bone density**) [51]	83 (SD ± 3)	124
FIT trial for alendronate (**low bone density, no fracture**) [52]	68 (SD ± 6)	26
Vitamin D trial Lips et al. [53] **Assisted living**	80 (SD ± 6)	107
Decalyos I Vitamin D trial [54] **Nursing home**	84 (SD ± 6)	523
Decalyos II Vitamin D trial [55] **Nursing home**	86 (SD ± 8)	553
Trial data secondary prevention after acute hip fracture		
Zurich hip fracture trial for vitamin D (**70 % community–dwelling, men and women within 1 week of acute hip fracture**)	84 (65–99)	520
HORIZON recurrent fracture trial for zolendronate (**100 % community–dwelling, men and women within 90 days of acute hip fracture**)	74 (50+)	164

colleagues, vertebral fractures increase exponentially after age 65 among men and women, and incidence rates for vertebral fractures project between hip and radius fractures for both genders after age 75 [42]. Graph 9.7 illustrates data from the SOF study on prevalence of vertebral fractures among women by age suggesting that 1 in 3 women will have a prevalent fracture at age 80 [60]. In regard to men, after age 80, vertebral fracture rates have been reported to be similar to those in women [67]. In fact, based on radiological deformities, data from a multi-center European study found equal sex incidence between the ages 50 and 79. The latter study further suggested a geographical variation of vertebral fractures within Europe with higher rates in Skandinavia [68].

More than 90 % of vertebral fractures in women result from mild to moderate trauma, while among men, this proportion is only 55 % [69]. Severe vertebral deformities appear to have a predilection between T10 and L1 [69]. Risk factors for a first radiographic vertebral fracture among women age 65 and older are shown in Table 9.2 [60].

Mortality After Fracture

Fractures contribute significantly to mortality at older age and mortality is highest after hip and

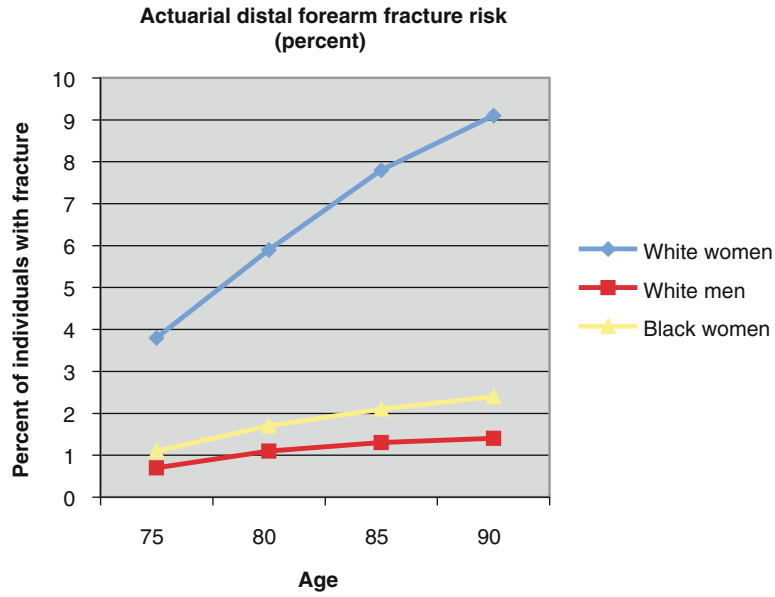
Table 9.2 Risk factors for first incident hip and radiographic vertebral fracture in women age 65 and older

Hip fracture	Radiographic vertebral fracture
Risk factors for first fracture	
Older age	Older age
Any previous fracture	Previous non-spine fracture
Low calcaneal bone density	Low bone density at all sites
No increase in weight since age 25	Low body mass index
Current smoking was not associated with risk of hip fracture	Current smoking
Low calcium intake was not associated with risk of hip fracture	Low milk consumption during pregnancy (<1 glass/day)
On feet < 4 h per day	Low levels of daily physical activity (walks < 1 block/day or < 1 h/day household chores)
(falls not considered in this model)	Having a fall
(antacid use not considered in this model)	Regular use of aluminum containing antacids
History of maternal hip fracture	**Maternal hip fracture was not associated with risk of vertebral fracture**
Tall at age 25	(Tall at age 25 not considered in this model)
Low self-rated health	**Self-rated health was not associated with risk of vertebral fracture**
Previous hyperparathyroidism	**Previous hyperparathyroidism was not associated with risk of vertebral fracture**
Current use of long-acting benzodiacepins	(long-acting benzodiacepin use not considered in this model)
Current use of anticonvulsant drugs	(anticonvulsant drug use not considered in this model)
Current caffeine intake	**Caffeine intake was not associated with risk of vertebral fracture**
Inability to rise from a chair	**Inability to rise from a chair was not associated with risk of vertebral fracture**
Resting pulse > 80 beats/min	(resting pulse not considered in this model)
Vitamin D deficiency / latitude	
Previous fall	

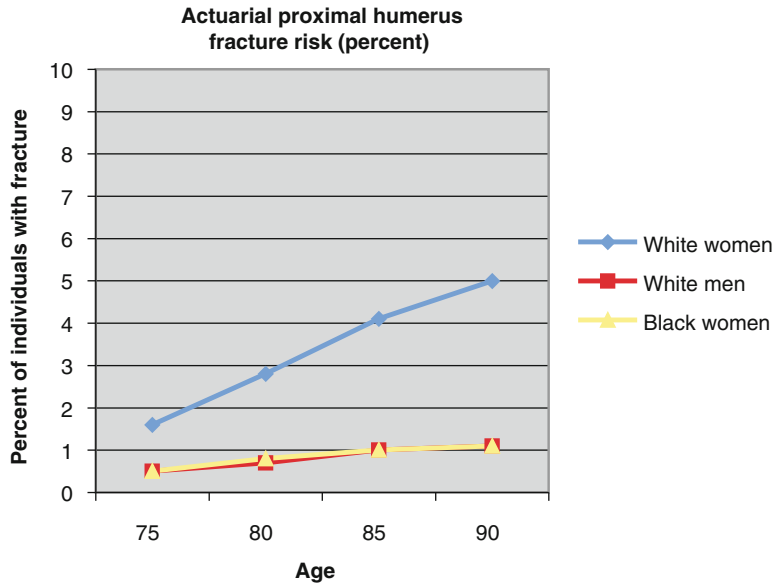
Table two summarizes and compares risk factors for hip and radiographic incident vertebral fractures assessed from the Study of Osteoporotic Fractures (SOF) among white women age 65 and older. Risk factors for both outcomes are based on multivariate analyses. Risk factors for hip fracture are adapted from Cummings et al. [11]. Hip fracture rates were 11 per 10,000 person-years among women with no more than two risk factors and normal calcaneal bone density. Hip fracture rates were 270 per 10,000 person-years among women with 5 or more risk factors plus a calcaneal bone density in the lowest third for their age. Added to the table in dark red are two established risk factors for hip fracture not assessed in the model within the SOF cohort (falls [12, 27, 38], vitamin D deficiency [56–58], and latitude away from the equator [59]). Risk factors for radiographic incident fractures are adapted from Nevitt MC et al.; Journal of Bone and Mineral Research 2005 [60]. For radiographic vertebral fractures, women in the lowest third of wrist bone density plus 5 or more risk factors had a 12-fold greater risk than women in the highest third of wrist bone density with no additional risk factors. Radiographic vertebral fracture was defined as a 20 % and at least 4-mm decrease in vertebral height

vertebral fractures [70]. Generally, the risk of death is highest in the first year following fracture compared with later time periods and among men compared with women [71].

Mortality from hip fractures has been estimated between 12 and 20 % among women in the first year after the event [5, 6] and decline thereafter [72]. Men, despite their lower incidence of hip fractures, have a two-fold higher risk of death after hip fracture compared to women [73]. The increased risk among men is still unclear. One explanation, however, has been suggested by the Baltimore Hip studies [74], where mortality rates after hip fracture were



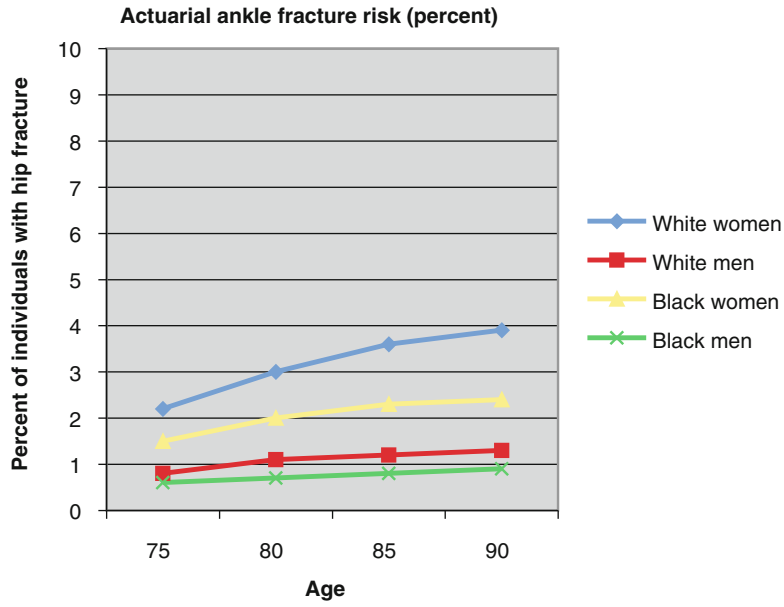
Graph 9.4 Actuarial risk of distal forearm fracture in percent of a 65 year old individual (Data is adapted from Barrett et al. [41]) More than 9 % of 65-year old white women and 1.4 % of white men, as well as 2.4 % of black women can expect to sustain a distal forearm fracture by age 90. Cases in black men were too small to explore. The actuarial risk takes into consideration that after age 75 death rates become substantial and reduce the number of individuals at risk for a fracture



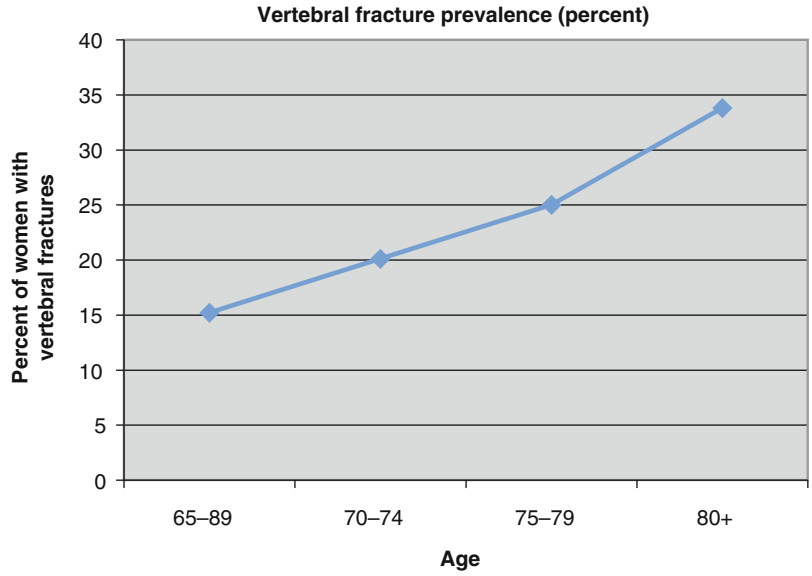
Graph 9.5 Actuarial risk of proximal humerus fracture in percent of a 65 year old individual (Data is adapted from Barrett et al. [41]) More than 5 % of 65-year old white women and 1.1 % of white men, as well as 1.1 % of black women can expect to sustain a distal forearm fracture by age 90. Cases in black men were too small to explore. The actuarial risk takes into consideration that after age 75 death rates become substantial and reduce the number of individuals at risk for a fracture

similar between men and women if deaths caused by infections were excluded. Deaths related to infections (pneumonia, influenza, and septicemia) explained the gender difference in the Baltimore cohort and the gender difference appeared to be maintained throughout the second year after hip fracture. Independent of gender, pre-existing morbidity and poor functional status have been identified as risk factors for mortality after hip fracture [75, 76].

In a Swedish cohort study [70], mortality in the first year after fracture events has been described to be 22 % for hip fractures, 6 % for forearm fractures, 13 % for shoulder fractures, and 28 % for spine fractures. Beyond the first year, mortality decreased in the subsequent years consistent with US data [71]. At 5 years, mortality was 59 % for hip fracture, 26 % for forearm fractures, 36 % for shoulder fractures, and 72 % for vertebral fractures [70].



Graph 9.6 Actuarial risk of ankle fracture in percent of a 65 year old individual (Data is adapted from Barrett et al. [41]) 3.9 % of 65-year old white women and 1.3 % of white men, as well as 2.4 % of black women and can expect to sustain a distal forearm fracture by age 90. Cases in black men were too small to explore. The actuarial risk takes into consideration that after age 75 death rates become substantial and reduce the number of individuals at risk for a fracture



Graph 9.7 Vertebral fracture prevalence by age among women (Adapted by Nevitt et al. [60]) Based on data from women of the Study of Osteoporotic Fractures (SOF) 1 in 3 will have a prevalent vertebral fracture at age 80+

Geographic and Seasonal Variations in Hip and Other Non-vertebral Fractures

Excess winter morbidity and mortality continue to be important public health problems, especially among older persons [77–79]. In addition to clear seasonal variations in respiratory [78–81] and cardiovascular diseases [82], fractures of the hip [83–89] and distal forearm [90] contribute to high winter morbidity rates in older persons.

Some studies indicate that falls due to snow and ice may play an important role in seasonality of fractures [84, 85]. One cause of the increased fracture risk in winter compared to summer may be that older persons are more likely to slip and fall during periods of snow and ice [91]. On the other hand, hip fractures, which

mostly occur indoors [29–31], may be less affected by snow and ice.

In a large population-based study from the United States, fracture rates for hip, distal forearm, proximal humerus, and ankle were higher in winter than in other seasons, although the winter peak was small for hip fractures [92]. This seasonal pattern was most evident in "warm" states that are only minimally affected by ice and snow. Furthermore, in the same study, hip fractures had strikingly different associations with weather than fractures of the distal forearm, proximal humerus, and ankle. In winter, total snowfall was associated with a reduced risk of hip fracture (−5 % per 20 in.) but an increased risk of non-hip fractures (6–12 %; $p<0.05$ at all sites). In summer, hip fracture risk tended to be lower during sunny weather (− 3 % per 2 weeks of sunny days; $p=0.13$), while there was an increased risk of the other fractures (15–20 %; $p<0.05$) in sunny weather [92].

One plausible explanation for the strikingly different seasonal and weather patterns between hip and non-hip fractures may be found in the circumstances surrounding these fractures. Hip fractures tend to occur indoors among relatively frail individuals [29–31], while the others tend to occur among more active individuals who are correspondingly more likely to be outdoors [32–34]. Clearly, weather would affect the latter group differently than the former [29]. It is likely, for example, that active individuals would expose themselves to adverse weather conditions more readily than their more frail counterparts, thus increasing their risks of ice- and snow –related falls and fractures. A possible support of this hypothesis is suggested by the subgroup analyses, in which individuals who are more likely to be frail and less active (women and individuals aged 80 years and older), had a smaller winter/summer difference in hip fracture risk than the more robust population groups (men and individuals younger than 80; see Table 9.3).

The protective association of sunshine with risk of hip fracture in the summer and fall may be due to the higher serum concentrations of 25-hydroxyvitamin D associated with sun exposure [93, 94]. Improved vitamin D status through supplementation with vitamin D may reduce the risk of falls [56], improve bone mineral density [95, 96] and reduce risk of fractures [54, 57, 58, 95] in older individuals. The benefit of sun exposure is supported by a recent review suggesting that for each 10° change in latitude from the equator (e.g., from Paris to Stockholm), fracture probability increased by 0.3 % in men, by 0.8 % in women and by 0.6 % in men and women combined [59]. On the other hand, for the fractures outside the hip, an incremental gain in vitamin D from sunlight exposure may be out-weighed by the increased risk associated with out-door activities in more active older persons in sunny weather.

Corroborating the findings on snowfall in winter being protective against hip fractures on a geographic level are studies indicating a distinct North–south gradient in hip fracture risk, with lower rates in the North of the US, where colder weather is more common [97]. At the same time, there no indication of a North–south gradient for non-hip fractures. Rather lower rates for non-hip fractures (distal forearm and proximal humerus) are found in the Western states and higher rates in the East [97]. Ankle fractures appear to have a somewhat similar pattern as distal forearm and proximal humerus, but not consistently so. All patterns appear to be similar in men and in women. Geographic variation of hip fractures have been investigated for Europe, where rates appear to be higher in the North compared to the South (Graph 9.8). This apparent inconsistency with the US pattern for hip fractures may be explained by additional genetic influences within Europe, or lower sunshine exposure with a greater distance from the equator [77].

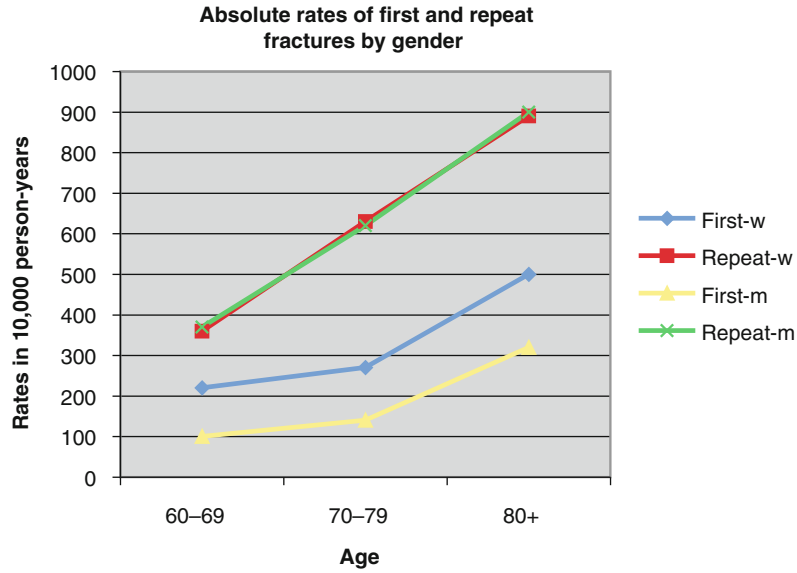
Repeat Fractures

Several large cohort studies have shown that after a first fracture, repeat fractures occur frequently, with a peak incidence in the first and tapering off after 3–5 years of the first fracture [23, 98, 99]. Based on a 16-year follow-up of the Dubbo Osteoporosis Study [23], the absolute risk for a repeat fracture increases steeply and equally in

Table 9.3 Winter/summer relative fracture risks, by fracture type in subgroups of the population

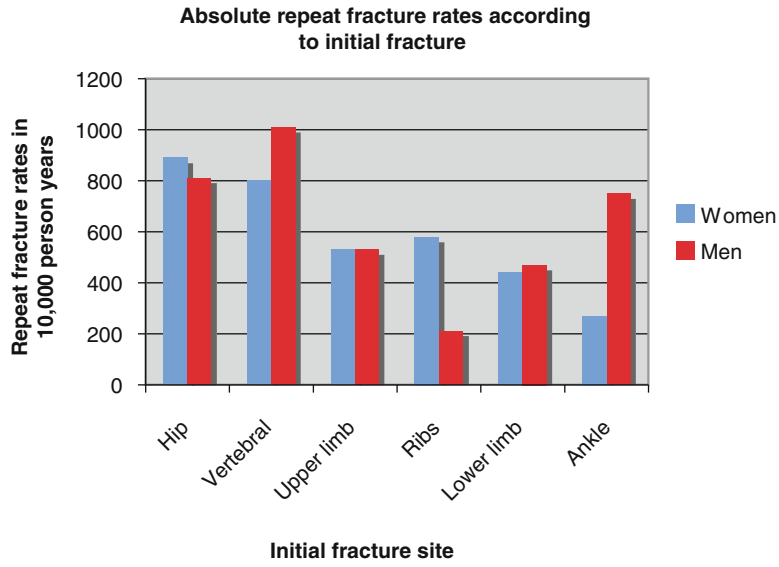
Fracture site	Winter-summer RR by gender		Winter-summer RR by age		Winter-summer RR by race	
	RR (95 % CI) Men	RR (95 % CI) Women	RR (95 % CI) Younger (65–80)	RR (95 % CI) Older (>80)	RR (95 % CI) White individuals	RR (95 % CI) Black individuals
Hip	1.15 [1.08–1.23]	1.07 [1.03–1.10]*	1.10 [1.05–1.15]	1.08 [1.04–1.12]	1.08 [1.05–1.12]	1.21 [1.03–1.42]
Distal forearm	1.51 [1.33–1.71]	1.15 [1.11–1.21]***	1.25 [1.19–1.32]	1.08 [1.00–1.16]**	1.20 [1.15–1.25]	1.05 [0.81–1.37]
Proximal humerus	1.23 [1.07–1.42]	1.19 [1.12–1.27]	1.28 [1.19–1.38]	1.10 [1.01–1.20]**	1.19 [1.12–1.26]	1.50 [1.02–2.20]
Ankle	1.25 [1.10–1.42]	1.21 [1.13–1. 29]	1.23 [1.15–1.31]	1.18 [1.04–1.34]	1.22 [1.14–1.29]	1.30 [1.01–1.68]

Adapted from Bischoff-Ferrari et al. [92]
RRs are based on Poisson Regression Models. The models by gender included age and race, the models by age included gender and race, and the model by race included gender and age. Stars indicate level of significance of difference by gender, age, and race in regard to winter-summer relative fracture risk,
*$p<0.05$; **$p<0.01$; ***$p<0.001$



Graph 9.8 Absolute rates of first and repeat fractures according to gender and age (Adapted from Center et al. [23]) "W" stands for women and "M" stands for men. The absolute risk for a first fracture increases with age in both genders with higher rates among women at all ages. Repeat fracture rates increase more steeply and are similar between men and women. Women age 80 or older have a 80 % increased risk for a repeat fracture (RR 1.80; 95 % CI 1.45–2.25). Men age 80 or older have a 2.77-fold increased risk for a repeat fracture (RR 2.77; 95 % CI 1.69–4.54)

men and women with age (see Graph 9.9) despite a lower absolute risk for a first fracture among men. The relative risk for a repeat fracture among women age 60–69, 70–79, and 80+ was 1.65 (95 % CI: 1.18–2.32), 2.36 (1.91–2.92), and 1.80 (1.45–2.25) respectively. The relative risk for a repeat fracture among men age 60–69, 70–79, and 80+ was 3.75 (2.19–6.43), 4.32 (3.00–6.21), and 2.77 (1.69–4.54) respectively. The absolute site-specific repeat fracture risk was highest for hip fracture as the incident fracture among women with a 2.79-fold increased risk for a repeat fracture (95 % CI: 2.06–3.77). Among men the incident fracture associated with the highest repeat fracture risk was a vertebral fracture with a 6.18-fold increased risk (95 % CI: 4.17–9.14). Absolute repeat fracture rates according to initial fracture site are illustrated in Graph 9.9 [23].



Graph 9.9 Absolute repeat fracture rates by initial fracture site and gender (Adapted from Center et al. [23]) Hip fractures among women and vertebral fractures among men age 60 years and older carry the highest gender-specific absolute risk for a repeat fracture

References

1. Melton 3rd LJ, Crowson CS, O'Fallon WM. Fracture incidence in Olmsted County, Minnesota: comparison of urban with rural rates and changes in urban rates over time. Osteoporos Int. 1999;9:29–37.
2. Nguyen ND, Ahlborg HG, Center JR, Eisman JA, Nguyen TV. Residual lifetime risk of fractures in women and men. J Bone Miner Res. 2007;12:12.
3. Magaziner J, Hawkes W, Hebel JR, et al. Recovery from hip fracture in eight areas of function. J Gerontol A Biol Sci Med Sci. 2000;55:M498–507.
4. Tinetti ME, Williams CS. Falls, injuries due to falls, and the risk of admission to a nursing home. N Engl J Med. 1997;337:1279–84.
5. Cummings SR, Kelsey JL, Nevitt MC, O'Dowd KJ. Epidemiology of osteoporosis and osteoporotic fractures. Epidemiol Rev. 1985;7:178–208.
6. Bischoff-Ferrari HA, Dawson-Hughes B, Platz A, et al. Effect of high-dosage cholecalciferol and extended physiotherapy on complications after hip fracture: a randomized controlled trial. Arch Intern Med. 2010;170:813–20.
7. Heyes GJ, Tucker A, Marley D, Foster A. Predictors for readmission up to 1 year following hip fracture. Arch Trauma Res. 2015;4, e27123.
8. Bischoff HA, Solomon DH, Dawson-Hughes B. Repeat hip fractures in a population-based sample of medicare recipi- ents in the US: rates, timing and gender differences. J Bone Miner Res. 2001;16 Suppl 1:291.
9. Birge SJ, Morrow-Howell N, Proctor EK. Hip fracture. Clin Geriatr Med. 1994;10:589–609.
10. Cummings SR, Rubin SM, Black D. The future of hip fractures in the United States. Numbers, costs, and potential effects of postmenopausal estrogen. Clin Orthop Relat Res. 1990;(252):163–6.
11. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med. 1995;332:767–73.
12. Fatalities and injuries from falls among older adults--United States, 1993–2003 and 2001–2005. MMWR Morb Mortal Wkly Rep. 2006;55:1221–4.
13. Bischoff-Ferrari HA. Fall prevention. Primer on the metabolic bone diseases and disorders of mineral metabolism. Clifford J Rosen (Editor-in-Chief), Roger Bouillon (Senior Associate Editor), Juliet E Compston (Senior Associate Editor), Vicki Rosen (Senior Associate Editor). 8th ed. 2013. p. 389.
14. Pluijm SM, Smit JH, Tromp EA, et al. A risk profile for identifying community-dwelling elderly with a high risk of recurrent falling: results of a 3-year prospective study. Osteoporos Int. 2006;17:417–25. Epub 2006 Jan 17.
15. EC. European economy: Special Report n° 1/2006. European commission, directorate-general for economic and financial affairs. http://ec.europa.eu/economy_finance/publications/publication423_en.pdf
16. Eberstadt N, Groth H. Europe's coming demographic challenge: unlocking the value of health. Washington, DC: American Enterprise Institute for Health Policy Research; 2007.
17. Europe Co. Recent demographic developments in Europe 2005. Strasbourg: European population Committee of the Council of Europe; 2006.
18. Eurostat. First demographic estimates for 2005: statistics in focus. http://epp.eurostat.ec.europa.eu/cache/ITY_OFFPUB/KS-NK-06-001/EN/KS-NK-06-001-ENPDF. 2006.

19. Lee RD. Global population aging and its economic consequences. Washington, DC: AEI Press; 2007.
20. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. N Engl J Med. 1988;319:1701–7.
21. Tinetti ME, Doucette J, Claus E, Marottoli R. Risk factors for serious injury during falls by older persons in the community. J Am Geriatr Soc. 1995;43:1214–21.
22. Bischoff-Ferrari HA, Orav JE, Kanis JA, et al. Comparative performance of current definitions of sarcopenia against the prospective incidence of falls among community-dwelling seniors age 65 and older. Osteoporos Int. 2015;26:2793–802.
23. Center JR, Bliuc D, Nguyen TV, Eisman JA. Risk of subsequent fracture after low-trauma fracture in men and women. JAMA. 2007;297:387–94.
24. Tinetti ME, Williams CS. The effect of falls and fall injuries on functioning in community-dwelling older persons. J Gerontol A Biol Sci Med Sci. 1998;53:M112–9.
25. Englander F, Hodson TJ, Terregrossa RA. Economic dimensions of slip and fall injuries. J Forensic Sci. 1996;41:733–46.
26. Cummings SR, Nevitt MC. Non-skeletal determinants of fractures: the potential importance of the mechanics of falls. Study of Osteoporotic Fractures Research Group. Osteoporos Int. 1994;4 Suppl 1:67–70.
27. Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV. Development of a nomogram for individualizing hip fracture risk in men and women. Osteoporos Int. 2007;17:17.
28. Nevitt MC, Cummings SR. Type of fall and risk of hip and wrist fractures: the study of osteoporotic fractures. The Study of Osteoporotic Fractures Research Group. J Am Geriatr Soc. 1993;41:1226–34.
29. Nevitt MC, Cummings SR. Type of fall and risk of hip and wrist fractures: the study of osteoporotic fractures. J Am Geriatr Soc. 1994;42:909.
30. Carter SE, Campbell EM, Sanson-Fisher RW, Gillespie WJ. Accidents in older people living at home: a community-based study assessing prevalence, type, location and injuries. Aust N Z J Public Health. 2000;24:633–6.
31. Campbell AJ, Borrie MJ, Spears GF, Jackson SL, Brown JS, Fitzgerald JL. Circumstances and consequences of falls experienced by a community population 70 years and over during a prospective study. Age Ageing. 1990;19:136–41.
32. O'Neill TW, Marsden D, Adams JE, Silman AJ. Risk factors, falls, and fracture of the distal forearm in Manchester, UK. J Epidemiol Community Health. 1996;50:288–92.
33. Graafmans WC, Ooms ME, Bezemer PD, Bouter LM, Lips P. Different risk profiles for hip fractures and distal forearm fractures: a prospective study. Osteoporos Int. 1996;6:427–31.
34. Keegan TH, Kelsey JL, King AC, Quesenberry Jr CP, Sidney S. Characteristics of fallers who fracture at the foot, distal forearm, proximal humerus, pelvis, and shaft of the tibia/fibula compared with fallers who do not fracture. Am J Epidemiol. 2004;159:192–203.
35. Vellas BJ, Wayne SJ, Romero LJ, Baumgartner RN, Garry PJ. Fear of falling and restriction of mobility in elderly fallers. Age Ageing. 1997;26:189–93.
36. Arfken CL, Lach HW, Birge SJ, et al. The prevalence and correlates of fear of falling in elderly persons living in the community. The relationship between fear of falling, activities of daily living and quality of life among elderly individuals. Fear of falling and restriction of mobility in elderly fallers. Am J Public Health. 1994;84:565–70.
37. Cummings SR, Nevitt MC, Kidd S. Forgetting falls. The limited accuracy of recall of falls in the elderly. J Am Geriatr Soc. 1988;36:613–6.
38. Lewis CE, Ewing SK, Taylor BC, et al. Predictors of non-spine fracture in elderly men: the MrOS study. J Bone Miner Res. 2007;22:211–9.
39. Stone KL, Ewing SK, Lui LY, et al. Self-reported sleep and nap habits and risk of falls and fractures in older women: the study of osteoporotic fractures. J Am Geriatr Soc. 2006;54:1177–83.
40. Bischoff-Ferrari HA. In three steps to unbreakable bones. IOF report World Osteoporosis Report 2011. 2011; http://www.iofbonehealth.org/sites/default/files/PDFs/WODReports/WOD11_Report.pdf.
41. Barrett JA, Baron JA, Karagas MR, Beach ML. Fracture risk in the U.S. Medicare population. J Clin Epidemiol. 1999;52:243–9.
42. Cooper C, Melton 3rd LJ. Epidemiology of osteoporosis. Trends Endocrinol Metab. 1992;314:224–9.
43. Gullberg B, Johnell O, Kanis JA. World-wide projections for hip fracture. Osteoporos Int. 1997; 7:407–13.
44. Kanis JA, Johnell O, De Laet C, Jonsson B, Oden A, Ogelsby AK. International variations in hip fracture probabilities: implications for risk assessment. J Bone Miner Res. 2002;17:1237–44.
45. Finsterwald M, Sidelnikov E, Orav EJ, et al. Gender-specific hip fracture risk in community-dwelling and institutionalized seniors age 65 years and older. Osteoporos Int. 2014;25:167–76.
46. Looker AC, Harris TB, Madans JH, Sempos CT. Dietary calcium and hip fracture risk: the NHANES I Epidemiologic Follow-Up Study. Osteoporos Int. 1993;3:177–84.
47. Samelson EJ, Zhang Y, Kiel DP, Hannan MT, Felson DT. Effect of birth cohort on risk of hip fracture: age-specific incidence rates in the Framingham Study. Am J Public Health. 2002;92:858–62.
48. Chang KP, Center JR, Nguyen TV, Eisman JA. Incidence of hip and other osteoporotic fractures in elderly men and women: Dubbo Osteoporosis Epidemiology Study. J Bone Miner Res. 2004;19:532–6.
49. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361:756–65.

50. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356:1809–22.
51. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med. 2001;344:333–40.
52. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA. 1998;280:2077–82.
53. Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. Ann Intern Med. 1996;124:400–6.
54. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. N Engl J Med. 1992;327:1637–42.
55. Chapuy MC, Pamphile R, Paris E, et al. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. Osteoporos Int. 2002;13:257–64.
56. Bischoff-Ferrari HA, Dawson-Hughes B, Willett CW, et al. Effect of vitamin D on falls: a meta-analysis. JAMA. 2004;291:1999–2006.
57. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ. 2003;326:469.
58. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA. 2005;293:2257–64.
59. Johnell O, Borgstrom F, Jonsson B, Kanis J. Latitude, socioeconomic prosperity, mobile phones and hip fracture risk. Osteoporos Int. 2007;18:333–7.
60. Nevitt MC, Cummings SR, Stone KL, et al. Risk factors for a first-incident radiographic vertebral fracture in women > or = 65 years of age: the study of osteoporotic fractures. J Bone Miner Res. 2005;20:131–40.
61. Amin S, Zhang Y, Felson DT, et al. Estradiol, testosterone, and the risk for hip fractures in elderly men from the Framingham Study. Am J Med. 2006;119:426–33.
62. Bischoff-Ferrari HA, Orav JE, Barrett JA, Baron JA. Effect of seasonality and weather on fracture risk in individuals 65 years and older. Osteoporos Int. 2007;18:1225–33.
63. Nevitt MC, Ettinger B, Black DM, et al. The association of radiographically detected vertebral fractures with back pain and function: a prospective study. Ann Intern Med. 1998;128:793–800.
64. Silverman SL, Minshall ME, Shen W, Harper KD, Xie S. The relationship of health-related quality of life to prevalent and incident vertebral fractures in postmenopausal women with osteoporosis: results from the Multiple Outcomes of Raloxifene Evaluation Study. Arthritis Rheum. 2001;44:2611–9.
65. Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. JAMA. 2001;285:320–3.
66. Hasserius R, Karlsson MK, Jonsson B, Redlund-Johnell I, Johnell O. Long-term morbidity and mortality after a clinically diagnosed vertebral fracture in the elderly--a 12- and 22-year follow-up of 257 patients. Calcif Tissue Int. 2005;76:235–42.
67. Praemer A, Furner S, Rice DP. Musculoskeletal conditions in the United States. Rosemont: American Academy of Orthopedic Surgeons; 1992. p. 145–70.
68. O'Neill TW, Felsenberg D, Varlow J, Cooper C, Kanis JA, Silman AJ. The prevalence of vertebral deformity in European men and women: the European Vertebral Osteoporosis Study. J Bone Miner Res. 1996;11:1010–8.
69. Melton 3rd LJ, Lane AW, Cooper C, Eastell R, O'Fallon WM, Riggs BL. Prevalence and incidence of vertebral deformities. Osteoporos Int. 1993;3:113–9.
70. Johnell O, Kanis JA, Oden A, et al. Mortality after osteoporotic fractures. Osteoporos Int. 2004;15:38–42.
71. Melton 3rd LJ, Achenbach SJ, Atkinson EJ, Therneau TM, Amin S. Long-term mortality following fractures at different skeletal sites: a population-based cohort study. Osteoporos Int. 2013;24:1689–96.
72. Melton 3rd LJ, Therneau TM, Larson DR. Long-term trends in hip fracture prevalence: the influence of hip fracture incidence and survival. Osteoporos Int. 1998;8:68–74.
73. Myers AH, Robinson EG, Van Natta ML, Michelson JD, Collins K, Baker SP. Hip fractures among the elderly: factors associated with in-hospital mortality. Am J Epidemiol. 1991;134:1128–37.
74. Wehren LE, Hawkes WG, Orwig DL, Hebel JR, Zimmerman SI, Magaziner J. Gender differences in mortality after hip fracture: the role of infection. J Bone Miner Res. 2003;18:2231–7.
75. Lyons AR. Clinical outcomes and treatment of hip fractures. Am J Med. 1997;103:51S–63; discussion S-4S.
76. Browner WS, Pressman AR, Nevitt MC, Cummings SR. Mortality following fractures in older women. The study of osteoporotic fractures. Arch Intern Med. 1996;156:1521–5.
77. Douglas AS, Allan TM, Rawles JM. Composition of seasonality of disease. Scott Med J. 1991;36:76–82.
78. Wilkinson P, Pattenden S, Armstrong B, et al. Vulnerability to winter mortality in elderly people in Britain: population based study. BMJ. 2004;17:17.
79. Wilkinson P, Pattenden S, Armstrong B, et al. Vulnerability to winter mortality in elderly people in Britain: population based study. BMJ. 2004;329:647. Epub 2004 Aug 17.
80. Lieberman D, Friger MD. Seasonal variation in hospital admissions for community-acquired pneumonia: a 5-year study. J Infect. 1999;39:134–40.

81. Vilkman S, Keistinen T, Tuuponen T, Kivela SL. Seasonal variation in hospital admissions for chronic obstructive pulmonary disease in Finland. Arctic Med Res. 1996;55:182–6.
82. Spencer FA, Goldberg RJ, Becker RC, Gore JM. Seasonal distribution of acute myocardial infarction in the second National Registry of Myocardial Infarction. J Am Coll Cardiol. 1998;31:1226–33.
83. Jacobsen SJ, Sargent DJ, Atkinson EJ, O'Fallon WM, Melton 3rd LJ. Population-based study of the contribution of weather to hip fracture seasonality. Am J Epidemiol. 1995;141:79–83.
84. Bulajic-Kopjar M. Seasonal variations in incidence of fractures among elderly people. Inj Prev. 2000;6:16–9.
85. Hemenway D, Colditz GA. The effect of climate on fractures and deaths due to falls among white women. Accid Anal Prev. 1990;22:59–65.
86. Jacobsen SJ, Goldberg J, Miles TP, Brody JA, Stiers W, Rimm AA. Seasonal variation in the incidence of hip fracture among white persons aged 65 years and older in the United States, 1984–1987. Am J Epidemiol. 1991;133:996–1004.
87. Lau EM, Gillespie BG, Valenti L, O'Connell D. The seasonality of hip fracture and its relationship with weather conditions in New South Wales. Aust J Public Health. 1995;19:76–80.
88. Mannius S, Mellstrom D, Oden A, Rundgren A, Zetterberg C. Incidence of hip fracture in western Sweden 1974–1982. Comparison of rural and urban populations. Acta Orthop Scand. 1987;58:38–42.
89. Zetterberg C, Andersson GB. Fractures of the proximal end of the femur in Goteborg, Sweden, 1940–1979. Acta Orthop Scand. 1982;53:419–26.
90. Jacobsen SJ, Sargent DJ, Atkinson EJ, O'Fallon WM, Melton 3rd LJ. Contribution of weather to the seasonality of distal forearm fractures: a population-based study in Rochester, Minnesota. Osteoporos Int. 1999;9:254–9.
91. Ralis ZA. Epidemic of fractures during period of snow and ice. Br Med J (Clin Res Ed). 1981; 282:603–5.
92. Bischoff-Ferrari HA, Orav JE, Barrett JA, Baron JA. Effect of seasonality and weather on fracture risk in individuals 65 years and older. Osteoporos Int. 2007;24:24.
93. Holick MF. The photobiology of vitamin D and its consequences for humans. Ann N Y Acad Sci. 1985;453:1–13.
94. Harris SS, Dawson-Hughes B. Seasonal changes in plasma 25-hydroxyvitamin D concentrations of young American black and white women. Am J Clin Nutr. 1998;67:1232–6.
95. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med. 1997;337:670–6.
96. Bischoff-Ferrari HA, Zhang Y, Kiel DP, Felson DT. Positive association between serum 25-hydroxyvitamin D level and bone density in osteoarthritis. Arthritis Rheum. 2005;53:821–6.
97. Karagas MR, Baron JA, Barrett JA, Jacobsen SJ. Patterns of fracture among the United States elderly: geographic and fluoride effects. Ann Epidemiol. 1996;6:209–16.
98. van Geel TA, van Helden S, Geusens PP, Winkens B, Dinant GJ. Clinical subsequent fractures cluster in time after first fractures. Ann Rheum Dis. 2009;68:99–102.
99. van Geel TA, Huntjens KM, van den Bergh JP, Dinant GJ, Geusens PP. Timing of subsequent fractures after an initial fracture. Curr Osteoporos Rep. 2010;8:118–22.

Falls as a Geriatric Syndrome: Mechanisms and Risk Identification

10

Manuel M. Montero-Odasso

"It takes a child one year to acquire independent movement and ten years to acquire independent mobility. An old person can lose both in a day Bernard Isaacs". [1]

Introduction

This quote from the late Bernard Isaacs, now four decades after being written, still portrays the crude consequence an older adult may experience after a single fall [1]. Falls, as a geriatric syndrome, certainly affect independent movement and mobility in older adults. Despite the enormous efforts of researchers and clinicians to comprehend the complexity of falls, there is still a significant gap in our complete understanding of this challenging syndrome. The aim of this chapter is to reduce this gap, address new areas of knowledge, including the role of certain aspect of cognition in falls mechanisms, and provide a rationale for the integration of a falls and fractures risk assessment into research on the emerging problem of osteoporosis in older populations.

Falls and fall-induced injuries in older people is a worldwide problem with substantial clinical and public health implications. They are both associated with advancing age and an increased risk of disability, dependency, premature nursing home admission, and mortality [2]. First described almost 40 years ago in context of the geriatric syndrome "instability," falls have become increasingly important in recent years [3]. A fall is defined as "an unintentional change in position resulting in coming to rest at a lower level or on the ground" [4]. Syncopal events, loss of consciousness due to seizures or acute stroke are not included in the fall definition, although they can also present as an episode of instability and a change of position to a lower level [5, 6]. While falls can have multiple and diverse aetiologies, they generally share similar risk factors as they frequently result from the accumulated effect of impairments in multiple systems. Therefore, an intelligent approach to addressing this complex problem must first take into consideration the most likely causes, contributing factors, and associated comorbidities. Since falls and fractures in older adults have an entangled relationship, a characterization of the risk factors for fractures must be also considered in this joint approach.

M.M. Montero-Odasso, MD, PhD, AGSF, FRCPC
Division of Geriatric Medicine, Department of Medicine, University of Western Ontario, London, ON, Canada

Lawson Health Research Institute, London, ON, Canada

Gait and Brain Lab, St. Joseph's Health Care & Parkwood Institute, London, ON, Canada
e-mail: mmontero@uwo.ca

G. Duque, D.P. Kiel (eds.), *Osteoporosis in Older Persons: Advances in Pathophysiology and Therapeutic Approaches*, DOI 10.1007/978-3-319-25976-5_10

Historical Perspectives and New Insights

Falls, as a geriatric syndrome, has been described for centuries as a natural accident that occurs commonly with older adults. For instance, the ancient Egyptians represented older persons in hieroglyphs as a man bent over using a cane, possibly indicating an understanding of an older individual's tendency to experience falls. This begs the question: if falls have been a known problem in the elderly for so long, why has interest in the topic increased today? One possibility may relate to the number of scientific discoveries and social improvements that have been made in recent decades. Advances in medicine, nutrition, and better social and working conditions have allowed the proportion of elderly people in the population to increase dramatically, a pattern seen in most of the western world. This increased longevity, however, has also been accompanied by increased levels of disability and incidence of falls and fractures, consequences that are now being studied and published in the medical literature. In the beginning, the primary focus of falls research was on the mechanical consequences of the fall namely physical injury and fractures, both of which were assumed to be an expected result of the normal ageing process. However, to consider falls as an inevitable or even normal phenomenon associated with aging, has significantly delayed the creation of a systematic approach to this syndrome. As a result, the initial approach was based exclusively on treating the consequences of falls, which generated a therapeutic nihilism to the syndrome itself.

With the creation of Geriatrics as a distinct medical specialty, this view has changed and falls have started to be considered as a syndrome with concomitant risk factors and aetiologies. Falls and fractures are principal components of the geriatric giants of "Instability" and "Immobility" [1] and both are principal components in the vicious circle involving fall and fractures in older adults. As shown in Fig. 10.1, once immobilization due to falls or muscle weakness starts, it exacerbates the neuromuscular impairment leading to deconditioning problems, and increasing muscle weakness and potentially sarcopenia, increasing the risk of future falls and fractures. Cohort and retrospective observational studies conducted during the early 1980's described the epidemiology, consequences, and underlying factors responsible for the falls syndrome [3, 4, 6–10]. Clinical trials conducted in the late 1980's demonstrated that interventions based on multifactorial and multidisciplinary approaches can prevent falls and their associated consequences [3, 11–15]. Despite the myriad of successful clinical trials in preventing falls, however, important gaps still exist in the current clinical knowledge of the area. This gap is even more evident when we look at the applicability of falls prevention and fractures treatment to everyday clinical scenarios.

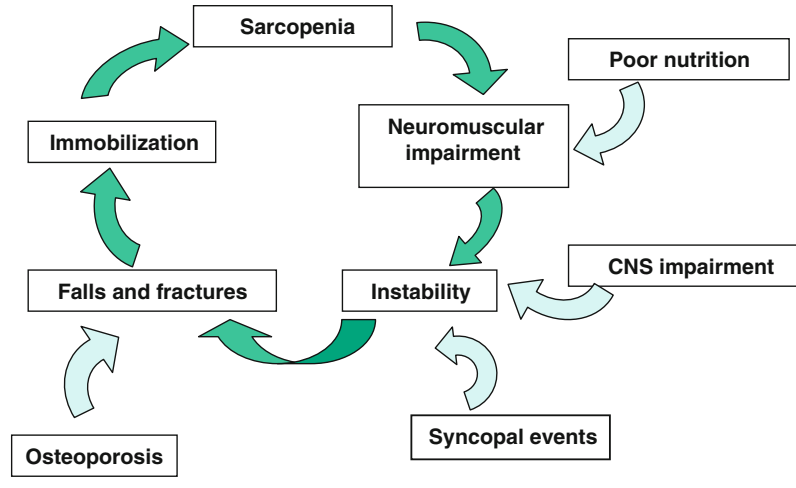


Fig. 10.1 Vicious cycle in falls and fractures and principal contributors. *Green arrows* is the circle. *Blue arrows* are the contributors. Note: CNS, central nervous system

Falls do not happen all the time in the same individual and there are key "trigger events" that act as contributors of the falls syndrome, which will be explored in the "risk factors" section of this chapter. Similarly, the role of cognitive processes, particularly attention and executive function deficits, are becoming increasingly thought as an important determinant of falls, even in those elderly considered cognitively normal [16]. These intriguing findings will be explored in this chapter under the "Cognitive aspects for fall risk" section.

Epidemiology of Falls

The incidence and severity of fall consequences rises steadily entering the sixth decade and tends to be higher among persons over 80 years old. However, the high incidence of falls in this group is not the actual problem as other populations, such as children and professional athletes, have an even higher frequency of falls. Rather, the problem for the elderly is the increased morbidity associated due to falls. Due to the number of comorbidities associated with the ageing process, in particular osteoporosis and the loss of the adaptive and defensive mechanisms related to falling, older people are much more susceptible to sustaining a serious injury even after a minor fall. Accidents are generally ranked as the fourth or fifth leading cause of death in the developed world, with falls being the leading cause of accidental death in older adults accounting for two thirds of these deaths [17].

The prevalence and incidence of falls vary according to the population and setting being analyzed. The reported incidence of falls in community dwelling older adults is about 30 % per year for ages 65 and older, and between 40 and 50 % for ages 80 and older [14]. Among individuals who have a history of falls in the previous year, the annual incidence is closer to 60 %. In older hospitalized patients the prevalence of falls rises to 40 %, while older adults living in long-term care facilities have a prevalence of falls ranging from 45 to 50 % [17–19]. As was stated earlier, falls constitute the largest single cause of injury related mortality in elderly individuals; moreover, falls are an independent determinant of functional decline, leading to 40 % of all nursing home admissions and substantial societal costs. This prevalence in institutional settings is due to a variety of factors including the intrinsic characteristics of the residents in nursing homes, with the majority being frail and/or cognitively impaired, and the more accurate reporting of falls that generally occurs in these settings [18].

Complications of Falling

Falls can have a number of serious medical, physiological, and social consequences that are sometimes underreported or underestimated in the literature (see Table 10.1).

Morbidity and Mortality

Complications and consequences resulting from falls are the leading cause of death from injury in men and women aged 65 and older. One rule of thumb used to describe the frequency of various outcomes of sustaining an unexpected fall by older adults: 20 % of the individuals develop a "fear of falling"; 15 % sustain sufficient injury that leads to frequent visits to emergency care due to the pain, bruises, or dizziness; 10 % sus-

Table 10.1 Frequent consequences of the fall syndrome in older people

Cause	Consequence
Medical	Haematoma
	Fracture
	Chronic pain
	Death
Psychological	Fear of falling
	Anxiety
	Loss of confidence
	Depression
Social	Dependency
	Isolation
	Placement in long term care
Functional	Immobility
	Deconditioning
	Disability and dependence

tain a severe injury but not a fracture (e.g. head injury, brain haematomas, or chest trauma), and 5 % sustain a fracture with 1 % of these being a hip fracture [18, 20]. These percentages can be more than doubled for women aged 75 and older [21].

It has long been understood that the way a person falls can determine the type of the injury they will sustain. For example, wrist fractures often result from forward falls onto a hand, hip fractures typically happen from falls on the side, while falling backwards tends to have the lowest rate of fracture. Older adults between the ages of 65 and 75 tend to have more wrist fractures, while those over the age of 75 suffer more hip fractures. Several hypotheses have been postulated in an attempt to explain this apparent shift from wrist to hip fractures. One of the most accepted theories explains the shift as a result of slower defensive reflexes in individuals over 75 years of age [22].

Psychological and Social Consequences

No less important, and in some cases even more frequent, are the social and psychological consequences of falls and how they may impact functional domains. Fear of falling has been described as a serious concern with prevalence rates ranging from 25 to 55 % amongst community-dwelling older adults [18, 23–25]. Fear of falling can strongly influence an elderly individual's quality of life as it can lead to isolation, depression, and poor satisfaction with life. Moreover, fear of falling itself has been shown to be a predictor of actually falling. The consensus is that individuals develop a fear of falling and depression secondary to recurrent falls. Fear of experiencing another fall (known as "post fall anxiety") may trigger something of a downward spiral for the individual in terms of their social and psychological life. The fear of experiencing another fall can lead the individual to restrict their social activities, possibly due to a decrease in confidence about their abilities. This in turn can gradually lead to isolation, feelings of loneliness, hopelessness, and potentially depression. What makes this pattern particularly unfortunate is that the social isolation stage may be the easiest point at which to affect change; however, it is frequently not reported or identified, which leads to much needless suffering for the individual.

Risk Factors for Falls

While it may be possible to determine the precipitating factor for a given fall, the actual underlying causes tend to be varied and complex. Multiple risk factors have been identified as contributors to the fall syndrome and accordingly, the list is highly heterogeneous including such things as age-associated changes, sensory impairments, muscular weakness, co-morbidities, cardiovascular mediated problems, polypharmacy, and environmental hazards, among others [8, 26, 27]. The most accepted classification of falls is based on whether risk factors are related to an extrinsic hazard or due to an intrinsic disorder [17, 28]. Extrinsic falls are usually related to environmental hazards that cause the individual to slip, trip, or sustain an externally induced displacement, whereas intrinsic falls are generally related to mobility or balance disorders, muscle weakness, orthopaedic problems, sensory impairment, or a neurally-mediated cardiovascular disorder such as postural hypotension or post-prandial hypotension [28]. However, for almost 80 % of fallers, this classification is of limited clinical applicability as their falls were caused by a combination of intrinsic and extrinsic factors [29].

Previous studies showed that the risk of falling increases consistently as the number of risk factors increase. While modifying only one of these risk factors may reduce incidence of falls, the risk reduction is likely to be greater when multiple risk factors are modified [15]. From a clinical point of view, it is more efficient to select interventions that simultaneously address several risk factors, this chapter proposes an

aggregation of risk factors into four categories related to potential interventions. These categories are the following: neuromuscular problems, medical problems, cardiovascular problems, and environmental problems. Table 10.2 lists these domains as well as their proposed risk factors, assessment measures and tests, and some potential interventions appropriate for each giving disorder. One important precipitator of falls is medications, which are included under medical problems. While there are inherent difficulties in studying the role of medications as a risk factor for falls, there already exists strong evidence that both the type and class of medications, in particular psychotropics, sedatives, and vasodilators, and the sheer number of medications taken can be important causes of falls in older adults [23, 31–33].

Mechanism and Pathophysiology of Falls

Basis of Posture Control

The human upright position is naturally unstable due to a narrow base of support with a high center of body mass. To maintain this delicate equilibrium while walking or standing the human body has a harmonious modulation of trunk/ankle flexibility. This equilibrium modulation is challenged by motor impairments (either weakness, slowness or poor coordination) that increases the risk of falling under physiological perturbations (e.g. body sway during standing or walking) or after an extrinsic destabilizing factors (e.g. during tripping). The rapid succession of strategies aimed at preserving body stability after a perturbation included first the "ankle strategy", a motor plan characterized by the release of trunk muscles and stiffening of the ankle joint [34–37]. When the perturbation is more severe and the ankle strategy is not efficient enough, the second motor plan is the "stepping strategy", during which the ankle joint is released and the subject performs one or more steps to enlarge the base of support. If these motor acts fail to preserve stability, the upper limbs play a major role in performing rescue strategies (e.g. holding on some support) or protective reactions (limiting the traumatic consequence of falling when it cannot be avoided). This model explains the pathophysiological link between trunk inflexibility (worsened by rigidity or fear of falling) and instability (i.e. ankle strategy), the mechanistic link between gait disorders and falling (i.e. "stepping strategy"), the need for an adequate flow of information through visual, vestibular and somatosensorial afferents, the need for attentive and executive resources to adapt to the environment and to the type of perturbation by rapidly switching from one strategy to the other. The motor determinants of a frequent faller are characterized by a disorder of either the base of support or the center of body mass [34]. A good study model of a "base of support" disorder is Parkinson's Disease. Patients with Parkinson's manifest disorders of both the base of support and the center of body mass and therefore fall much more frequently than elderly subjects. Additional ageing processes not strictly confined to the dopaminergic systems play a major role in the pathogenesis of the axial impairment. Interestingly, in recent years, mild Parkinsonian signs have been recognized in elderly subjects without PD. These patients present features recognized as risk factors for falling, such as an almost exclusive involvement of gait and postural stability as well as executive cognitive function.

Postural stability can be viewed as a strategy per se. As such, the central nervous system adapting to the environmental constrains should rapidly select the appropriate stabilizing strategy for each circumstance which evolves from postural perturbation, including a protective reaction when fall cannot be avoided. Seniors with a higher rate of injuries show an impaired protective arm response during falling. The relevance of the protective arm response is also highlighted by the observation that elderly fallers with the combined fractures of distal radius and hip have a better prognosis than the peers with isolated hip fracture.

Table 10.2 Cause of falls according risk factor identification and grouped regarding potential management based on observational and trial evidence

Domain assessed	Risk factor/disease	Level of evidence[a]	Screen/assessment	Management
Neuromuscular	Parkinsonism syndrome	Ia	Gait velocity test	1. Supervised programmes (structural gait retraining, balance, transfer and mobility interventions, progressive limb strengthening and flexibility exercises)
	Balance and gait problems	Ia	Get Up and Go	2. Provision of appropriate walking aids when needed
	Lower extremity weakness	Ia	POMA	3. Vitamin D and calcium supplementation
Medical	Dizziness or vertigo	II	History and examination, incl. review of drugs, visual acuity assessment, echocardiograph, short Geriatric Depression Scale	1. Appropriate investigation and management of untreated medical problems
	Visual impairment	Ib for cataracts, III for visual acuity	CAGE questionnaire	2. Review and modification of psychotropic drugs, other culprit drugs, and polypharmacy. Alcohol counselling if indicated
	Peripheral neuropathy	n/a		3. Optical correction by an optician or referral to an ophthalmologist
	Psychoactive medication/ alcohol	Ia		4. Formal psychogeriatric assessment
	Hip problems or deformity	n/a		
	Cognitive problems or depression	III		
Environmental	Environmental fall hazards	Ia	Occupational therapy: assessment of environmental fall hazards using a standard checklist	1. Home hazard modification using standard protocol
	Footwear	III	Check footwear	2. Advise to wear well-fitting shoes of low heel height and high surface contact
	Multifocal eyeglasses	II		3. Avoid multifocal eyeglasses while walking

Table 10.2 (continued)

Domain assessed	Risk factor/disease	Level of evidence[a]	Screen/assessment	Management
Cardiovascular	Orthostatic hypotension	Ia	Cardiac evaluation including heart rate, morning orthostatic blood pressure, and carotid sinus massage supine and tilted upright, prolonged head-up tilt, if indicated	1. Advice on avoiding precipitants and modification of drugs
	Postprandial hypotension	Ib		2. Postural hypotension: compression hosiery, fludrocortisone, or midodrine
	Vasovagal syndrome	Ia		3. Cardioinhibitory carotid sinus hypersensitivity: permanent pacemaker
	Carotid sinus hypersensitivity	Ib		4. Symptomatic vasodepressor carotid sinus hypersensitivity or vasovagal syncope: fludrocortisone or midodrine

[a]Level of evidence based on reference [30] as following: class Ia, evidence from at least 2 randomized controlled trials; Ib, evidence from 1 randomized controlled trial or meta-analysis of randomized controlled trials; II, evidence from at least 1 nonrandomized controlled trial or quasi-experimental study; III, evidence from prospective cohort study; IV, based on expert committee opinion or clinical experience in absence of other evidence

Cognitive Aspects of Falls Risk

Although walking has long been considered a primarily automatic motor task, emerging evidence suggests that this view is overly simplistic [39]. Walking in the real world requires paying attention to various environmental features and recovering from postural perturbations to avoid stumbles or falls. Therefore, it is not surprising that deficits in attention and executive function processes are independently associated with risk of postural instability, impairment in activities of daily living, and future falls [40].

The research on "dual-task walking", i.e. the abilities to perform a secondary task simultaneous to walking, has been driven by the observation that the failure to maintain a conversation while walking ("stop walking when talking") is a strong predictor of future falls [41]. Dual-task walking abilities worsen due to the impairment of automaticity and attentional related cognitive resources. Even during standing, postural sway increases when a cognitive task is performed concurrently with a postural task, suggesting that constant dynamic control of postural adjustments during standing also requires certain level of cognitive attentional resources. Similarly, locomotion requires certain level of attention resources.

Even among healthy older adults with "normal" cognition, low performance in executive function was prospectively associated with falls [42]. A systematic review and meta-analysis found that executive dysfunction was associated with 1.44 times increased risk for any fall and falls associated with serious injury [16].

In patients with neurological overt disease, such as stroke, Parkinson's Disease or dementia syndromes, their gait deteriorates even more during dual tasking [43–45]. The involvement of cognitive control in normal gait could explain why falls are so common in patients with cognitive impairment and dementia and why they are

susceptible to fall while multitasking. Daily life activities involve many attention demanding events which explain the high occurrence of falling while performing a secondary attentional demanding task.

Finally, additional evidence for the role evidence for the role of attention deficits in postural control come from the side effects of drugs impairing cognition. On the other hand, cognitive enhancers, including donepezil, which are usually used for the treatment of dementia, has been found to significantly reduce falls rather than near-falls in patients with PD with cognitive impairment, thus indicating that the drug did not improve stability, but rather cognitive resources. Similarly, cognitive enhancers have improved gait and mobility in people with AD [46, 47].

Risk Identification for Falls

Falls Classification and the Value of Gait Performance

Falls can be classified in a number of diverse ways including by their number (single fall vs. multiple falls); whether or not an injury was sustained (injurious falls vs. non-injurious falls); and what risk factors may have been involved (intrinsic vs. extrinsic factors). The traditional classification, based on the presence of intrinsic and extrinsic factors, has been validated and widely accepted [28]; however, to attribute a fall solely to an to an extrinsic factor is difficult as the majority of environmentally related falls result from an interaction with the intrinsic factors of that individual. Although the intrinsic-extrinsic categorization was originally intended to separate and identify multiple contributors to the fall, older people who experience an extrinsic fall often have an underlying intrinsic condition that decreases their ability to compensate for the hazardous situation. In other words, there may be an intrinsic incapacity to avoid the external factors. As explained earlier, falls are often related to a complex interaction among these factors that can challenge postural control and the ability of the individual to maintain an upright position.

Problems in balance and gait performance are common in older people and have a profound impact on health and quality of life [23, 48–50]. A number of disorders associated to the aging process affect mobility and gait in older persons: loss of muscle mass and strength, also known as sarcopenia, decrease in visual acuity, impairment in proprioception and nerve conduction with loss of the defence reflexes, to list a few. In addition to these age-related changes, many chronic diseases and conditions, including arthritis, neurological problems, and cardiac and respiratory conditions, have marked effects on gait and balance [51, 52]. More frequent factors that can affect gait performance in older persons include muscle weakness, chronic pain, reduced joint mobility and impaired central nervous system processing [48].

Gait performance is a complex task that depends on the normal functioning of multiple systems working in a highly coordinated and integrated manner [48, 53]. As impairments in different domains can alter this delicate system, it has been hypothesized that different chronic conditions such as visual or hearing problems, muscular weakness, osteoarthritis, or peripheral neuropathy could be evidenced through gait performance [53]. In addition, certain psychotropic medications such as benzodiazepines and neuroleptics, which have central nervous system action, may also affect gait performance. Therefore, gait performance can be seen as a common pathway affected by different factors that can cause the fall syndrome. This fact may explain why gait problems "per se" are among the highest predictive risk factor for falls in older adults [6, 48, 53, 54].

In clinical practice, rather than looking for a single, rare disease that causes gait problems in older people, such as myelopathy or normal pressure hydrocephalus, more prevalent causes should be sought in order to establish the potential cause of the gait impairment. The identification of these major contributors will allow the formulating of an operational diagnosis for the individual's gait problem and, in turn provide further information on which to base a therapeutic plan.

Clinical observation is sufficient to detect gait problems in the majority of the older adults, so formal testing in a gait laboratory is not necessary.

However, gait high-tech analysis might be useful in particular cases, or for developing specific rehabilitation strategies, measuring changes in gait quantitative markers, and for research purposes. A focussed and careful clinical observation of the gait performance can detect subtle abnormalities, underlying impairments, and the pathologic process involved. Table 10.3 describes some of the common causes of falls and gait problems in older adults and their relation to performance based evaluation. Operationally, the underlying impairments on gait can be grouped into three major hierarchical categories based on the sensorimotor level involved, as outlined in Table 10.4. Nutt and Alexander have proposed this classification of gait disorder in the elderly based on sensorimotor levels coining the term "lower-level gait disorders" to refer to an altered gait that is a result of lower extremity problems or peripheral dysfunction [48, 55]. This impairment can be attributed to joint and/or muscular problem as well to a peripheral nervous disease. Lower extremity motor problems are prevalent in older adults and can lead to compensatory changes in gait as a result of chronic pain, joint and foot deformities, or focal muscle weakness. Using this approach, Hough and colleagues have found that at least 50 % of ambulatory elderly seeking a consultation for gait impairment have joint or muscle problems in the lower limbs [56]. A systematic review of the literature found that lower limb muscle weakness is significantly associated with falls and subsequent disability in older adults [57].

Table 10.3 Common causes of falls and abnormal mobility and gait in older adults in relation to performance based evaluation

Symptom	Potential cause
Difficulty rising from a chair	Weakness
	Osteoarthritis
Instability on first standing	Hypotension
	Weakness
Instability with eyes closed	Problems related to proprioception
Decreased step height/length	Parkinsonism
	Frontal lobe disease
	Fear of falling

At the middle sensorimotor level, the problem is based on the modulation of sensory and motor control of gait without affecting the ignition of the walking problem. Typical examples are the gait disturbances due to Parkinson's disease or due to spasticity secondary to hemiplegia. However, at the high sensorimotor level, gait characteristic become less specific, cognitive dysfunction, attentional problems, and fear of falling become more prominent features. This category includes "frontal gait" problems, "ignition gait" disturbances, and the "cautious gait" due to fear of falling. Finally, combinations of these levels are frequently found as older adults may have deficits at more than one level.

Among those older adults who do have a gait disturbance, the cause may be easily identifiable (e.g., Parkinson's disease or previous stroke with hemiparesis), however, there are many older adults with an impaired gait for whom there does not appear to be a well-defined disease. Sudarsky and colleagues found that in patients attending a neurology clinic, the cause of the gait disturbance was frequently "unknown", even after neuroimaging, in about 10–20 % of older adults with a disturbed gait [50]. In a study of the "oldest old", whose ages ranged from 87 to 97 years, Bloem and colleagues observed that about 20 % of those studied had a normal gait, 69 % had a gait disorder due to known disease, and about 11 % of the subjects had an idiopathic "senile gait disorder," that is to say a gait disorder of unknown origin [49]. Interestingly, those subjects with a gait disorder of unknown origin had a higher risk of falls, fractures, hospitalizations and mortality after a 2–3 year follow up period, compared to a group of age-matched subjects with a normal gait [54, 58].

An additional value of gait assessment is to help rule out cardiovascular contributors to falls. It has been postulated that falls secondary to neurally-mediated cardiovascular causes may be expressed by a different mechanism, without necessarily chronically affecting gait performance [54, 59]. Although the exact mechanism by which a neurally-mediated cardiovascular problem causes a fall remains unclear, there is growing clinical evidence for its association with unexplained falls [60]. Therefore, the absence of gait problems in

Table 10.4 Common cause of gait disorder in older people according the hierarchic level

Level	Deficit/condition	Gait characteristic
Low	Peripheral sensory ataxia: posterior column, peripheral nerves, vestibular and visual ataxia	Unsteady, uncoordinated (especially without visual input)
	Peripheral motor deficit due to hip problems	Avoids weight bearing on affected side
	Arthritis (antalgic gait, joint deformity)	Painful knee flexed
		Painful spine produces short slow steps and decreased lumbar lordosis, kyphosis and ankylosing spondylosis produce stooped posture
	Peripheral motor deficit due to myopathic and neuropathic conditions (weakness)	Proximal motor neuropathy produces waddling and foot slap
		Distal motor neuropathy produces distal weakness
Middle	Spasticity from hemipeligia, hemiparisis	Leg swings outward and in a semi-circle from hip (circumduction)
	Spasticity from paraplegia, paresis	Circumduction of both legs; steps are short, shuffling, and scraping
	Parkinsonianism	Small shuffling steps, hesitation, acceleration (festination), falling forward (propulsion)
	Cerebral ataxia	Wide-based gait with increased trunk sway, irregular stepping
High	Cautious gait	Fear of falling with appropriate postural responses, normal to widened gait base, shortened stride, slower turning en bloc. Performance improve with assistance or evaluator walking on the side
	Ignition Failure	Frontal gait disorder: difficulty initiating gait; short, shuffling gait, like Parkinsonian, but with a wider base, upright posture, and arm swing presence

Source: Adapted with permission from Nutt et al. [55] and Alexander [48]

older adults with recurrent falls, should be aware of cardiovascular causes in those individuals [61].

Dual-Task Gait Assessments

As explained above, dual-task gait has been proposed and used as an instrument to detect the role of cognitive deficits in gross motor performance, gait stability and navigation, and in falls risk. Specifically, dual-task gait performance isolates the role of attention and executive function deficits in the regulation of brain gait control [43, 44, 62]. Emerging evidence is suggesting that "dual-task gait" can help to identify risk of falls [62]. During the dual-task gait test, the individual performs an attention-demanding task while walking to assess any modifications, compared to the reference, single task condition, in either the cognitive or the walking subtasks [63]. The underlying hypothesis is that two simultaneously performed tasks interfere and compete for brain cortical resources [40]. Therefore, dual-task gait can act as a stress test to the brain to detect impeding mobility problems and risk of fall. Gait modifications during dual-tasking (also known as dual-task costs), such as slowing of gait, are interpreted as the increased cost of involvement of cortical attention processes while walking. The role of dual-task costs as a marker of future falls has been evaluated with mixed results in the literature due to the heterogeneity of studies, small sample sizes, limited prospective fall ascertainment, and the lack of standardization in dual-task procedures [64]. Although clinically meaningful cut off values of dual-task costs for predicting falls are still controversial and other unanswered questions remain, a growing body of evidence supports the potential clinical utility of this paradigm for falls prediction: it is neither costly nor invasive, can easily be

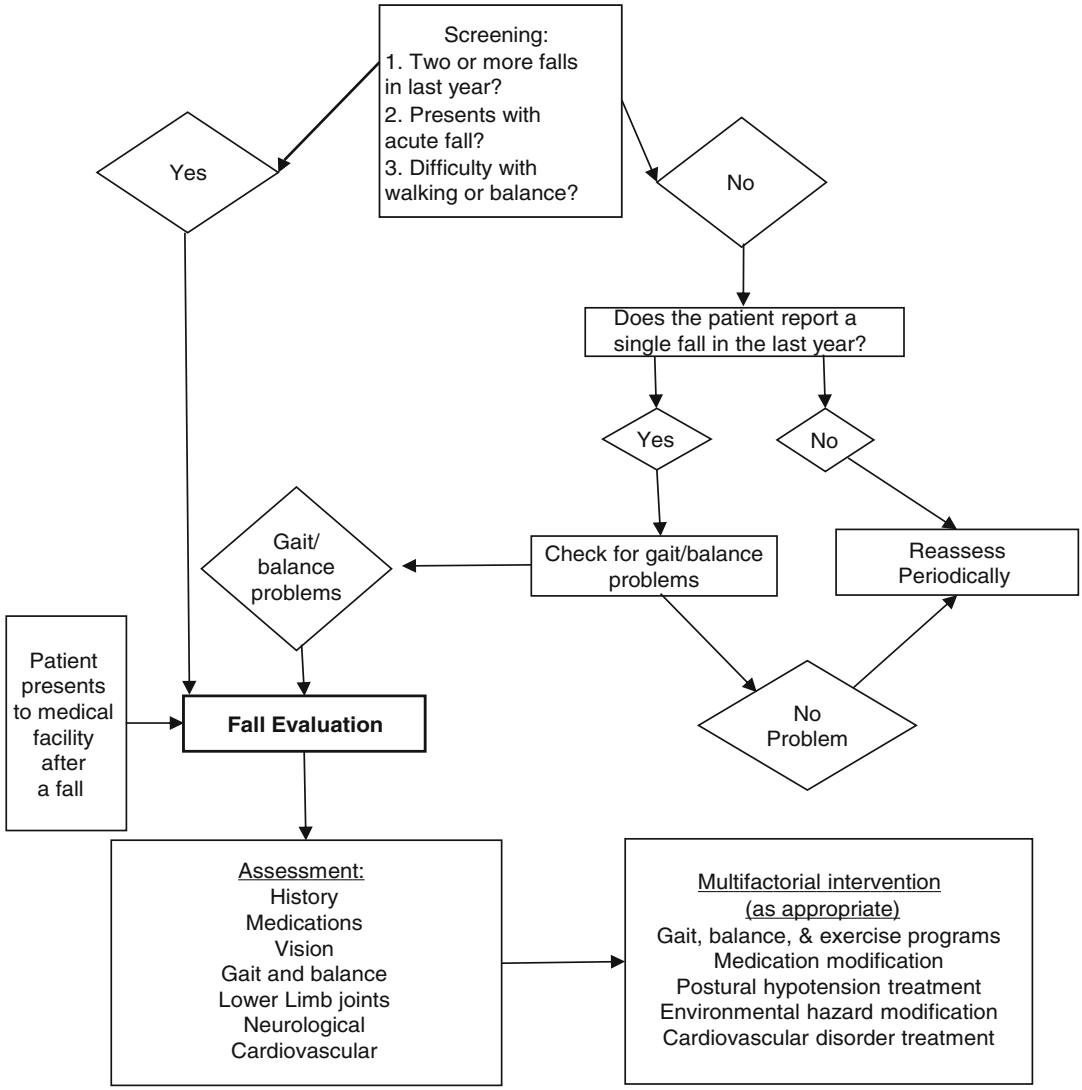


Fig. 10.2 American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons approach to falls (Source: Adapted from Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. Panel on Prevention of Falls in Older Persons, American Geriatrics Society and British Geriatrics Society [17]. Used with permission of Wiley)

implemented, and provides a valid and sensitive means of assessing motor-cognitive interactions and fall risk. Based on recent studies, a dual-task cost higher than 20 % may denote individuals at higher risk of falls when they sustain a gait velocity of 95 cm/s or faster, highlighting the sensitivity and predictive ability in older adults who have a relatively normal gait velocity [65].

Falls and Fracture Risk Assessment: Who to Assess? How to Assess?

Falls are highly prevalent across the older population; consequently, screening strategies have been developed and a systematic approach has been recommended as summarized in Fig. 10.2 [17].

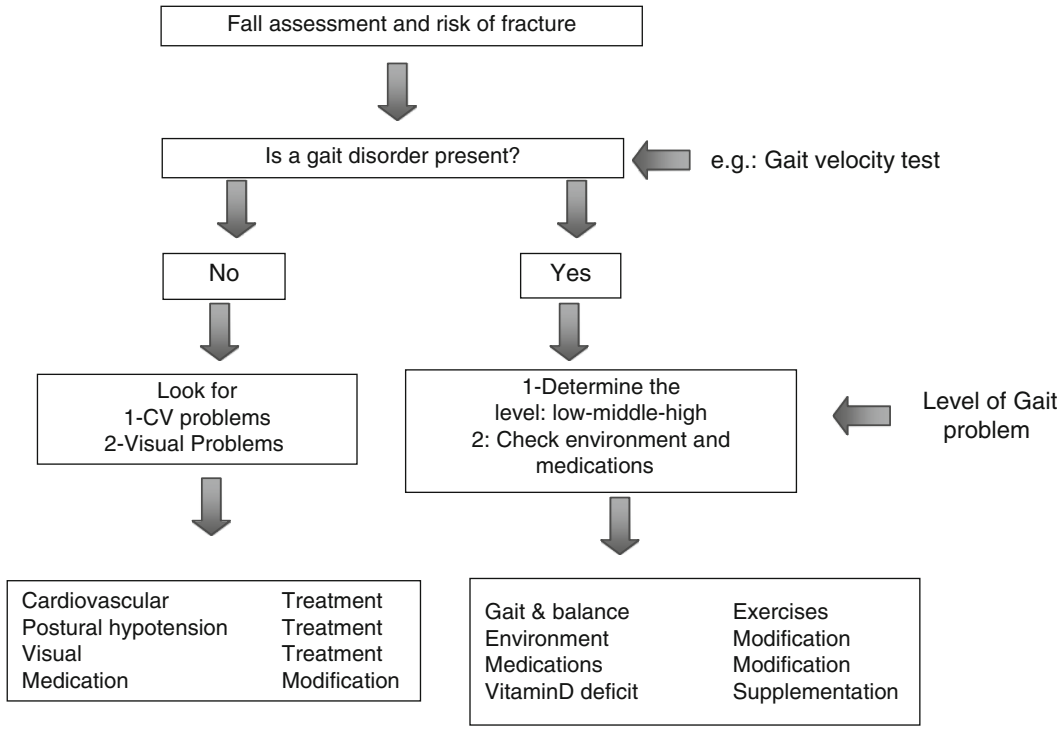


Fig. 10.3 Proposed approach to analyze falls in person with unexplained falls (Source: adapted with permission from Montero-Odasso et al. [63])

We propose a modified approach that is summarized in Fig. 10.3. First, a comprehensive anamnesis which includes ascertaining a history of previous falls since this is the most important predictor for future falls, should be taken. For patients who present with a positive history of falls during the past year, a complete and comprehensive fall evaluation is needed since they sustain a probability of future falls of 35–65 %. The evaluation should include an assessment of balance and gait, vision acuity, and documentation of medication history. This triad is considered to be of high predictive value for detecting older adults at a higher risk for falls in the community [17]. In addition, review of basic and instrumental activities of daily living, cognition, and home environmental hazards is recommended [66]. Table 10.2 summarizes the domains needed to be assessed in individuals with a history of falls.

For 10–20 % of individuals who have fallen are related to a haemodynamic episode such as postural hypotension and vasovagal syncope, therefore these entities should also be considered [59]. Information regarding the circumstances of the falls is necessary in order to detect if "medical or environmental patterns". For instance, falls after taking certain medications or in specific places of the house may lead to the identification of associated drugs (e.g. diuretics, vasodilators, and benzodiazepines) or environmental factors that may have contributed to the fall (e.g. a loose carpet, poor lighting, or a displaced piece of furniture).

On the other hand, older individuals who have not already fallen sustain a probability of a fall in the upcoming year from 19 to 36 %. When there is a negative history of falls, gait and balance evaluation is considered to be the more important part of the assessment mainly because in longitudinal studies, they more frequently predicted future falls than other domains, suggesting that gait and balance assessment should remain a mainstay of screening [17, 26, 48, 53, 67].

Gait can be assessed from either a quantitative or qualitative perspective. Several tests have been

validated that assess gait performance in older adults, however, as is common with most tests, each has its own set of advantages and disadvantages. The majority of the tests in use today have evolved from a test first described by Mathias and Isaacs, namely the "Get Up and Go Test" [68]. Briefly, the "Get Up and Go" consists of rising from a chair, walking 3 meters, turning around, walking back to the start point, and sitting down again. A timed version, "Timed Up and Go," has been validated and widely adopted. [69]. Since TUG was initially created to evaluate frail older adults, high functioning people generally perform well on the task which introduces a ceiling effect [70]. Therefore, for these individuals a cut-off time of 12 s has been proposed to detect those vulnerable to suffer future falls [71]. More complex tests such as the "Performed Oriented Mobility Assessment" (POMA) test and the "Berg Balance Scale" have been described and validated for assessing risk of falling in different scenarios [72–74]. Gait evaluation in the POMA assesses the following nine components: initiation of gait, step height and length, step symmetry and continuity, path deviation, trunk stability, walking stance, and turning while walking [74]. Each component is scored as 1 (normal) or 0 (abnormal) providing a final score, which ranged from 0 to 12, with a higher score indicating a better gait performance.

A powerful test that can be used in different settings is the gait velocity test. This test has been demonstrated to be sensitive for detecting mobility impairment and a strong predictor of falls, even in high functioning older people. Gait velocity is measured as the time taken to walk a known and predetermined distance (e.g. the middle 8 m of 10 m) and it is usually timed by a chronometer [53] with the participants being instructed to "walk at a comfortable and secure pace". The only limitation of the gait velocity test appears when it is tested in older people using assistive devices. In this situation, changes in functionality may show less effect on gait velocity [70].

The proper gait and balance test needs to be selected in regard to the population being assessed. For instance, in long-term care facilities or when evaluating frail older adults with poor functionality, the "Get Up and Go" test may provide good discrimination for detecting those at risk. For higher functioning older adults, such as older persons without disability, a more continuous measurement without ceiling effects, such as the gait velocity test may be more appropriate. Once a gait problem has been detected with a quantitative test, it can be categorized with clinical observation using the hierarchical classification (Table 10.4) or using an established quantitative protocol such as that of the POMA test.

Gait velocity tests may serve as an initial step in the approach and different cut-off points for detecting individuals at high risk of falls can be established according to the population evaluated. For example, it has been suggested that a gait velocity cut off of 1 m/s in community elderly without disability, 0.8 m/s in older persons with disabilities, and 0.6 m/s in older persons living in nursing homes are strong predictors of falls [48, 53, 54]. The role of dual-task gait test to predict falls seems to be important in those with gait velocity over 1 m/s or when the subtle cognitive impairment is suspected to affect motor control.

Finally, assessments of the risk of injuries due to falls should be performed. Specifically, the identification of those at risk of falls in the first step should prompt the assessment of risk of fracture. The more important factors for fracture risk are the history of previous osteoporosis fracture; the use of psychotropic medication, the presences of cognitive impairment, and presence of sarcopenia and impaired mobility [75]. This stepped approach is summarised in Fig. 10.3. Once assessment is completed and risk categorisation determined, appropriate and focussed strategies and interventions can be instituted.

Conclusions

Falls and fractures represent an important and sometimes neglected feature in older adults. A systematic approach based on clinical assessment and performed based measurements or using simple gait assessment can detect those at higher risk. During the evaluation of the risk of injuries, special attention should be paid to frail older adults.

Older adults with previous falls need to have a comprehensive evaluation addressing

all the potential factors previously described. Gait and balance is the domain that will yield more information for falls risk in those without history of falls. There is no evidence that the remaining domains (orthostatic hypotension, visual impairment, medication review, activities of daily living, and cognitive impairment) should be screened in older adults without history of falls if the only purpose is to determine risk of falling [66]. These domains were less frequently, or not at all, independently associated with falls in comprehensive longitudinal studies. If previous history of falls is present, a comprehensive evaluation is needed as described in Table 10.2. Certain cognitive aspects including attention and executive function need to be part of the fall risk evaluation.

Based on the deficits and impairments detected on evaluation, a logical treatment should emerge that involves a combination of medical, rehabilitative, environmental and psychosocial interventions.

Acknowledgement I am indebted to Anam Islam, and Brittany Barnes, Research Coordinators at the "Gait and Brain Lab", Division of Geriatric Medicine at St. Joseph's Health Care, London, ON, Canada, for her endless assistance in the preparation of the manuscript.

References

1. Isaacs B. The giants of geriatrics. The challenge of geriatric medicine. Oxford/New York: Oxford University Press; 1992. p. 1–7.
2. Rubenstein LZ, Robbins AS, Josephson KR, et al. The value of assessing falls in an elderly population. A randomized clinical trial. Ann Intern Med. 1990; 113:308–16.
3. Tinetti ME. Where is the vision for fall prevention? J Am Geriatr Soc. 2001;49:676–7.
4. Wild D, Nayak US, Isaacs B. Description, classification and prevention of falls in old people at home. Rheumatol Rehabil. 1981;20:153–9.
5. King MB, Tinetti ME. A multifactorial approach to reducing injurious falls. Clin Geriatr Med. 1996;12: 745–59.
6. Tinetti ME, Speechley M. Prevention of falls among the elderly. N Engl J Med. 1989;320:1055–9.
7. Campbell AJ, Spears GF, Borrie MJ, et al. Falls, elderly women and the cold. Gerontology. 1988;34:205–8.
8. Campbell AJ, Borrie MJ, Spears GF. Risk factors for falls in a community-based prospective study of people 70 years and older. J Gerontol. 1989;44: M112–7.
9. Campbell AJ, Borrie MJ, Spears GF, et al. Circumstances and consequences of falls experienced by a community population 70 years and over during a prospective study. Age Ageing. 1990;19:136–41.
10. Young SW, Abedzadeh CB, White MW. A fall-prevention program for nursing homes. Nurs Manage. 1989;20:80Y–80AA. 80DD, 80FF.
11. Kerse N, Butler M, Robinson E, et al. Fall prevention in residential care: a cluster, randomized, controlled trial. J Am Geriatr Soc. 2004;52:524–31.
12. Shaw FE, Bond J, Richardson DA, et al. Multifactorial intervention after a fall in older people with cognitive impairment and dementia presenting to the accident and emergency department: randomised controlled trial. BMJ. 2003;326:73.
13. Theodos P. Fall prevention in frail elderly nursing home residents: a challenge to case management: part II. Lippincotts Case Manag. 2004;9:32–44.
14. Tinetti ME, Baker DI, McAvay G, et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. N Engl J Med. 1994;331:821–7.
15. Tinetti ME, McAvay G, Claus E. Does multiple risk factor reduction explain the reduction in fall rate in the Yale FICSIT Trial? Frailty and Injuries Cooperative Studies of Intervention Techniques. Am J Epidemiol. 1996;144:389–99.
16. Muir SW, Gopaul K, Montero Odasso MM. The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis. Age Ageing. 2012;41:299–308.
17. Panel on Prevention of Falls in Older Persons, American Geriatrics Society and British Geriatrics Society. Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. J Am Geriatr Soc. 2011;59(1):148–57.
18. Rubenstein LZ, Josephson KR, Osterweil D. Falls and fall prevention in the nursing home. Clin Geriatr Med. 1996;12:881–902.
19. Vu MQ, Weintraub N, Rubenstein LZ. Falls in the nursing home: are they preventable? J Am Med Dir Assoc. 2004;5:401–6.
20. Tinetti ME. Clinical practice. Preventing falls in elderly persons. N Engl J Med. 2003;348:42–9.
21. Kannus P, Sievanen H, Palvanen M, et al. Prevention of falls and consequent injuries in elderly people. Lancet. 2005;366:1885–93.
22. Kannus P, Leiponen P, Parkkari J, et al. A sideways fall and hip fracture. Bone. 2006;39:383–4.
23. Isaacs B. Clinical and laboratory studies of falls in old people. Prospects for prevention. Clin Geriatr Med. 1985;1:513–24.
24. Lach HW. Incidence and risk factors for developing fear of falling in older adults. Public Health Nurs. 2005; 22:45–52.

25. Lach HW. Self-efficacy and fear of falling: in search of complete theory. J Am Geriatr Soc. 2006;54: 381–2.
26. Bloem BR, Boers I, Cramer M, et al. Falls in the elderly. I. Identification of risk factors. Wien Klin Wochenschr. 2001;113:352–62.
27. Tinetti ME, Doucette J, Claus E, et al. Risk factors for serious injury during falls by older persons in the community. J Am Geriatr Soc. 1995;43:1214–21.
28. Lach HW, Reed AT, Arfken CL, et al. Falls in the elderly: reliability of a classification system. J Am Geriatr Soc. 1991;39:197–202.
29. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. N Engl J Med. 1988;319:1701–7.
30. Tinetti ME, Kumar C. The patient who falls: "it's always a trade-off". JAMA. 2010;303:258–66.
31. Agostini JV, Tinetti ME. Drugs and falls: rethinking the approach to medication risk in older adults. J Am Geriatr Soc. 2002;50:1744–5.
32. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. J Am Geriatr Soc. 1999;47:40–50.
33. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. J Am Geriatr Soc. 1999;47:30–9.
34. Maki BE, McIlroy WE. Postural control in the older adult. Clin Geriatr Med. 1996;12:635–58.
35. Maki BE, McIlroy WE. The role of limb movements in maintaining upright stance: the "change-in-support" strategy. Phys Ther. 1997;77:488–507.
36. McIlroy WE, Maki BE. Preferred placement of the feet during quiet stance: development of a standardized foot placement for balance testing. Clin Biomech (Bristol, Avon). 1997;12:66–70.
37. McIlroy WE, Maki BE. The control of lateral stability during rapid stepping reactions evoked by antero-posterior perturbation: does anticipatory control play a role? Gait Posture. 1999;9:190–8.
38. Montero-Odasso M, Hachinski V. Preludes to brain failure: executive dysfunction and gait disturbances. Neurol Sci. 2014;35:601–4.
39. Hausdorff JM, Yogev G, Springer S, et al. Walking is more like catching than tapping: gait in the elderly as a complex cognitive task. Exp Brain Res. 2005;164:541–8.
40. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. Mov Disord. 2008;23:329–42.
41. Lundin-Olsson L, Nyberg L, Gustafson Y. "Stops walking when talking" as a predictor of falls in elderly people. Lancet. 1997;349:617.
42. Herman T, Mirelman A, Giladi N, et al. Executive control deficits as a prodrome to falls in healthy older adults: a prospective study linking thinking, walking, and falling. J Gerontol A Biol Sci Med Sci. 2010; 65:1086–92.
43. Montero-Odasso M, Bergman H, Phillips NA, et al. Dual-tasking and Gait in people with mild cognitive impairment. The effect of working memory. BMC Geriatr. 2009;9:41.
44. Montero-Odasso M, Muir SW, Speechley M. Dual-task complexity affects gait in people with mild cognitive impairment: the interplay between gait variability, dual tasking, and risk of falls. Arch Phys Med Rehabil. 2012;93:293–9.
45. Muir SW, Speechley M, Wells J, et al. Gait assessment in mild cognitive impairment and Alzheimer's disease: the effect of dual-task challenges across the cognitive spectrum. Gait Posture. 2011;35: 96–100.
46. Montero-Odasso M, Wells J, Borrie M. Can cognitive enhancers reduce the risk of falls in people with dementia? An open-label study with controls. J Am Geriatr Soc. 2009;57:359–60.
47. Montero-Odasso M, Muir-Hunter SW, Oteng-Amoako A, et al. Donepezil improves gait performance in older adults with mild Alzheimer's disease: a phase II clinical trial. J Alzheimers Dis. 2015;43:193–9.
48. Alexander NB. Gait disorders in older adults. J Am Geriatr Soc. 1996;44:434–51.
49. Bloem BR, Gussekloo J, Lagaay AM, et al. Idiopathic senile gait disorders are signs of subclinical disease. J Am Geriatr Soc. 2000;48:1098–101.
50. Sudarsky L. Geriatrics: gait disorders in the elderly. N Engl J Med. 1990;322:1441–6.
51. Dawson-Hughes B, Harris SS, Krall EA, et al. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med. 1997;337:670–6.
52. Dhesi JK, Jackson SH, Bearne LM, et al. Vitamin D supplementation improves neuromuscular function in older people who fall. Age Ageing. 2004;33: 589–95.
53. Montero-Odasso M, Schapira M, Varela C, et al. Gait velocity in senior people. An easy test for detecting mobility impairment in community elderly. J Nutr Health Aging. 2004;8:340–3.
54. Montero-Odasso M, Schapira M, Soriano ER, et al. Gait velocity as a single predictor of adverse events in healthy seniors aged 75 years and older. J Gerontol A Biol Sci Med Sci. 2005;60:1304–9.
55. Nutt JG, Marsden CD, Thompson PD. Human walking and higher-level gait disorders, particularly in the elderly. Neurology. 1993;43:268–79.
56. Hough JC, McHenry MP, Kammer LM. Gait disorders in the elderly. Am Fam Physician. 1987;35:191–6.
57. Moreland JD, Richardson JA, Goldsmith CH, et al. Muscle weakness and falls in older adults: a systematic review and meta-analysis. J Am Geriatr Soc. 2004;52:1121–9.
58. Woo J, Ho SC, Yu AL. Walking speed and stride length predicts 36 months dependency, mortality, and institutionalization in Chinese aged 70 and older. J Am Geriatr Soc. 1999;47:1257–60.
59. Carey BJ, Potter JF. Cardiovascular causes of falls. Age Ageing. 2001;30 Suppl 4:19–24.
60. Lipsitz LA. Orthostatic hypotension in the elderly. N Engl J Med. 1989;321:952–7.

61. Montero-Odasso M, Schapira M, Duque G, et al. Gait disorders are associated with non-cardiovascular falls in elderly people: a preliminary study. BMC Geriatr. 2005;5:15.
62. Montero-Odasso M, Verghese J, Beauchet O, et al. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. J Am Geriatr Soc. 2012;60:2127–36.
63. Woollacott M, Shumway-Cook A. Attention and the control of posture and gait: a review of an emerging area of research. Gait Posture. 2002;16:1–14.
64. Beauchet O, Annweiler C, Dubost V, et al. Stops walking when talking: a predictor of falls in older adults? Eur J Neurol. 2009;16:786–95.
65. Yamada M, Aoyama T, Arai H, et al. Dual-task walk is a reliable predictor of falls in robust elderly adults. J Am Geriatr Soc. 2011;59:163–4.
66. Ganz DA, Bao Y, Shekelle PG, et al. Will my patient fall? JAMA. 2007;297:77–86.
67. Perell KL, Nelson A, Goldman RL, et al. Fall risk assessment measures: an analytic review. J Gerontol A Biol Sci Med Sci. 2001;56:M761–6.
68. Mathias S, Nayak US, Isaacs B. Balance in elderly patients: the "get-up and go" test. Arch Phys Med Rehabil. 1986;67:387–9.
69. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991;39:142–8.
70. Montero-Odasso M. The value of gait velocity test for high-function populations. J Am Geriatr Soc. 2006;54:1949–50.
71. Bischoff HA, Stahelin HB, Monsch AU, et al. Identifying a cut-off point for normal mobility: a comparison of the timed 'up and go' test in community-dwelling and institutionalised elderly women. Age Ageing. 2003;32:315–20.
72. Berg K, Norman KE. Functional assessment of balance and gait. Clin Geriatr Med. 1996;12:705–23.
73. Berg KO, Wood-Dauphinee SL, Williams JI, et al. Measuring balance in the elderly: validation of an instrument. Can J Public Health. 1992;83 Suppl 2:S7–11.
74. Tinetti ME. Performance-oriented assessment of mobility problems in elderly patients. J Am Geriatr Soc. 1986;34:119–26.
75. Gass M, Dawson-Hughes B. Preventing osteoporosis-related fractures: an overview. Am J Med. 2006; 119:S3–11.

Non-pharmacological Treatments for Falls and Fractures

11

Stephen R. Lord, Jacqueline C.T. Close, and Catherine Sherrington

There is strong evidence to support interventions in the prevention of falls in older people. Strategies shown to successfully reduce falls in randomized controlled trials include exercise including balance training, occupational therapy interventions incorporating education and home hazard modification, enhanced podiatry, restriction of multifocal glasses use, psychotropic medication withdrawal, expedited cataract extraction, cardiac pacing for carotid sinus hypersensitivity and targeted multifactorial interventions. As most fractures result from falls where the force exerted on a weakened skeleton is sufficient to break a bone, fall prevention strategies also have direct implications for fracture prevention.

S.R. Lord, PhD, DSc (✉)
Falls and Balance Research Group, Neuroscience Research Australia, UNSW, Randwick, NSW 2031, Australia
e-mail: s.lord@neura.edu.au

J.C.T. Close, PhD
Prince of Wales Hospital, Prince of Wales Clinical School and NeuRA, UNSW, Randwick, NSW 2031, Australia
e-mail: j.close@neura.edu.au

C. Sherrington, PhD, MPH, BAPPSC
Musculoskeletal Division, Ageing and Physical Disability Program, Sydney, NSW, Australia

The George Institute, University of Sydney, Sydney, NSW, Australia
e-mail: csherrington@georgeinstitute.org.au

There continues to be a rapid growth in studies testing the impact of fall prevention interventions. It has become evident that interventions need to be specific to the target population and setting and based on a sound knowledge of the evidence base. If applied to the wrong population, it appears some interventions can actually increase risk of falling. As with any intervention, attention to adherence is also important. Prescription of effective fall prevention interventions that are not received cannot have the intended impact. Some trials in residential aged care settings have found that hip protectors, if worn, prevent hip fractures. However, poor compliance is a major issue limiting the effectiveness of this intervention.

This chapter describes and discusses the non-pharmacological approaches to the prevention of falls and fall related injuries in older people, and emphasises the strategies shown to be effective in a range of population groups.

Exercise

Exercise is a thoroughly evaluated approach to fall prevention and has been shown to be successful as a single intervention strategy in community dwelling people and also effective in residential aged care facilities when part of multifactorial interventions [1, 2]. Exercise covers a wide range of physical tasks (balance, strength, flexibility

G. Duque, D.P. Kiel (eds.), *Osteoporosis in Older Persons: Advances in Pathophysiology and Therapeutic Approaches*, DOI 10.1007/978-3-319-25976-5_11

etc.) delivered in numerous formats. While there are many health and social benefits from a range of exercise regimes, systematic review evidence indicates balance training impacts most significantly on fall rates [3].

Home-Based Exercise Programs

The Otago Exercise Programme comprises a combination of strength and balance exercises supplemented with a walking program. It is designed to be individually prescribed by a trained professional, undertaken 2–3 times per week and progressed over time. This program has been evaluated in a series of randomised controlled trials (RCTs). In the original study, among women aged over 80 years [4], there was a significant reduction in falls over a 12-month period (between group difference = 0.47, 95 % CI = 0.04–0.90). At the end of a second year (with 69 % of intervention and 74 % of control group continuing from the original study) the reduction in fall rates remained significant (Relative Risk (RR) = 0.69, 95 % CI = 0.49–0.97 [5].

Further evaluation of the Otago Exercise Programme was undertaken in an RCT with community-dwelling older people, but this time the program was delivered by a community nurse trained by a physiotherapist [6]. In a controlled trial it was also repeated in routine health care settings [6]. Again, falls were reduced with both these approaches (Incident Rate Ratio (IRR) = 0.54, 95 % CI = 0.32–0.90) and (IRR = 0.70, 95 % CI = 0.59–0.84) respectively. Subsequent meta-analysis and economic evaluation of the Otago Exercise Programme demonstrated that maximum benefits are achieved by targeting people aged 80 years and over and those with a history of falls [7]. The meta-analysis also showed that fall-related injuries were reduced by 35 % (IRR = 0.65, 95 % CI = 0.53–0.81).

A recent trial found that home exercises can be successfully incorporated in an older person's daily routine and can prevent falls when delivered this way [8]. For example, participants were asked to practice standing on one leg while waiting for the jug to boil and to practice knee bends while putting out the washing. This program led to a 31 % reduction in falls compared to a sham gentle exercise program (IRR 0.69, 95 % CI 0.48–0.99).

Reduced muscle strength is an important risk factor for falls but the role of strength training as a single intervention in fall prevention is less clear. In a well-designed and executed RCT of older people recently discharged from hospital [9], seated quadriceps strengthening exercises failed to reduce fall rates and was associated with a significant risk of musculoskeletal injury (RR = 3.6, 95 % CI = 1.5–8.0). However many successful exercise programs have included a strength training component in addition to balance training [1].

Group Exercise Programs

Several studies have demonstrated the effectiveness of a group exercise approach to fall prevention. This is an encouraging finding as many older people enjoy the social interaction and opportunity to leave the home that a group exercise program offers. Group exercises may be individualized and tailored to the needs of the older person or generalized to all participants undertaking the same exercises at the same intensity. Not all programs are progressed over time, which may limit the benefits of exercise. A range of exercise programs have been tested in clinical trials in a number of settings and have targeted populations ranging from fit/healthy to frailer people.

Several studies have found that group exercise programs that combine balance, strength, and functional components can prevent falls [10–16]. Most have been individually tailored and progressive and many include supplementary home exercises. For example, Skelton et al. [10] used exercises based on the Otago program, and reduced falls when compared to an attention control group (IRR = 0.69, 95 % CI = 0.50–0.96). Similarly, Barnett et al. found that group-based balance and strength exercises significantly reduced falls in community-dwelling people (IRR = 0.60, 95 % CI = 0.36–0.99) [11]. A cluster randomised trial targeting residents of retirement villages and hostels tested a 12-month group exercise program designed to address fall risk factors and improve physical functioning [12].

This intervention resulted in an 18 % reduction in falls in the intervention compared to the control group (IRR = 0.78, 95 % CI = 0.62–0.99).

Tai Chi programs have also been effective in preventing falls. The first study in this area by Wolf et al. [15], found that Tai Chi was successful in increasing the time to first fall (unadjusted RR = 0.63, 95 % CI = 0.45–0.89). A similar study in a population that had not been involved in strenuous activity in the previous 3 months [16] also showed reduced fall rates after adjustments for covariates (RR = 0.46, 95 % CI = 0.26–0.8). Wolf et al. also used a cluster randomised trial of congregate living facilities to target more impaired older adults with a 48 week Tai Chi program [17]. Within this selected population, there was no significant reduction in falls, but a trend towards improvement (RR = 0.75, 95 % CI = 0.52–1.08). It seems that this population was unable to adequately perform the exercises to obtain the same level of benefit gained by the younger, fitter participants in the other Tai Chi trials.

There have also been a number of trials that have failed to show benefits of exercise in preventing falls [18–23]. Comparisons with successful trials suggest that this may be due to low adherence to interventions, exercises being insufficiently challenging to balance, or a failure to progress exercise over time.

Exercise in High-Risk Populations

Recent studies have questioned the utility of exercise as a single intervention in certain very high-risk populations. This is in contrast to the findings in the general community-dwelling population where it is clear that exercise as a single intervention can prevent falls. In recent trials an exercise program similar to the Otago Programme failed to prevent falls in long-term stroke survivors [24] or in frail older people [25]. A home based exercise program significantly increased falls in older people recently discharged from hospitals (IRR = 1.43, 95 % CI 1.07–1.93) [26]. This area requires further investigation but it seems that other interventions may be needed to prevent falls in people with these more complex conditions.

Exercise for Preventing Fractures

As most fractures involve a fall it is likely that fall prevention interventions can also prevent fractures. No single trial undertaken to date has been large enough to examine the impact of exercise as a single intervention on fall-related fractures. However there is mounting systematic review evidence that exercise can prevent fractures. For example El-Khoury et al. [27] conducted a systematic review and meta-analysis of 17 trials involving 4305 participants and found that exercise significantly reduced: all injurious falls, RR = 0.63 (0.51–0.77 – 10 trials); falls requiring medical care, RR = 0.70 (0.54–0.92, 8 trials); serious injuries, RR = 0.57 (0.36 to 0.90, 7 trials) and falls resulting in fractures, RR = 0.39 (0.22–0.66, 6 trials).

Interventions to Improve Vision

As visual loss is often correctable or modifiable in older people [28–30], simple intervention strategies such as regular eye examinations, use of correct prescription glasses, cataract surgery, and the removal of tripping hazards in the home and public places have the potential to prevent falls in older people. Bi- and multifocal glasses have been identified as a risk factor for falls in community-dwelling older people [31], and particularly so in higher-risk situations such as negotiating stairs and walking outside the home.

Two related trials have examined the effects of expedited cataract surgery in reducing fall rates. The first study involving 306 women aged 70 years and over [32] examined the efficacy of cataract surgery on the first eye. Participants were randomised to either expedited (approximately 4 weeks) or routine (12 months wait) surgery. Vision, visual disability, physical activity levels, anxiety, depression and balance confidence improved significantly in the operated group at the 6-month retest and over the 12 months of follow-up, the fall rate in the operated group was reduced by 34 % compared with the controls (IRR = 0.66, 95 % CI = 0.45–0.96). Although the number of cases were few – four participants in the operated group

(3 %) and 12 (8 %) in the control group – this trial also demonstrated that an intervention to remove cataracts can be effective in reducing fractures (p = 0.04).

A follow-on study by the same group, aimed to determine if second eye cataract surgery leads to a further reduction in falls as well as measuring associated health gains [33]. Two hundred and thirty nine women over 70, who had been referred to a hospital ophthalmology department with one un-operated cataract, were randomized to either expedited (approximately 4 weeks) or routine (12 months wait) surgery. Visual function (especially stereopsis), confidence, visual disability and handicap all improved in the operated compared with the control group. Over the 1-year prospective period, the rate of falls was reduced by 32 % in the operated group, although this was a non-significant reduction, likely due to reduced power from the smaller sample size.

In recent complementary research, one longitudinal population study examined over 28,000 hospital records for participants who had received cataract surgery and found that the rate of hospital admissions for fall-related injuries increased in the 2 years following surgery to each eye [34]. It is worth noting, however, that this is in comparison to their fall rate before surgery and not in comparison to a control group. In contrast, a population study conducted in the USA that examined over one million records including those who did and those who did not receive cataract surgery, found that cataract surgery effectively reduced the rate of falls [35].

Three randomized controlled trials have evaluated the efficacy of other visual interventions in preventing falls [14, 36, 37]. The first involved 1090 people aged 70 years and over, and used a factorial design to assess the independent effects of interventions aimed at vision improvement, home hazard reduction and group exercise [14]. The visual improvement intervention comprised a referral to the participant's usual eye-care provider if the participant had impaired vision (poor visual acuity, decreased stereopsis and/or reduced field of vision) and he or she was not already receiving treatment for this problem. The eye-care provider was also given the screening assessment results. Those randomized to the visual intervention had an estimated reduction of 4.4 % in the annual fall rate (rate ratio for time to first fall = 0.89, 95 % CI = 0.75–1.04), a difference which did not reach statistical significance.

The second trial was conducted in a group of 616 community-dwellers aged 70 years and over who were randomized to either an intervention group or a control group and prospectively followed up for falls for 12 months [36]. Forty-four percent of the intervention group received vision-related treatments, most often a new pair of glasses (n = 92). During the follow-up period, participants in the intervention group reported significantly more falls than those in the control group (RR = 1.57, 95 % CI = 1.20–2.95). The authors concluded that the intervention participants might have required more time to adapt to their new glasses that often contained significantly altered prescriptions or that they adopted more risk-taking activities (thus increasing the exposure to falls) subsequent to their vision improvement.

The third intervention aimed to limit the use of multifocal glasses, rather than updating glasses to a correct prescription [37]. This randomized controlled trial, involving 606 older people and 13 months follow-up, assessed whether the provision of single-lens distance glasses to older multifocal glasses wearers reduced falls. The intervention was aimed at older multifocal glasses wearers at increased risk of falls (suffered a fall in past year or had a Timed Up and Go test >15 s). As multifocal glasses have benefits for activities that require changes in focal length, including everyday tasks of driving, shopping and cooking, wearing single lens glasses was recommended primarily for outdoor activities. Overall, the intervention resulted in a non-significant 8 % reduction in all falls: incidence rate ratio (IRR) = 0.92 (95 % CI 0.73–1.16). The intervention was effective in preventing falls in people who more regularly undertook outside activities. In this group there were significant reductions in all falls (IRR = 0.60, 95 % CI = 0.43–0.85), falls outside the home (IRR = 0.61, 95 % CI = 0.42–0.87) and injurious falls (IRR = 0.62, 95 % CI = 0.42–0.92). However, there was a significant increase in outside falls in people who undertook little outside activity in the intervention

group (IRR = 1.56, 95 % CI = 1.11–2.19). These findings suggest that, with appropriate counselling, compliance with the intervention was acceptable and that the provision of single-lens glasses for older multifocal wearers who take part in regular outdoor activities can be an effective fall prevention strategy. The intervention may be harmful, however, in multifocal wearers with low levels of outdoor activity.

Medication Use

Medications can both increase and decrease the risk of an older person falling. Studies undertaken in both community and institutional settings have consistently found strong associations between use of multiple medications and centrally acting drugs (sedative/hypnotics, antidepressants and antipsychotics) and risk of falls [38–40]. Results of studies into use of antihypertensive medications have been conflicting and have also highlighted the importance of examining drug class rather than grouping all antihypertensive medications together [41]. In fact, there is preliminary evidence that some classes of antihypertensive agents may be protective against falls [42, 43] but this requires further research before any firm conclusions can be drawn.

Given the link between centrally acting medications and fall risk, it could be expected that withdrawal of centrally acting medications would be of benefit. In a factorial randomised controlled trial of gradual psychoactive medication withdrawal and home-based exercise, Campbell et al. [44] found a significant 65 % reduction in falls in the older community-dwelling women randomised to the medication withdrawal arms of the study (relative hazard = 0.34, 95 % CI = 0.16–0.74). However, there were considerable problems encountered in undertaking this study, which emphasize how difficult it is for older people to stop using psychoactive medications. First, it proved very difficult to recruit participants into the trial with 400 of the 493 (81 %) eligible participants declining participation. Further, of the 48 participants who agreed to participate and were randomized to the psychoactive withdrawal programs, only 17 (35 %) completed the trial. Eight of the 17 participants who successfully completed the trial also restarted psychoactive medications within 1 month of study completion. Given the difficulties in undertaking this trial, it is clear that avoiding prescribing these drugs if possible would be a preferred approach.

Psychosocial treatments are effective in the treatment of anxiety, depression and sleep disturbances in older people and provide alternative or complementary approaches to the pharmacological management of these conditions. Simple behavioural and environmental interventions and the prescription of exercise also offer additional means of enhancing sleep quality in this group and may enhance mood [45] without the increase in falls that might come with drug therapy.

There is evidence to support the use of vitamin D as a single intervention to reduce the risk and rate of falls in older people. The evidence is strongest for those identified as being vitamin D deficient [1] and those living in residential aged care facilities [2].

Other approaches to enhanced medication review and management have been tested. Three trials involving medication review by a pharmacist (or nurse or geriatrician) but requiring implementation by participants' family physicians were not effective in reducing falls [1] However, an intensive educational program for primary care physicians that included academic detailing, financial incentives and patient involvement, significantly reduced risk of falling in older people under their care (RR 0.61, 95 % CI 0.41–0.91) [46].

Pacemaker Insertion for Treatment of Carotid Sinus Hypersensitivity

Studies indicate that the cardioinhibitory form of carotid sinus hypersensitivity (CSH), one factor underlying unexplained dizziness, drop attacks and syncope, may be responsible for a proportion of the unexplained falls in older people [47]. Prospective case–control studies have found that CSH (diagnosed by a 3 s period of asystole, a 50 mmHg drop in blood pressure or both following carotid sinus

massage) is present in one-third of patients admitted to hospital for fractured neck of femur [48–50].

Three studies have evaluated the efficacy of implantation of pacemakers as a fall prevention strategy for people with the cardioinhibitory form of CSH. Overall these studies indicate that insertion of a dual chamber pacemaker is effective in reducing drop attacks and syncope and reducing fall frequency [51–53]. With significant reductions in falls, the case is well made for appropriate cardiovascular assessment including carotid sinus massage for those people with recurrent unexplained falls and syncope. However, the applicability of these findings beyond this group is questionable. The potential neurological complications should also not be overlooked and so informed consent is essential for this procedure [54].

Reducing Hazards in the Home

Most homes contain potential hazards and many older people attribute their falls to trips or slips inside the home or immediate home surroundings. However the existence of home hazards alone is insufficient to cause falls and the interaction between an older person's physical abilities and their exposure to environmental stressors appears to be more important [55].

Three studies have targeted interventions closely to at-risk groups. Cumming et al. [56] conducted a study among 530 community-dwellers, most of whom had been recently hospitalised. The intervention group received a home visit by an occupational therapist who assessed the home for environmental hazards and facilitated any necessary home modifications. There was no significant reduction in falls in the intervention group as a whole. There was however a significant reduction in the rate of falls among those who had fallen in the year prior to the study (RR=0.64, 95 % CI=0.50–0.83). Falls in this group were significantly reduced both inside and outside of the home, suggesting that the home modifications alone may not have been the major factor in the reduction in fall rates. Other aspects of the occupational therapy intervention, which included advice on footwear and behaviour, may have played an important role.

The Falls-HIT trial specifically addressed home modifications and reported a significant reduction in falls [57]. This study involved 361 people with mobility limitations who had recently been discharged from hospital. The intervention consisted of home assessment and recommendations in addition to training in the use of mobility aids. At 1-year follow-up, the intervention group had 31 % fewer falls than the control group (incidence rate ratio (IRR)=0.69, 95 % CI=0.51–0.97), with subgroup analysis revealing that the intervention was particularly effective in those with a history of multiple falls (IRR=0.63, 95 % CI=0.43–0.94).

The third randomized controlled trial involved a factorial design in 391 community-dwelling people aged 75 year and over with visual acuity of 6/24 or worse 40 [58]. The participants received an occupational therapy delivered home assessment and modification program (n=100), an exercise program prescribed at home by a physiotherapist plus vitamin D supplementation (n=97), both interventions (n=98), or social visits (n=96). Fewer falls occurred in the group randomised to the home safety program (IRR=0.59, 95 % CI=0.42–0.83) where 90 % complied partially or completely with one or more of the OT recommendations.

Reducing hazards in the home appears not to be an effective fall prevention strategy in the general older population and those at low risk of falls [55, 56]. However, home hazard reduction is effective if targeted to older people with a history of falls and vision and mobility limitations [59]. The effectiveness of home safety interventions may depend on/be maximized by improved transfer abilities or other behavioural changes. Environmental assessment and modification by trained individuals also appears to contribute to the success of multi-faceted fall prevention programs in at-risk groups. Overcoming potential barriers to an individual's adoption of home modifications such as education and financial assistance need to be considered and addressed.

Multifactorial Interventions

Multifactorial interventions involve identifying a range of risk factors associated with falls and interventions based on the identified risk profile.

Multifactorial interventions have been shown to be effective in a number of settings and in hospitals and residential aged care facilities, most effective fall interventions have been multifactorial. This is perhaps a reflection of the complexity of these populations and the multiple risk factors present.

The first successful evaluation of a multifactorial intervention program conducted by Tinetti et al. was published in 1994 and used targeted risk factors as a means of identifying an at-risk population and guiding intervention [60]. Interventions included: medication adjustment, behavioural change recommendations, education and training, and home exercise programs. During the one-year follow-up period, 47 % of the control group fell compared with only 35 % of the intervention group ($p=0.04$). The adjusted incidence ratio for falling in the intervention group as compared with the control group was 0.69 (95 % CI = 0.52–0.90).

A large randomised trial of a multi-factorial fall prevention program undertaken by Wagner et al. [61] showed some benefits of targeted intervention strategies. This study involved 1559 members of a Health Maintenance Organisation. One group received a home-based assessment conducted by a nurse and follow-up interventions (targeting inadequate exercise, alcohol use, medication use and hearing and visual impairments). A second group received a general health promotion nurse visit and the third group received usual care. The intervention group experienced significantly fewer falls than the usual care group over the first year of follow-up. However, differences between the nurse assessment with follow-up intervention group and the general health promotion nurse visit group were not significant. Benefits were not well maintained in the second year of follow-up with no difference in falling rates between the groups at this time. This suggests the need for ongoing monitoring of and intervention for fall risk factors.

Several fall prevention programs have used group education sessions. In a randomised trial involving 3182 independently-living Health Maintenance Organisation members aged 65 and over, Hornbrook et al. [62], found that a home assessment and advice on modifications followed by a group education, exercise and discussion program, reduced falls by 11 %. Furthermore, Reinsch et al. [22] found that a general non-targeted education program involving classes on exercise, relaxation and health and safety topics was not effective in preventing falls among community-dwellers attending senior citizens centres.

There is some evidence of the efficacy of home-based health and disability screening for older people. While these programs have broader aims than reducing falls they can involve the identification of risk factors for falling. Carpenter et al. [63] conducted a randomised trial involving 539 people aged 75 and over. The intervention group were visited and assessed by volunteers at regular intervals. Participants who developed increasing disability were referred to their family doctor for interventions as required. The number of falls reported by the control group doubled between the first and last interview but remained the same for the intervention group. However, another study [64] found only a trend to a decreased fall rate following one screening visit by a physician's assistant or nurse and two follow-up visits by trained volunteers. Potential problems identified by the screening tool were addressed with referral and/or advice. The screening visit was followed by a letter outlining findings and recommendations.

Patients presenting to the Emergency Department represent an easily identifiable high risk population. A study by Close et al. [65] looked specifically at older people with a fall-related presentation to an Emergency Department. The authors found that a medical and occupational therapy assessment and subsequent tailored intervention resulted in a significant decrease in fall rates over a 1 year period. A substantial reduction in the risk of falling (OR = 0.39, 95 % CI = 0.23–0.66) and the risk of recurrent falls (OR = 0.33, 95 % CI = 0.16–0.68) was reported. The intervention also had a significant impact on functional ability when compared to usual care. Similar results have been reported by Davison et al. again highlighting the benefits of a multifaceted approach to intervention in Emergency Department attendees [66].

As with any intervention it is important that fall prevention strategies that are indicated are actually received by individuals. This is highlighted in a trial by Elley et al. [67] which failed to prevent falls with a General Practice based program that involved screening for past falls and

a home-based individualised fall risk assessment by a nurse with referral to relevant community services. The authors suggest that the lack of effectiveness (IRR 0.96, 95 % CI 0.7–1.34) may have been due to the relatively poor uptake of the interventions.

Preventing Falls in Hospital Patients

Preventing falls in hospitals has become a high profile safety and quality activity with many hospitals now having policies, protocols and processes aimed at reducing falls and harm associated with falls in the hospital setting. The evidence to support interventions to prevent falls in this setting continues to evolve with the results of 17 trials and 29,972 participants undertaken in the acute and subacute care settings reported in the most recent Cochrane review [2].

Single, multifaceted and multifactorial interventions have all been evaluated and the results suggest that preventing falls in hospital is most likely to be effective when there is a co-ordinated multidisciplinary approach taken and preferably where assessment and intervention is integrated into routine clinical care. Apart from exercise undertaken in the subacute/rehabilitation setting, other single approaches to intervention (education, provision of information, medication intervention or bed exit alarms) have largely been shown to be ineffective while one study evaluating the potential benefits of carpeted floors over vinyl floors found that this intervention actually increased fall rates [68].

Four RCTs have evaluated the effects of multifactorial fall prevention programs in hospital settings. Haines et al. [69] developed a targeted, multifactorial intervention fall prevention program and evaluated this in an RCT among 626 patients of three sub-acute wards in Australia. Interventions included a fall risk alert card with information brochure, an exercise program, an education program and hip protectors. Participants in the intervention group experienced 30 % fewer falls than participants in the control group; a difference that was significant (P = 0.045) but not until after 45 days of observation. The results, whilst positive, have limited value when extrapolating to acute and other sub-acute settings where length of stay is considerably shorter.

Healy et al. conducted a cluster RCT in matched pairs of eight aged care wards and associated community units of a district general hospital in northern England [70]. The intervention involved a care plan for patients identified at risk of falling with targeted interventions addressing visual impairment, medication use, low or high blood pressure, abnormal urine test results, immobility and poor footwear. The intervention also considered a bedrail risk/benefit assessment, bed height, simple environmental modifications and patients' position in the ward. Compared with baseline fall rates, falls were significantly reduced only in the intervention wards, with a significant between-group difference (RR = 0.71, 95 % CI = 0.55–0.90).

Stenvall et al. evaluated the effect of a change in approach to the model of service provision for older people who had suffered hip fractures [71]. Whilst the control group were cared for on an orthopaedic ward, the intervention group were cared for on a geriatric ward with staff who had undergone specific training both in comprehensive geriatric assessment and management as well as care of a hip fracture benefits. There were a number of reported benefits of this approach including a reduction in falls.

One of the largest cluster RCTs to date in the hospital setting was by Cumming et al. The trial recruited 3999 patients across 12 acute and subacute hospitals in Australia [72]. The intervention wards were provided with a research nurse and physiotherapist who provided risk assessment of falls, education to staff and patients, exercise programmes, "up" alarms and advice on environmental modifications. The intervention failed to show any reduction in rate of falls when compared to the control group. It is possible that the addition of research staff hours to the ward took away both ownership and accountability for falls from the existing ward staff and as a result there was no change in practice ultimately embedded into the ward culture and practice.

More work is required with respect to preventing falls in hospitals although whether this is best

achieved using the traditional RCT approach is less clear. The application of high quality health care improvement methodologies with rigorous evaluation may be more likely to be effective and better reflect the challenges of changing practice. Change management practices also need to involve a whole of hospital approach including visible senior executive support in organisations.

Preventing Falls in Aged Care Facility Residents

As fall risk is an important determining factor for fractures and other injuries in institutionalized older people, there is agreement that all residents of residential aged care facilities should be assessed for fall risk. Recently, Whitney et al. [73] devised and evaluated a fall risk screen that is easy to administer and contains items that are routinely collected in residential aged care facilities (RACFs). They found that the tool was useful for identifying older people living in RACFs who were at increased risk of falls and provided important information about risk factors amenable to intervention (impulsivity, medication use, poor balance). Risk of falling over a 6-month prospective period increased from 0 % in those with no risk factors to 100 % in those with 6+ risk factors.

The most recent Cochrane systematic review of interventions for preventing falls in older people in nursing care facilities and hospitals [2] reported that multifactorial interventions provided by a multidisciplinary team reduced the rate of falls (RR 0.60, 95 % CI 0.51–0.72; 4 trials, 1651 participants) in nursing care facilities. The review also concluded that there was evidence supporting the correction of vitamin D deficiency as an effective intervention to prevent falls in this setting (RR 0.72, 95 % CI 0.55–0.95; 4 trials, 4512 participants), but that the evidence for any beneficial effects of exercise as a stand-alone fall prevention intervention in nursing care facilities is uncertain. There is also some evidence that medication reviews focused on evidence-based prescribing and minimization of use of benzodiazepines, other psychotropic medications and medicines that contribute to a high drug burden index (i.e., those with anticholinergic or sedative properties [74]) can prevent falls in the RACF setting [75–77].

The multifactorial interventions conducted to date have been quite varied with respect to their intervention content which may account for their differing efficacy. While all have included multiple interventions some have focussed more on risk factors pertaining to the individual whereas others have focussed more on environmental modifications and staff education. Three examples of multifactorial interventions conducted in RACFs and their reported efficacy are illustrated below.

Jensen et al. [78] conducted a cluster RCT among 439 residents of nine residential care facilities in Sweden. An 11-week multidisciplinary program of general and resident-specific tailored strategies significantly reduced falls during a 34-week follow-up period (adjusted IRR = 0.60, 95 % CI = 0.50–0.73). This program involved educating staff, modifying the environment, implementing exercise programs, supplying and repairing aids, reviewing drug regimens, providing hip protectors, having post-fall problem-solving conferences and guiding staff. A sub-group analysis of this study showed that only people with a Mini-Mental State Examination Score of >18 benefited from the intervention thus leaving open the question as to the value of intervention in those with cognitive impairment and dementia.

Becker et al. [79] conducted a cluster RCT among 981 long-stay residents of six nursing homes and found a lower incidence density ratio of falls in the intervention group compared with the control group over a 12-month period (RR = 0.55, 95 % CI = 0.41–0.73). Fifty-two percent of the control group were fallers compared with 37 % of the intervention group (RR = 0.75, 95 % CI = 0.57–0.98). The intervention involved staff training and feedback, information provision and education for residents, environmental adaptations, exercise (balance exercises and progressive resistance training with ankle weights and dumbbells), and hip protectors. Interestingly, intervention effects were not apparent before 6 months, and the authors suggested that it may have taken this long for improvement in the mediating variables (physical performance, staff

adherence and environmental adaptations) to take effect.

In contrast to the above two studies, Kerse et al. [80] reported an increased fall rate following a trial that involved altering existing staff resources and implementing individualised fall-risk management for residents (IRR = 1.34, 95 % CI = 1.06–1.72). This intervention was less intensive than the above two RCTs and the authors suggested that by diverting staff resources, low intensity interventions may be worse than usual care.

Preventing Hip Fractures with Hip Protectors

The likelihood that a fall will result in a fracture can be reduced by changing the interaction between the person and the surface on which they fall. This can be undertaken by modifying the surface or by placing a barrier between the person and the hard surface. Hip protectors are designed to fulfil the latter role.

Hip protectors are designed to absorb energy and to transfer load from the bone to the surrounding soft tissues [81]. The original hip protectors [82] incorporated a firm outer shell and an inner foam section. Other versions are made of dense plastic without an outer shell [83]. Hip protectors either fit into pockets of underwear or are built into underwear. The original protectors were tested in a randomized controlled study among 701 residents of a nursing home [82]. The risk of fracture was significantly decreased in the intervention group (RR = 0.44). Although eight members of the intervention group suffered hip fractures, none were wearing the hip protectors at the time of fracture. A further study in Sweden [84] tested a different model of hip protector and also found a decreased fracture rate among residents of a randomly selected nursing home that was offered hip protectors compared with a control nursing home (relative risk 0.33).

Subsequent research into the efficacy and practicality of hip protector use has been less encouraging. The most recent Cochrane Collaboration review concluded that for older people living in nursing care facilities, providing a hip protector probably decreases the risk of a hip fracture (RR 0.82, 95 % CI 0.67–1.00, 11,808 participants, 14 trails) but may increase the small chance of a pelvic fracture slightly [85]. For older people living in the community, the review concluded there is little or no evidence that hip protectors can prevent hip fractures (RR 1.15, 95 % CI 0.84–1.585 trials, 5614 participants).

Poor compliance appears to markedly limit hip protector effectiveness. For example, O'Halloran et al. [87] found initial acceptance of the hip protectors at only 37 %, and adherence fell to only 20 % at 72 weeks. While wearing hip protectors has few side effects such as skin irritation [86], several studies have found that many older people decline involvement (e.g., 79 % declined in Birks et al.) [87]. Key reasons for poor compliance include: discomfort, the extra effort needed to wear them, urinary incontinence and physical difficulties/illnesses. In some settings, cost may also be a barrier to hip protector use [88]. Although systematic review evidence provides only limited efficacy of hip protectors to prevent hip fracture, there may be a role for them when used correctly by high risk individuals. Clearly more data are needed since the hip protectors themselves differ substantially in their energy absorbing capacity [89].

Conclusions

There is strong evidence to support the effectiveness of fall prevention programs. By using assessments based on evidence-based risk factors amenable to correction, it is possible to intervene in those most likely to benefit from targeted intervention strategies. Balance training has been shown to be the most effective single intervention in the prevention of falls. However, a multi-factorial approach is needed in higher risk individuals such as those in hospital or residential care and those presenting to the emergency department as a result of a fall.

Poor adherence has been highlighted as an issue limiting the effectiveness of hip protectors to prevent fractures but there is mounting systematic review evidence to support fall prevention as a means of fracture prevention. However, to have a meaningful impact on fracture rates, it is imperative that bone health

and fall prevention are considered together. Comparative studies are also required to establish the clinical effectiveness and cost efficiency of the interventions on offer.

References

1. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev. 2012;9, Art. No.: CD007146. doi:10.1002/14651858.CD007146.pub3.
2. Cameron ID, Gillespie LD, Robertson MC, Murray GR, Hill KD, Cumming RG, et al. Interventions for preventing falls in older people in care facilities and hospitals. Cochrane Database Syst Rev. 2012; 12. Art. No.:CD005465. doi:10.1002/14651858.CD005465.pub3.
3. Sherrington C, Whitney JC, Lord SR, Herbert RD, Cumming RG, Close JCT. Effective approaches to exercise in the prevention of falls – a systematic review and meta-analysis. J Am Geriatr Soc. 2008;56: 2234–43.
4. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Tilyard MW, Buchner DM. Randomised controlled trial of a general practice programme of home based exercise to prevent falls in elderly women. BMJ. 1997;315:1065–9.
5. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Buchner DM. Falls prevention over 2 years: a randomized controlled trial in women 80 years and older. Age Ageing. 1999;28:513–8.
6. Robertson MC, Devlin N, Gardner MM, Campbell AJ. Effectiveness and economic evaluation of a nurse delivered home exercise programme to prevent falls. 1: randomised controlled trial. BMJ. 2001;322: 697–701.
7. Robertson MC, Gardner MM, Devlin N, McGee R, Campbell AJ. Effectiveness and economic evaluation of a nurse delivered home exercise programme to prevent falls. 2: controlled trial in multiple centres. BMJ. 2001;322:701–4.
8. Clemson L, Fiatarone Singh MA, Bundy A, Cumming RG, Manollaras K, O'Loughlin P, et al. Integration of balance and strength training into daily life activity to reduce rate of falls in older people (the LiFE study): randomised parallel trial. BMJ. 2012;345:e4547.
9. Latham NK, Anderson CS, Lee A, Bennett DA, Moseley A, Cameron ID, et al. A randomized, controlled trial of quadriceps resistance exercise and vitamin D in frail older people: the Frailty Interventions Trial in Elderly Subjects (FITNESS). J Am Geriatr Soc. 2003;51:291–9.
10. Skelton D, Dinan S, Campbell M, Rutherford O. Tailored Group Exercise (FaME) reduces falls in community dwelling older frequent fallers (an RCT). Age Ageing. 2005;34:636–9.
11. Barnett A, Smith B, Lord SR, Williams M, Baumand A. Community-based group exercise improves balance and reduces falls in at-risk older people: a randomised controlled trial. Age Ageing. 2003;32:407–14.
12. Lord SR, Castell S, Corcoran J, Dayhew J, Matters B, Shan A, et al. The effect of group exercise on physical functioning and falls in frail older people living in retirement villages: a randomized, controlled trial. J Am Geriatr Soc. 2003;51:1685–92.
13. Day L, Fildes B, Gordon I, Fitzharris M, Flamer H, Lord S. Randomised factorial trial of falls prevention among older people living in their own homes. BMJ. 2002;325:128.
14. Buchner DM, Cress ME, de Lateur BJ, Esselman PC, Margherita AJ, Price R, et al. The effect of strength and endurance training on gait, balance, fall risk, and health services use in community-living older adults. J Gerontol. 1997;52:M218–24.
15. Wolf SL, Barnhart HX, Kutner NG, McNeely E, Coogler C, Xu T. Reducing frailty and falls in older persons: an investigation of Tai Chi and computerized balance training. Atlanta FICSIT Group. Frailty and Injuries: Cooperative Studies of Intervention Techniques. J Am Geriatr Soc. 1996;44:489–97.
16. Li F, Harmer P, Fisher KJ, McAuley E, Chaumeton N, Eckstrom E, et al. Tai Chi and fall reductions in older adults: a randomized controlled trial. J Gerontol. 2005;60:M187–94.
17. Wolf SL, Sattin RW, Kutner M, O'Grady M, Greenspan AI, Gregor RJ. Intense tai chi exercise training and fall occurrences in older, transitionally frail adults: a randomized, controlled trial. J Am Geriatr Soc. 2003;51:1693–701.
18. Bunout D, Barrera G, Avendano M, de la Maza P, Gattas V, Leiva L, et al. Results of a community-based weight-bearing resistance training programme for healthy Chilean elderly subjects. Age Ageing. 2005; 34:80–3.
19. Carter ND, Khan KM, McKay HA, Petit MA, Waterman C, Heinonen A, et al. Community-based exercise program reduces risk factors for falls in 65- to 75-year-old women with osteoporosis: randomized controlled trial. Can Med Assoc J. 2002;167: 997–1004.
20. Lord SR, Ward JA, Williams P, Strudwick M. The effect of a 12-month exercise trial on balance, strength, and falls in older women: a randomized controlled trial. J Am Geriatr Soc. 1995;43:1198–206.
21. Morgan RO, Virnig BA, Duque M, Abdel-Moty E, Devito CA. Low-intensity exercise and reduction of the risk for falls among at-risk elders. J Gerontol. 2004;59:M1062–7.
22. Reinsch S, MacRae P, Lachenbruch PA, Tobis JS. Attempts to prevent falls and injury: a prospective community study. Gerontologist. 1992;32:450–6.
23. Steinberg M, Cartwright C, Peel N, Williams G. A sustainable programme to prevent falls and near falls in community dwelling older people: results of a randomised trial. J Epidemiol Community Health. 2000;54:227–32.

24. Dean C, Rissel C, Sherrington C, Sharkey M, Cumming RG, Lord SR, et al. Exercise to enhance mobility and prevent falls after stroke: the community stroke club randomised trial. Neurorehabil Neural Repair. 2012;36:1046–57.
25. Fairhall N, Sherrington C, Lord SR, Kurrle SE, Langron C, Lockwood K, et al. Effect of a multifactorial, interdisciplinary intervention on risk factors for falls and fall rate in frail older people: a randomised controlled trial. Age Ageing. 2014;43:31–7.
26. Sherrington C, Lord SR, Vogler CM, Close JCT, Howard K, Dean CM, et al. A post-hospital home exercise program improved mobility but increased falls in older people: a randomised controlled trial. PLoS One. 2014;9(9):e104412. doi:10.1371/journal.pone.0104412.
27. El-Khoury F, Cassou B, Charles MA, Dargent-Molina P. The effect of fall prevention exercise programmes on fall induced injuries in community dwelling older adults: systematic review and meta-analysis of randomised controlled trials. BMJ. 2013;347:f6234.
28. Teilsch JM, Sommer A, Witt K, Katz J, Royall RM. Blindness and visual impairment in an American urban population: the Baltimore Eye Survey. Arch Ophthalmol. 1990;108:286–90.
29. Attebo K, Ivers RQ, Mitchell P. Refractive errors in an older population: the Blue Mountains Eye Study. Ophthalmology. 1999;106:1066–72.
30. Jack CI, Smith T, Neoh C, Lye M, McGalliard JN. Prevalence of low vision in elderly patients admitted to an acute geriatric unit in Liverpool: elderly people who fall are more likely to have low vision. Gerontology. 1995;41:280–5.
31. Lord SR, Dayhew J, Howland A. Multifocal glasses impair edge contrast sensitivity and depth perception and increase the risk of falls in older people. J Am Geriatr Soc. 2002;50:1760–6.
32. Harwood RH, Foss AJE, Osborn F, Gregson RM, Zaman A, Masud T. Falls and health status in elderly women following first eye cataract surgery: a randomised controlled trial. Br J Ophthalmol. 2005;89:53–9.
33. Foss AJ, Harwood RH, Osborn F, Gregson RM, Zaman A, Masud T. Falls and health status in elderly women following second eye cataract surgery: a randomised controlled trial. Age Ageing. 2006;35:66–71.
34. Meuleners LB, Fraser ML, Ng J, Morlet N. The impact of first-and second-eye cataract surgery on injurious falls that require hospitalisation: a whole-population study. Age Ageing. 2014;43:341–6.
35. Tseng VL, Yu F, Lum F, Coleman AL. Risk of fractures following cataract surgery in medicare beneficiaries. JAMA. 2012;308:493–501.
36. Cumming RG, Ivers R, Clemson L, Cullen J, Hayes MF, Tanzer M, et al. Improving vision to prevent falls in frail older people: a randomized trial. J Am Geriatr Soc. 2007;55:175–81.
37. Haran MJ, Cameron ID, Ivers RQ, Simpson JM, Lee BB, Tanzer M, et al. The effect on falls of providing single lens distance vision glasses to multifocal glasses wearers: the VISIBLE randomised controlled trial. BMJ. 2010;340:c2265.
38. Woolcott JC, Richardson KJ, Wiens MO, Patel B, Marin J, Khan KM, Marra CA. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Arch Intern Med. 2009;169:1952–60.
39. Hartikainen S, Lönnroos E, Louhivuori K. Medication as a risk factor for falls: critical systematic review. J Gerontol A Biol Sci Med Sci. 2007;62:1172–81.
40. Taipale HT, Bell JS, Uusi-Kokko M, Lönnroos E, Sulkava R, Hartikainen S. Sedative load among community-dwelling people aged 75 years and older: a population-based study. Drugs Aging. 2011;28:913–25.
41. Gribbin J, Hubbard R, Gladman JRF, Smith C, Lewis S. Risk of falls associated with antihypertensive medication: population-based case–control study. Age Ageing. 2010;39(5):529–7.
42. Wong AKW, Lord SR, Sturnieks DL, Delbaere K, Trollor JN, Close JCT. Angiotensin system blocking medications are associated with fewer falls over 12 months in community dwelling older people. J Am Geriatr Soc. 2013;61:776–81.
43. Witham MD, Sumukadas D, McMurdo MET. ACE inhibitors for sarcopenia—as good as exercise training? Age Ageing. 2008;37:363–5.
44. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Buchner DM. Psychotropic medication withdrawal and a home based exercise programme to prevent falls: results of a randomised controlled trial. J Am Geriatr Soc. 1999;47:850–3.
45. Lord SR, Sherrington C, Menz H, Close JCT. Falls in older people: risk factors and strategies for prevention. 2nd ed. Cambridge, UK: Cambridge University Press; 2007.
46. Pit SW, Byles JE, Henry DA, Holt L, Hansen V, Bowman DA. A quality use of medicines program for general practitioners and older people: a cluster randomised controlled trial. Med J Aust. 2007;187:23–30.
47. Ward C, McIntosh S, Kenny R. Carotid sinus hypersensitivity – a modifiable risk factor for fractured neck of femur. Age Ageing. 1999;28:127–33.
48. Davies AJ, Kenny RA. Falls presenting to the accident and emergency department: types of presentation and risk factor profile. Age Ageing. 1996;25:362–6.
49. Richardson DA, Bexton RS, Shaw FE, Kenny RA. Prevalence of cardioinhibitory carotid sinus hypersensitivity in patients 50 years or over presenting to the accident and emergency department with "unexplained" or "recurrent" falls. Pacing Clin Electrophysiol. 1997;20:820–3.
50. Davies A, Steen N, Kenny R. Carotid sinus hypersensitivity is common in older patients presenting to an accident and emergency department with unexplained falls. Age Ageing. 2001;30:289–93.
51. Kenny R, Richardson D, Steen N, Bexton R, Shaw F, Bond J. Carotid sinus syndrome: a modifiable risk

factor for nonaccidental falls in older adults (SAFE PACE). J Am Coll Cardiol. 2001;38:1491–6.
52. Parry SW, Steen N, Bexton RS, Tynan M, Kenny RA. Pacing in elderly recurrent fallers with carotid sinus hypersensitivity: a randomised, double-blind, placebo controlled crossover trial. Heart. 2009;95:405–9.
53. Ryan DJ, Nick S, Colette SM, Roseanne K. Carotid sinus syndrome, should we pace? A multicentre, randomised control trial (Safepace 2). Heart. 2010;96: 347–51.
54. Richardson D, Bexton R, Shaw F, Steen N, Bond J, Kenny R. Complications of carotid sinus massage – a prospective series of older patients. Age Ageing. 2000;29:413–7.
55. Lord SR, Menz HB, Sherrington S. Home environment risk factors for falls in older people and the efficacy of home modifications. Age Ageing. 2006; 35(S2):ii55–9.
56. Cumming RG, Thomas M, Szonyi G, Salkeld G, O'Neill E, Westbury C, et al. Home visits by an occupational therapist for assessment and modification of environmental hazards: a randomized trial of falls prevention. J Am Geriatr Soc. 1999;47:1397–402.
57. Nikolaus T, Bach M. Preventing falls in community-dwelling frail older people using a home intervention team (HIT): Results from the randomised falls-HIT trial. J Am Geriatr Soc. 2003;51:300–5.
58. Campbell AJ, Robertson MC, La Grow SJ, Kerse NM, Sanderson GF, Jacobs RJ, et al. Randomised controlled trial of prevention of falls in people aged > or = 75 with severe visual impairment: the VIP trial. BMJ. 2005;331:817–925.
59. Clemson L, Mackenzie L, Ballinger C, Close JCT, Cumming RG. Environmental interventions to prevent falls in community-dwelling older people. A meta-analysis of randomized trials. J Aging Health. 2008;20:954–71.
60. Tinetti ME, Baker DI, McAvay G, Claus EB, Garrett P, Gottschalk M, et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. N Engl J Med. 1994;331:821–7.
61. Wagner EH, LaCroix AZ, Grothaus L, Leveille SG, Hecht JA, Artz K, et al. Preventing disability and falls in older adults: a population-based randomized trial. Am J Public Health. 1994;84:1800–6.
62. Hornbrook MC, Stevens VJ, Wingfield DJ, Hollis JF, Greenlick MR, Ory MG. Preventing falls among community-dwelling older persons: results from a randomized trial. Gerontologist. 1994;34:16–23.
63. Carpenter G, Demopoulos G. Screening the elderly in the community: controlled trial of dependency surveillance using a questionnaire administered by volunteers. BMJ. 1990;300:253–6.
64. Fabacher D, Josephson K, Pietruszka F, Linderborn K, Morley J, Rubenstein L. An in-home preventive assessment programme for independent older adults. J Am Geriatr Soc. 1994;42:630–8.
65. Close J, Ellis M, Hooper R, Glucksman E, Jackson S, Swift C. Prevention of falls in the elderly trial (PROFET): a randomised controlled trial. Lancet. 1999;353:93–7.
66. Davison J, Bond J, Dawson P, Steen IN, Kenny RA. Patients with recurrent falls attending Accident & Emergency benefit from multifactorial intervention – a randomised controlled trial. Age Ageing. 2005; 34:162–8.
67. Elley CR, Robertson MC, Garrett S, Kerse NM, McKinlay E, Lawton B, et al. Effectiveness of a falls-and-fracture nurse coordinator to reduce falls: a randomized, controlled trial of at-risk older adults. J Am Geriatr Soc. 2008;56:1383–9.
68. Donald IP, Pitt K, Armstrong E, Shuttleworth H. Preventing falls on an elderly care rehabilitation ward. Clin Rehabil. 2000;14:178–85.
69. Haines TP, Bennell KL, Osborne RH, Hill KD. Effectiveness of targeted falls prevention programme in subacute hospital setting: randomised controlled trial. BMJ. 2004;328:676.
70. Healey F, Monro A, Cockram A, Adams V, Heseltine D. Using targeted risk factor reduction to prevent falls in older in-patients: a randomised controlled trial. Age Ageing. 2004;33:390–5.
71. Stenvall M, Olofsson B, Lundstrom M, Englund U, Borssen B, Svensson O, et al. A multidisciplinary, multifactorial intervention program reduces postoperative falls and injuries after femoral neck fracture. Osteoporos Int. 2007;18:167–75.
72. Cumming RG, Sherrington C, Lord SR, Simpson JM, Vogler C, Cameron ID, et al. Cluster randomised trial of a targeted multifactorial intervention to prevent falls in hospital. Br Med J. 2008;336(7647): 758–60.
73. Whitney J, Close JCT, Lord SR, Jackson SHD. Identification of high risk fallers among older people living in residential care facilities: a simple screen based on easily collectable measures. Arch Gerontol Geriatr. 2012;55:690–5.
74. Wilson NM, Hilmer SN, March LM, Cameron ID, Lord SR, Seibel MJ, et al. Associations between drug burden index and falls in older people in residential aged care. J Am Geriatr Soc. 2011;59:875–80.
75. Zermansky AG, Alldred DP, Petty DR, Raynor DK, Freemantle N, Eastaugh J, et al. Clinical medication review by a pharmacist of elderly people living in care homes—randomised controlled trial. Age Ageing. 2006;35:586–91.
76. Nishtala PS, Hilmer SN, McLachlan AJ, Hannan PJ, Chen TF. Impact of residential medication management reviews on drug burden index in aged-care homes: a retrospective analysis. Drugs Aging. 2009; 26:677–86.
77. Nishtala PS, McLachlan AJ, Bell JS, Chen TF. Psychotropic prescribing in long-term care facilities: impact of medication reviews and educational interventions. Am J Geriatr Psychiatry. 2008;16: 621–32.
78. Jensen J, Lundin-Olsson L, Nyberg L, Gustafson Y. Fall and injury prevention in older people living in

residential care facilities: a cluster randomized trial. Ann Intern Med. 2002;136:733–41.
79. Becker C, Kron M, Lindemann U, Sturm E, Eichner B, Walter-Jung B, et al. Effectiveness of a multifaceted intervention on falls in nursing home residents. J Am Geriatr Soc. 2003;51:306–13.
80. Kerse N, Butler M, Robinson E, Todd M. Fall prevention in residential care: a cluster, randomized, controlled trial. J Am Geriatr Soc. 2004;52:524–31.
81. Mills N. The biomechanics of hip protectors. Proc Inst Mech Eng H J Eng Med. 1996;210:259–66.
82. Lauritzen JB, Petersen MM, Lund B. Effect of external hip protectors on hip fractures. Lancet. 1993;341:11–3.
83. Wallace RB, Ross JE, Huston JC, Kundel C, Woodworth G. Iowa FICSIT trial: the feasibility of elderly wearing a hip joint protective garment to reduce hip fractures. J Am Geriatr Soc. 1993;41:338–40.
84. Ekman A, Mallmin H, Michaelsson K, Ljunghall S. External hip protectors to prevent osteoporotic hip fractures. Lancet. 1997;350:563–4.
85. Santesso N, Carrasco-Labra A, Brignardello-Petersen R. Hip protectors for preventing hip fractures in older people. Cochrane Database Syst Rev. 2014;3. Art. No.:CD001255. doi:10.1002/14651858.CD001255.pub5.
86. O'Halloran P, Cran G, Beringer T, Kernohan G, O'Neill C, Orr J, et al. A cluster randomised controlled trial to evaluate a policy of making hip protectors available to residents of nursing homes. Age Ageing. 2004;33:582–8.
87. Birks Y, Porthouse J, Addie C, Loughney K, Saxon L, Baverstock M, Primary Care Hip Protector Trial Group, et al. Randomized controlled trial of hip protectors among women living in the community. Osteoporos Int. 2004;15:701–6.
88. van Schoor N, Deville W, Bouter L, Lips P. Acceptance and compliance with external hip protectors: a systematic review of the literature. Osteoporos Int. 2002; 13:917–24.
89. Laing AC, Feldman F, Jalili M, Chun Min T, Robinovitch SN. The effects of pad geometry and material properties on the biomechanical effectiveness of 26 commercially available hip protectors. J Biomech. 2011;44:2627–35.

Medical Treatment of Age Related Osteoporosis

12

Eric Kai-Chung Wong, Lisa Ha-Yeon Kim, and Alexandra Papaioannou

Introduction

Osteoporosis risk and complications increase with age. The syndrome of osteoporosis of old age is different from postmenopausal osteoporosis because both men and women are affected as they age. The aim of osteoporosis treatment is to prevent fractures by preventing falls and strengthening the skeleton. Bone mineral density (BMD) is used as a guide to predict future fracture risk. Numerous clinical trials have tested the efficacy of both nutritional supplements (calcium and vitamin D) and pharmacologic therapies to reduce fracture risk in those with osteoporosis. However, not all trials included patients who were very old, despite the fact that they are at increased risk of fractures. Trials also sometimes demonstrated efficacy in preventing only certain types of fractures but not others. This chapter reviews the evidence supporting osteoporosis treatments.

Targets of Therapies

Preceding chapters have described the pathophysiology of osteoporosis. The pharmacologic targets of treatment are closely linked to pathophysiology. A fundamental part of therapy is ensuring adequate calcium intake, which is the primary mineral that lends to bone strength. Vitamin D is intricately linked to calcium homeostasis, both promoting calcium absorption from the gut and reversing secondary hyperparathyroidism [1], a consequence of vitamin D insufficiency. The combination of these effects reduces bone turnover and increases calcium content of bones. Vitamin D also reduces falls by strengthening muscles and improving proprioception [2].

In addition to calcium and vitamin D, effective medications are available for those at high risk of fracture. These include (i) bisphosphonates, (ii) denosumab, and (iii) teriparatide, (iv) estrogen hormone replacement, (v) selective estrogen receptor modulator (SERM), and (vi) strontium ranelate. In addition, calcitonin, a drug once available for osteoporosis treatment, has been taken off the market in Europe and Canada because of (i) weak effect on fracture prevention and (ii) increased cancer risk, but it is still available in the United States.

E.K.-C. Wong, BSc, MD (✉)
L.H.-Y. Kim, BHSc, MD
Department of Internal Medicine,
McMaster University,
Hamilton, ON L8S 4K1, Canada
e-mail: eric.wong@medportal.ca;
Lisa.kim@medportal.ca

A. Papaioannou, BScN, MD, MSc, FRCP(C), FACP
Geriatric Medicine, McMaster University,
St. Peter's Hospital, 88 Maplewood Ave,
Hamilton, ON L8M 1W9, Canada

Department of Medicine, McMaster University,
Hamilton, ON L8S 4L8, Canada
e-mail: papaioannou@hhsc.ca

G. Duque, D.P. Kiel (eds.), *Osteoporosis in Older Persons: Advances in Pathophysiology and Therapeutic Approaches*, DOI 10.1007/978-3-319-25976-5_12

These drugs are all *anti-resorptive agents* because the ultimate effect is to reduce osteoclast-mediated bone resorption, thus reversing the primary mechanism of increased bone resorption after menopause. Certain drugs, such as teriparatide and strontium, are *anabolic agents* because they also increase bone formation via increased osteoblastic activity. New bone is formed as a result. The mechanisms of each drug are briefly described here:

- *Bisphosphonates* work by attaching to hydroxyapatite minerals in bones. When osteoclasts resorb bones, bisphosphonates are taken into osteoclast cells along with hydroxyapatite, inducing apoptosis or inhibiting bone resorption activities [3]. Because absorbed bisphosphonates readily bind to hydroxyapatite, the effect of these drugs lasts for many months after discontinuation.
- *Denosumab* is a monoclonal antibody directed against the receptor activator of nuclear factor kappa-B ligand (RANKL), which is a necessary signal for osteoclast survival and differentiation [4, 5]. Denosumab is a potent inhibitor of osteoclast activity.
- *Teriparatide* is a synthetic peptide containing the first 34 amino acids of the parathyroid hormone (PTH), which is available in North America and Europe. The whole peptide of PTH is available in Europe; however, in the U.S., the full 1–84 amino acid peptide is available for treatment of hypoparathyroidism. Although high levels of PTH in hyperparathyroidism are known to cause osteoporosis, intermittent pulses of the hormone actually attenuates and even reverses this effect [6]. This drug has an anabolic effect, shifting the balance toward bone formation. The use of this drug is limited to 2 years because the trials were stopped early due to fears of serious adverse effect potential on osteosarcoma risk that was later felt to be negligible. After discontinuing teriparatide at 2 years, rapid bone loss ensues, negating the beneficial effects accrued during active treatment. Thus anti-resorptive therapy after 2 years of treatment is needed.

Caveats of Studies in Osteoporosis

The literature has a number of randomized controlled trials (RCTs) and meta-analyses of osteoporosis therapeutic studies. However, it is important to consider caveats to the analysis of this literature. One important caveat is the outcome measured. Not all studies include patient-important outcomes, such as fractures, mortality, or quality of life. BMD, while a predictor of future fracture risk, does not completely predict which individual will sustain a fracture. Previous studies of bisphosphonates, calcium, and vitamin D showed that a reduction in fracture risk is not necessarily related to improvement in BMD [7–9]. However, newer studies of denosumab and zoledronic acid indicate a stronger association between BMD increase and fracture risk reduction [10, 11]. Furthermore, not all fractures are of equal importance to patients [12]. Hip fractures tend to bear significant consequences, including mortality [12], need for nursing home, and disability [13]. Vertebral fractures are similarly associated with increased mortality and recurrent fracture risk [13]. Fractures of the arms or wrists tend to bear less consequence. Therefore, even if a study uses fractures as an endpoint, the type of fracture matters.

Another caveat is the age, sex, and multiple comorbidities of participants in trials. Some clinical trials exclude or recruit few subjects over the age of 80, and yet a substantial proportion of fragility fractures occur in this age group. Post-hoc analyses of some clinical trials show greater hip fracture reduction in this specific population [14, 15], a finding obscured in original trial results because of a wide age range. Because of the prevalence of postmenopausal osteoporosis, the vast majority of trials only include postmenopausal women and not men. Osteoporosis affecting individuals of advanced age is pathophysiologically distinct from postmenopausal osteoporosis [16] and affects both sexes, so treatment for men should not be neglected. Existing evidence for male osteoporosis treatment is limited, and clinical trials were not powered for fracture risk reduction [17–19]. The generalizability of clinical trials may be questioned when applied to

men, although the general consensus among experts is that therapeutic effectiveness of these agents applies to men equally. There are very few trials specifically focused on individuals of advanced age. As is true for many of the drugs that are used to treat seniors, we must extrapolate the findings in younger individuals to the specific population of seniors of advanced age who are the most likely to receive the above osteoporosis drugs.

Calcium and Vitamin D

There is controversy regarding whether to supplement calcium and vitamin D to the elderly for fracture prevention. Numerous systematic reviews and meta-analyses have been done. The findings can be summarized as follows:

- In vitamin D deficient individuals, which constitutes 40–100 % of elderly individuals [20], supplementation of at least 800 IU/day of vitamin D_3 (cholecalciferol) can prevent fractures of the vertebra and hips particularly those in long-term care settings [21]. Supplementing with 400 IU/day of vitamin D_3 or equivalent has no effect on fracture prevention.
- In those who are vitamin D replete (above 75 nmol/L), there is no additional benefit of supplementation. Supplementing supratherapeutic doses of vitamin D_3 at 500,000 IU in intermitted pulses is associated with increased fracture risk [22]. The Institute of Medicine's upper limit of tolerance (UL) is 4000 IU/day, although European guidelines state that up to 10,000 IU/day is safe [23].
- Elemental calcium daily intake of 1000–1200 mg/day with vitamin D repletion reduces hip fracture risk in postmenopausal women [24]. The ideal method of intake is through dietary intake instead of supplementation [25]. There is a small increased risk of renal stones (HR 1.17) [26] and perhaps constipation with calcium supplements [27]. There is controversy as to whether calcium supplements increase cardiovascular disease, with two meta-analysis of randomized clinical trials reaching different conclusions [28, 29]. Arterial wall calcium deposition is *not* increased in those who are supplemented [30, 31], putting the mechanism of this association into question.
- Adherence to calcium and vitamin D supplementation is related to outcomes. In the Women's Health Initiative (WHI) clinical trial, adherence rate was 60 % and those who were adherent had reduced hip fracture risk [26]. A large observational cohort in Spain including both males and females had an adherence rate of 20 %, with 27 % of participants stopping therapy altogether after 1 year of treatment [32]. Therefore, real life adherence may be even less than that of clinical trials, and adherence is linked to reduced fracture risk.

Calcium and vitamin D supplementation has become routine practice for reduction of fracture risk in institutionalized and community-dwelling elderly individuals. The evidence for institutionalized elderly individuals (vast majority being women) is strong in a meta-analysis of 3 clinical trials (total n = 3998), which showed a relative risk (RR) of 0.71 (95 % CI 0.57–0.89) in reduction of hip and total fractures with low heterogeneity ($I^2 = 0$ %) [24]. Elemental calcium 1200 mg/day and vitamin D 800–1000 IU/day were used in those trials.

In community-dwelling elderly individuals (n = 43,549), there is a similar trend toward reduced fracture risk in the same meta-analysis, although the relationship is non-significant (RR 0.89, 95 % CI 0.76–1.04) and there is moderate heterogeneity ($I^2 = 27$ %). The finding is driven by the largest clinical trial, the WHI (n = 36,282), which showed no difference in fracture risk when supplementing with 1000 mg/day of elemental calcium and 400 IU/day of vitamin D over an average follow-up period of 7 years in women aged 50–79 [26]. However, the hip fracture risk was significantly lower when those who were non-adherent were excluded in a subgroup analysis, HR 0.71 (0.52–0.97) [26]. This corresponded to a significantly improved BMD at the hip but not spine after 3 or more years of therapy. Since hip fractures are the most devastating of all

fractures, consideration should be given to this important finding. Another issue is the suboptimal dose of vitamin D used in the WHI study. A later meta-analysis showed a dose–response relationship between hip fractures and serum vitamin D level [21]. At least 800 IU/day is required for fracture reduction, and the 400 IU/day used in the WHI trial is insufficient. Therefore, calcium and vitamin D supplementation is likely to be of benefit in community-dwelling elderly individuals, especially women.

While adequate calcium may be achieved through diet, vitamin D almost certainly requires supplementation, particularly for institutionalized individuals. The active form of vitamin D is synthesized through UVB radiation to the skin from the sun. Institutionalized individuals and community-dwelling elderly individuals living away from the equator do not get enough sunshine for optimal vitamin D levels [20]. Most experts [23, 33] recommend targeting serum 25(OH)D level at >50 nmol/l, and optimally 75 nmol/l. The Institute of Medicine considers serum levels >125 nmol/l to be associated with adverse events, including hypercalcemia [34]. Oral intake of 800 IU/day of vitamin D_3 will make 97.5 % of the population reach the minimal serum 25(OH)D level of 50 nmol/l, and 1600 IU/day is required to reach a serum level of 75 nmol/l [35]. A 2012 meta-analysis of vitamin D supplementation clinical trials showed that doses of 800–2000 IU/day significantly reduced hip (RR 0.70, 0.58–0.86) and any non-vertebral (RR 0.86, 0.76–0.96) fractures compared with lower doses. Both institutionalized and community-dwelling individuals age >65 benefit from high dose vitamin D in this analysis. Therefore, from all existing clinical and physiologic data, vitamin D supplementation of at least 800 IU/day is recommended for optimal bone health.

The recommended intake of elemental calcium of 1200 mg/day for elderly men and women should be acquired through diet [25]. When dietary intake is less than adequate, supplemental calcium should be given to meet requirements. The safety of calcium supplements has received attention recently. Self-reported gastrointestinal (GI) complaints such as constipation and bloating were more common in calcium-supplemented individuals in a meta-analysis of RCTs (n = 10,128) comparing calcium and placebo [36]. However, this meta-analysis did not include data from the large WHI trial (n = 36,282), which reported similar rates of GI symptoms between calcium and placebo groups [26]. The occurrence of renal stones was higher in the calcium group in the WHI trial (HR 1.17, 1.02–1.34), but baseline calcium intake was high, making the overall daily intake higher than 1200 mg. Other trials have not found increased calculi risk [37]. High dietary calcium typically protects from renal stones by binding to and excreting oxalate in stool. Therefore, the minimal risk of constipation and renal stones, even if present, is likely negligible compared to the benefits of fracture prevention.

The risk of cardiovascular disease has been widely publicized based on a 2010 meta-analysis of RCTs showing increased myocardial infarction (MI) risk in calcium-supplemented groups [38]. Self-reported MIs were used to reach this conclusion. Subsequent studies have shown significant bias in self-report cardiovascular events, especially if there are increased GI complaints, which can mimic chest pain [36]. A 2014 meta-analysis of RCTs (n = 63,563) with *verified* cardiovascular events showed no difference between calcium supplements and placebo (RR 1.02, 0.96–1.09), with low heterogeneity ($I^2 = 0$ %) and low publication bias [28]. Furthermore, in a subset of the WHI participants (n = 792) who underwent cardiac CT to determine levels of coronary artery calcification, a strong predictor of cardiovascular risk, showed no difference in calcification level between calcium and placebo groups [30]. Cardiovascular events are common in the elderly, but calcium supplementation with vitamin D does not appear to increase risk of these events. Furthermore, all RCTs of osteoporosis medications required participants to have adequate intake of both calcium and vitamin D at these targets, indicating a commonly accepted prerequisite for proper bone health.

Bisphosphonates

Bisphosphonates are the first line therapy for senile osteoporosis. There is evidence for preventing vertebral and hip fractures [39–41], in

older women [14, 41], in men [17], in dementia [42], and in glucocorticoid-induced osteoporosis [43]. Adherence is about 50 % in real-world usage [44], which is poor and leads to reduced efficacy [45]. In general, major clinical trials of bisphosphonates have included older women with osteoporosis, both with and without pre-existing fractures. Most trials exclude "severe medical illness," which may reduce external validity for institutionalized elderly patients with advanced dementia, although this group of geriatric patients is not explicitly excluded. Given the well-established benefit of bisphosphonates and high morbidity and mortality associated with fractures, bisphosphonates are still considered first-line therapy for all patients of advanced age with osteoporosis. However, since bisphosphonates are renally excreted, renal impairment with creatinine clearance less than 30 mL/min is a contraindication for use. Also, the high prevalence of dysphagia in institutionalized patients [46] makes oral formulations less tolerable.

Alendronate [40, 47], risedronate [41, 48], and zoledronic acid [49] are the most well-studied bisphosphonates and all have efficacy in preventing hip and vertebral fractures, although risedronate is not approved by the U.S. Food and Drug Administration for hip fracture prevention. Clodronate and ibandronate are less preferred for various reasons, including the lack of proven effectiveness in preventing hip fractures [50, 51]. The Fracture Intervention Trials (FIT I [40] and II [47]) were the first large-scale RCTs of bisphosphonate therapy for osteoporosis powered for fracture risk reduction. Women aged 55–81 with femoral neck T-score $\leq$2.1 and (i) a prior vertebral fractures (FIT I, n = 2027) or (ii) no prior fractures (FIT II, n = 4432) were randomized to alendronate 5 mg daily (increased to 10 mg daily after 24 months) or placebo for 3 and 4 years, respectively. In those with a prior vertebral fracture (FIT I), alendronate significantly reduced the risk of vertebral (RR 0.53, 95 % CI 0.41–0.68), hip (RR 0.49, 95 % CI 0.23–0.99), wrist, and all clinical fractures combined. In those without prior fracture (FIT II), alendronate reduced new vertebral fractures (RR 0.56, 95 % CI 0.39–0.80), but did not significantly reduce hip or all clinical fractures. Selecting individuals at high risk for fractures (e.g. those with prior fractures) increases the chances of detecting a significant treatment effect, which is a common theme among osteoporosis trials.

A meta-analysis of alendronate and zoledronic acid RCTs showed a significant reduction in hip fractures with postmenopausal women using alendronate (n = 9808, HR 0.61, 95 % CI 0.40–0.93) and zoledronic acid (n = 9863, HR 0.62, 95 % CI 0.46–0.82) [49]. The same meta-analysis also found significant reduction in vertebral fractures for alendronate (n = 7145, HR 0.54, 95 % CI 0.44–0.66) and zoledronic acid (n = 7802, HR 0.38, 95 % CI 0.22–0.67). There was low heterogeneity in these results, except for vertebral fractures between the two large zoledronic acid trials [39, 52]. The reason is that one of the trials did not use radiographic evidence to detect vertebral fractures, which likely under-detected actual vertebral fracture incidence [52].

Zoledronic acid also appears to have a mortality benefit in a specific population after hip fracture. The HORIZON-R clinical trial randomized 2127 patients, both men and women age 50–98, within 90 days of having a surgically repaired hip fracture to zoledronic acid 5 mg IV once yearly vs. placebo [52]. These patients had to be intolerant to or unable to take an oral bisphosphonate. Although the study was not powered to detect a difference in recurrent hip fractures, there was a significant reduction in the primary outcome of all clinical vertebral fractures and secondary outcome of mortality. After an average follow-up of 1.9 years, the hazard ratio for all-cause mortality was 0.72 (95 % CI 0.56–0.93). However this benefit was only protective for patients with normal cognition; those with cognitive impairment did not benefit from this reduction in death [53]. A large prospective cohort in Dubbo, Australia demonstrated similar mortality benefits of bisphosphonate therapy in community dwelling elderly women with osteoporosis (adjusted HR 0.31, 95 % CI 0.17–0.59) [54], suggesting the importance of bisphosphonate therapy beyond fracture prevention.

Risedronate has been studied in similar populations. Two of the initial large trials, VERT-MN and VERT-NA, established risedronate's safety and efficacy in reducing vertebral fractures in

postmenopausal women with established osteoporosis and at least one vertebral fracture [55, 56]. Subsequently, the larger HIP trial was done to detect risedronate's efficacy in preventing hip fractures in two groups of women: (1) age 70–79 with osteoporosis and (2) age greater than 80 at risk for fractures, but not necessarily with osteoporosis [41]. The HIP trial showed efficacy for the entire pooled population (n = 9331) for significantly reducing hip fractures after 2 years of therapy, RR 0.7 (95 % CI 0.6–0.9). However, in the predefined subgroups, only women ages 70–79 (n = 5445) with established osteoporosis had a significant benefit (RR 0.6, 95 % CI 0.4–0.9), while the other group of older women with risk factors alone (n = 3886) did not benefit in terms of hip fractures (RR 0.8, 95 % CI 0.6–1.2). This difference is likely due to lack of power to detect this rare event rather than the medication not benefitting this older age group.

Adherence is linked to better outcomes for bisphosphonate therapy [45], and intermittent dosing helps improve adherence [57]. Risedronate has demonstrated non-inferiority using once monthly [58] and once weekly [59] dosing compared with the daily dosing used in the aforementioned trials. Intermittent risedronate showed similar gains in BMD, reductions in bone turnover, and number of new vertebral fractures. Alendronate also has a once weekly dosing that is non-inferior to daily dosing used in the large clinical trials [60]. However, the alendronate study demonstrates only BMD and bone turnover non-inferiority without fracture data. These weekly or monthly formulations are considered first line therapy over daily dosing. Should a patient not tolerate oral bisphosphonate because of GI side effects or inability to sit up for 30 min after ingestion, they should be offered yearly intravenous zoledronic acid or biannually subcutaneous denosumab.

Much controversy has been generated over the risk of osteonecrosis of the jaw (ONJ) and atypical femur fractures (AFF) with bisphosphonate use. ONJ is defined as exposed bone in the jaw that does not heal by 8 weeks. It is associated with poor dental hygiene, dental procedures, glucocorticoid therapy, proton-pump inhibitor use, and bisphosphonate use [61]. Although the risk of ONJ is moderate with cancer-related bisphosphonate therapy (400 in 100,000 patient-years), the risk is very low in osteoporosis-related therapy (1 in 100,000 patient-years) [62]. In contrast, the risk of a major osteoporotic fracture in women with low, medium, and high risk is 650 in 100,000, 1600 in 100,000, and 3100 in 100,000 patient-years, respectively [61]. An AFF is one that occurs in the subtrochanteric region or femur shaft, typically without any trauma. The risk increases with the length of bisphosphonate therapy, with 1.78 in 100,000 patient-years with 1 year of use and increasing to 113.1 in 100,000 patient-years with 8 years of use [63]. As such, some clinicians discontinue bisphosphonates in low-to-moderate risk patients taking a bisphosphonate after 3–5 years, with regular reassessment for possible re-initiation. Those with existing fragility fracture or those at high fracture risk should probably be considered for continued treatment because the risk of a major osteoporotic fracture (hip or vertebral) is more than 30 times higher than AFF [61].

Estrogen and Selective Estrogen Receptor Modulator (SERM)

Hormone replacement therapy with estrogen has high quality evidence of effectiveness in preventing both hip and vertebral fractures in all postmenopausal women regardless of fracture risk. This was shown in the famous Women's Health Initiative (WHI) trial that randomized 16,608 postmenopausal women aged 50–79 to estrogen plus progesterone therapy vs. placebo for an average of 5.6 years [64], which was terminated early. There were significantly more cases of coronary artery disease, breast cancer, stroke, and pulmonary embolism [65] that basically negates any global benefit [64]. Estrogen is no longer routinely recommended therapy because of other drugs with more favorable risk-benefit profiles. Consideration is given to short courses for those with concomitant menopausal symptoms, understanding the risks of estrogen therapy.

Selective estrogen receptor modulators (SERMs) act as estrogen agonists in bone and liver but not other tissues. Raloxifene is a well-studied SERM that reduces vertebral fractures and improves BMD, but there is *no* demonstrated reduction in hip and nonvertebral fractures [66]. Raloxifene treatment also significantly increases the risk of venous thromboembolism, RR 3.1 (95 % CI 1.5–6.2), but significantly reduces the risk of breast cancer, RR 0.3 (95 % CI 0.2–0.6) [67]. Overall, bisphosphonates, denosumab, and teriparatide should be considered over raloxifene because they are more effective and have better risk-benefit profiles than raloxifene.

Newer third-generation SERMs, including bazedoxifene and lasofoxifene, are approved in the European Union for high-risk postmenopausal osteoporosis; bazedoxifene is also approved by the FDA in the United States. Despite significant benefit in reducing vertebral fractures, both drugs have not been shown to reduce hip fractures [68–70]. There is a significantly increased risk for deep venous thrombosis in both drugs. Again, other osteoporotic agents should be considered before using these new SERMs.

Strontium Ranelate

Strontium ranelate is a metallic salt that is effective in reducing both vertebral and hip fractures [71]. In the phase 3 TROPOS study, postmenopausal women (n = 5091) aged 50–100 years were randomized to strontium ranelate 2 g/day vs. placebo for 5 years with a preplanned statistical analysis at 3 years. There was a preplanned subgroup of high-risk patients for analysis of hip fractures as well as a subgroup of patients over the age of 80 years for analysis of all fractures [72]. At both the 3- and 5-year mark, there were significantly fewer vertebral fractures in the entire group and subgroup of patients age ≥80, and there were significantly fewer hip fractures in the high risk group [71, 73]. The small subgroup of 1488 patients age ≥80 did not have enough power to detect a difference in hip fractures.

Despite its initial promising results with seemingly limited side effects, several serious safety concerns of strontium were identified in recent years. The European Medicines Agency (EMA) released post-marketing surveillance data that revealed significant side effects not captured in the initial trial data [74]. In pooled analysis of seven studies encompassing 7572 women, treatment with strontium ranelate demonstrated an increased in risk of non-fatal myocardial infarction (OR 1.6, 95 % CI 1.07–2.38) [75]. The increased risks were only seen in patients with pre-existing cardiovascular risk factors such as poorly controlled hypertension (BP >160/90 mmHg) or known ischemic heart disease. Furthermore, there was an increased risk of venous thromboembolism in the elderly population (age >80 years), RR 1.87 (95 % CI 1.06–3.31) [75]. In addition, since its launch up to September 2011, 86 cases of *Drug Reaction* (or Rash) with *Eosinophilia and Systemic Symptoms* (4 fatal cases) and 10 cases of *Toxic Epidermal Necrolysis* or *Stevens Johnson Syndrome* (3 fatal cases) were reported in the post-marketing setting [76].

Given the risks found in post-marketing surveillance, especially for elderly individuals, other medications should be considered for treatment of osteoporosis.

Denosumab

Denosumab is a human monoclonal antibody against the human receptor activator of the nuclear factor κB ligand (RANKL) [5]. In the FREEDOM trial, postmenopausal women with osteoporosis aged 60–90 years (n = 7868) were randomized to denosumab 60 mg subcutaneous injections every 6 months for 36 months vs. placebo [77]. At 3 years, the active treatment group showed a reduction of new radiographic vertebral fractures by 68 % (RR 0.32, 95 % CI 0.26–0.41; p = 0.001) and hip fractures by 20 % (RR 0.60, 95 % CI 0.37–0.97; p = 0.05).

In the FREEDOM extension study interim report at 6 years of exposure, the denosumab group maintained reduced bone turnover, increased BMD at the spine and hip, and the fracture incidence remained low for vertebral, hip, and other non-vertebral fractures [78]. The

investigators had the placebo group crossover to active treatment for 3 years, and the participants quickly achieved similar benefits in fracture reduction.

With regards to safety, denosumab was generally well tolerated in the FREEDOM trial. There have been some concerns regarding potential risks of infection and malignancy as RANKL is also expressed by immune cells. In the original 3-year study, an increased occurrence of cellulitis was detected in the denosumab group vs. placebo (0.3 % vs. <0.1 %, p=0.002) [77], but this was not observed in those participating in the extension study [78]. There was no increase in the rate of malignancy in either the original or extension studies [77, 78]. Six cases of ONJ and 1 case of AFF were adjudicated to be related to denosumab in the FREEDOM extension study (n=4550), while none were identified in the first 3 years of the original trial [78]. At 6 years into the extension study, 2 more cases of ONJ and no new cases of AFF were found [79].

Denosumab has several advantages over bisphosphonates. First, it increases BMD and reduces bone turnover more than bisphosphonates as shown by several head-to-head trials comparing denosumab with alendronate, risedronate, and ibandronate for 12 months in osteoporotic women [80–82]. However, fracture data were not collected in these studies. Safety appears to be similar between denosumab and bisphosphonates. Second, with subcutaneous administration and infrequent dosing (once every 6 months), denosumab usage is more convenient than oral bisphosphonates (once daily, weekly or monthly dosing) and less invasive than intravenous zoledronic acid. Third, recent cost-effectiveness analyses using US, UK, and Canadian healthcare models suggest cost-effectiveness or dominance over oral bisphosphonates currently used [83–85]. The US price of 1 injection of denosumab is $1057.86, while the cost of 6 months of generic alendronate is $491.70 USD, and 6 months of generic risedronate is $1400.34 USD [86].

Limitations of denosumab include unclear ideal duration of therapy and relatively less usage experience compared to bisphosphonates. Denosumab is an effective therapy for postmenopausal women with osteoporosis, especially in those who cannot tolerate bisphosphonate therapy.

Teriparatide

There are two recombinant parathyroid hormone analogs: PTH 1-34 (teriparatide) and PTH 1-84 (full-length hormone). Both are anabolic agents that stimulate bone remodeling by inducing an increase in bone formation followed by a slower increase in bone resorption [87].

The Fracture Prevention Trial randomized 1637 ambulatory postmenopausal women with osteoporosis and prior vertebral fracture, aged 42–86, to teriparatide 20 mcg, 40 mcg, or placebo injections daily for 21 months [87]. Both doses of teriparatide demonstrated a 65 % relative risk reduction in the risk of new vertebral fracture (RR 0.35, 95 % CI 0.22–0.55), and a 53 % reduction in non-vertebral fractures (RR 0.47, 95 % CI 0.25–0.88). However, the study population was not powered to detect a difference in hip fractures. Since both doses were equivalent, the lower 20 mcg subcutaneous daily dosing is now approved for use.

The safety and efficacy of teriparatide is established in elderly patients older than 80 years. In a post-hoc analysis of the Fracture Prevention Trial, there was no age interaction with the effectiveness of fracture prevention or occurrence of adverse events between those younger than 75 or age 75 years and older [88]. Contraindications to teriparatide use are conditions that abnormally increase bone turnover such as hypercalcemia, hyperparathyroidism, Paget's disease of the bone, increased alkaline phosphatase, or patients with skeletal malignancies [89]. Severe renal impairment is also a contraindication because teriparatide is renally excreted. To date, the initial concerns regarding the increased osteosarcoma with teriparatide use have not been clinically substantiated in humans [90].

An added benefit of teriparatide is its analgesic property for those suffering back pain secondary to vertebral fractures. A meta-analysis of 5 randomized clinical trials comparing teriparatide with placebo, alendronate, and hormone replacement therapy

showed significantly lower back pain when comparing teriparatide to each control group [91], and this effect persists up to 30 months after discontinuing teriparatide [92].

Combination and sequential therapy with teriparatide and other agents have been investigated. Sequential therapy where bisphosphonate users are switched to teriparatide shows a transient reduction in hip BMD for the first 6 months that reverses consistently to bone formation after [93]. There is no convincing evidence that the combination therapy of teriparatide and alendronate offers synergistic effects on BMD [18, 94]. In contrast, combined treatment with teriparatide and denosumab led to a greater increase in BMD in all skeletal sites, compared to teriparatide or denosumab alone [95]. Sequential therapy of an anti-resorptive agent after PTH therapy is important to prevent bone resorption. A randomized trial comparing 1 year of alendronate vs. placebo after 1 year of parathyroid hormone (PTH 1–84) treatment in 223 postmenopausal women showed continued rise in BMD with alendronate, but decreased spine BMD with placebo [96]. Therefore, following parathyroid hormone treatment, anti-resorptive therapy is recommended.

Teriparatide is effective for postmenopausal osteoporosis [87], male osteoporosis [18], and glucocorticoid-induced osteoporosis [97]. It is approved in Canada, US, and Europe for those indications. PTH 1–84 is effective for postmenopausal osteoporosis [98], but is only available in Europe for this indication. Because of the high cost and inconvenient daily injections, these drugs are limited to patients with severe osteoporosis despite alternative therapy.

Conclusion

The landscape of osteoporosis treatment for seniors of advanced age is expansive, but there are yet newer therapies on the horizon [99, 100]. In summary of the discussion in this chapter, the following therapeutic options are recommended for osteoporosis in the elderly.

- Vitamin D supplementation of 800–2000 IU daily with elemental calcium 1200 mg/day, the latter ideally achieved through diet, is effective in preventing vertebral and hip fractures. Active monitoring of side effects is helpful to improve adherence.
- In addition to vitamin D and calcium repletion, an anti-resorptive or anabolic agent should be used in those with osteoporosis or prior fragility fractures.
- Bisphosphonates are first line therapy for osteoporosis. In particular, alendronate, risedronate, and zoledronic acid have proven efficacy in preventing vertebral and hip fractures when used properly. Consider intermittent formulations (weekly or monthly) to increase adherence. While counseling patients on the risk of ONJ and AFF, it is important to stress the much higher incidence of fractures, regardless of the fracture risk, compared to the small risk of these adverse events. Discontinuation of bisphosphonates can be considered for those at low-to-moderate fracture risk after 3–5 years of bisphosphonate therapy. Should bisphosphonates be discontinued, regular reassessment is needed to decide when and if to restart therapy.
- In patients intolerant of bisphosphonates or in those who have renal failure, denosumab is the next recommended choice of therapy. Denosumab is effective for preventing vertebral and hip fractures. The risks of ONJ and AFF are low, similar to bisphosphonates.
- In patients with severe osteoporosis despite anti-resorptive therapy, teriparatide is an anabolic agent that can be used in place of bisphosphonates or in combination with denosumab for up to 2 years, followed by continuation of anti-resorptive therapy. Special consideration for those with back pain secondary to vertebral fractures can be made for teriparatide for its analgesic properties.
- SERMs and strontium ranelate can be considered for postmenopausal osteoporosis only if treatment with the above medications is not possible. The risks of these therapies must be weighed against the benefits of fracture prevention. Note that

SERMs have not demonstrated efficacy in reducing hip or non-vertebral fractures. Also note the significant adverse events when strontium is used in the elderly population.

- Hormone replacement therapy should not be used for the sole purpose of treating osteoporosis. The harms outweigh any benefits.

References

1. Lips P. Vitamin D, deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr Rev. 2001;22:477–501. doi:10.1210/edrv.22.4.0437.
2. Kalyani RR, Stein B, Valiyil R, Manno R, Maynard JW, Crews DC. Vitamin D treatment for the prevention of falls in older adults: systematic review and meta-analysis. J Am Geriatr Soc. 2010;58:1299–310. doi:10.1111/j.1532-5415.2010.02949.x.
3. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. Nature. 2003;423:337–42. doi:10.1038/nature01658.
4. William J. Boyle WSS& DLL. Osteoclast differentiation and activation. Clin Calcium. 2007;17:484–92. doi:10.1038/nature01658.
5. Chitre M, Shechter D, Grauer A. Denosumab for treatment of postmenopausal osteoporosis. Am J Health Syst Pharm. 2011;68:1409–18. doi:10.2146/ajhp100493.
6. Deal C. Potential new drug targets for osteoporosis. Nat Clin Pract Rheumatol. 2009;5:20–7. doi:10.1038/ncprheum1027.
7. Watts NB, Cooper C, Lindsay R, Eastell R, Manhart MD, Barton IP, et al. Relationship between changes in bone mineral density and vertebral fracture risk associated with risedronate: greater increases in bone mineral density do not relate to greater decreases in fracture risk. J Clin Densitom. 2004;7:255–61.
8. Watts NB, Geusens P, Barton IP, Felsenberg D. Relationship between changes in BMD and nonvertebral fracture incidence associated with risedronate: reduction in risk of nonvertebral fracture is not related to change in BMD. J Bone Miner Res. 2005;20:2097–104. doi:10.1359/JBMR.050814.
9. Rabenda V, Bruyère O, Reginster J-Y. Relationship between bone mineral density changes and risk of fractures among patients receiving calcium with or without vitamin D supplementation: a meta-regression. Osteoporos Int. 2011;22:893–901. doi:10.1007/s00198-010-1469-x.
10. Jacques RM, Boonen S, Cosman F, Reid IR, Bauer DC, Black DM, et al. Relationship of changes in total hip bone mineral density to vertebral and nonvertebral fracture risk in women with postmenopausal osteoporosis treated with once-yearly zoledronic acid 5 mg: the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res. 2012;27:1627–34. doi:10.1002/jbmr.1644.
11. Austin M, Yang Y-C, Vittinghoff E, Adami S, Boonen S, Bauer DC, et al. Relationship between bone mineral density changes with denosumab treatment and risk reduction for vertebral and nonvertebral fractures. J Bone Miner Res. 2012;27:687–93. doi:10.1002/jbmr.1472.
12. Johnell O, Kanis JA, Odén A, Sernbo I, Redlund-Johnell I, Petterson C, et al. Mortality after osteoporotic fractures. Osteoporos Int. 2004;15:38–42. doi:10.1007/s00198-003-1490-4.
13. Shuid AN, Khaithir TMN, Mokhtar SA, Mohamed IN. A systematic review of the outcomes of osteoporotic fracture patients after hospital discharge: morbidity, subsequent fractures, and mortality. Ther Clin Risk Manag. 2014;106:937. doi:10.2147/TCRM.S72456.
14. Boonen S, McClung MR, Eastell R, El-Hajj Fuleihan G, Barton IP, Delmas P. Safety and efficacy of risedronate in reducing fracture risk in osteoporotic women aged 80 and older: implications for the use of antiresorptive agents in the old and oldest old. J Am Geriatr Soc. 2004;52:1832–9. doi:10.1111/j.1532-5415.2004.52506.x.
15. Boonen S, Adachi JD, Man Z, Cummings SR, Lippuner K, Törring O, et al. Treatment with denosumab reduces the incidence of new vertebral and hip fractures in postmenopausal women at high risk. J Clin Endocrinol Metab. 2011;96. doi:10.1210/jc.2010-2784.
16. Riggs BL, Wahner HW, Seeman E, Offord KP, Dunn WL, Mazess RB, et al. Changes in bone mineral density of the proximal femur and spine with aging. Differences between the postmenopausal and senile osteoporosis syndromes. J Clin Invest. 1982;70:716–23.
17. Orwoll E, Ettinger M, Weiss S, Miller P, Kendler D, Graham J, et al. Alendronate for the treatment of osteoporosis in men. N Engl J Med. 2000;343:604–10. doi:10.1056/NEJM200008313430902.
18. Finkelstein JS, Hayes A, Hunzelman JL, Wyland JJ, Lee H, Neer RM. The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. N Engl J Med. 2003;349:1216–26. doi:10.1056/NEJMoa035725.
19. Orwoll ES, Miller PD, Adachi JD, Brown J, Adler RA, Kendler D, et al. Efficacy and safety of a once-yearly i.v. infusion of zoledronic acid 5 mg versus a once-weekly 70-mg oral alendronate in the treatment of male osteoporosis: a randomized, multicenter, double-blind, active-controlled study. J Bone Miner Res. 2010;25:2239–50. doi:10.1002/jbmr.119.
20. Holick MF. Vitamin D, deficiency. N Engl J Med. 2007;357:266–81. doi:10.1056/NEJMra070553.
21. Bischoff-Ferrari HA, Willett WC, Orav EJ, Oray EJ, Lips P, Meunier PJ, et al. A pooled analysis of

vitamin D dose requirements for fracture prevention. N Engl J Med. 2012;367:40–9. doi:10.1056/NEJMoa1109617.
22. Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA. 2010;303:1815–22. doi:10.1001/jama.2010.594.
23. Rizzoli R, Boonen S, Brandi M-L, Bruyère O, Cooper C, Kanis JA, et al. Vitamin D supplementation in elderly or postmenopausal women: a 2013 update of the 2008 recommendations from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Curr Med Res Opin. 2013;29:305–13. doi:10.1185/03007995.2013.766162.
24. Chung M, Lee J, Terasawa T, Lau J, Trikalinos TA. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. Ann Intern Med. 2011;155:827–38. doi:10.7326/0003-4819-155-12-201112200-00005.
25. Bauer DC. Clinical practice. Calcium supplements and fracture prevention. N Engl J Med. 2013;369:1537–43. doi:10.1056/NEJMcp1210380.
26. Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006;354:669–83. doi:10.1056/NEJMoa055218.
27. Reid IR. Osteoporosis treatment: focus on safety. Eur J Intern Med. 2013;24:691–7. doi:10.1016/j.ejim.2013.03.012.
28. Lewis JR, Radavelli-Bagatini S, Rejnmark L, Chen JS, Simpson JM, Lappe JM, et al. The effects of calcium supplementation on verified coronary heart disease hospitalization and death in postmenopausal women: a collaborative meta-analysis of randomized controlled trials. J Bone Miner Res. 2015;30:165–75. doi:10.1002/jbmr.2311.
29. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's health initiative limited access dataset and meta-analysis. BMJ. 2011;342:d2040.
30. Manson JE, Allison MA, Carr JJ, Langer RD, Cochrane BB, Hendrix SL, et al. Calcium/vitamin D supplementation and coronary artery calcification in the Women's Health Initiative. Menopause. 2010;17:683–91. doi:10.1097/gme.0b013e3181d683b5.
31. Wang TKM, Bolland MJ, van Pelt NC, Horne AM, Mason BH, Ames RW, et al. Relationships between vascular calcification, calcium metabolism, bone density, and fractures. J Bone Miner Res. 2010;25:2777–85. doi:10.1002/jbmr.183.
32. Castelo-Branco C, Cortés X, Ferrer M. Treatment persistence and compliance with a combination of calcium and vitamin D. Climacteric. 2010;13:578–84. doi:10.3109/13697130903452804.
33. Lips P, Bouillon R, van Schoor NM, Vanderschueren D, Verschueren S, Kuchuk N, et al. Reducing fracture risk with calcium and vitamin D. Clin Endocrinol (Oxf). 2010;73:277–85. doi:10.1111/j.1365-2265.2009.03701.x.
34. Aloia JF. Clinical review: the 2011 report on dietary reference intake for vitamin D: where do we go from here? J Clin Endocrinol Metab. 2011;96:2987–96. doi:10.1210/jc.2011-0090.
35. Gallagher JC, Sai A, Templin T, Smith L. Dose response to vitamin D supplementation in postmenopausal women: a randomized trial. Ann Intern Med.2012;156:425–37.doi:10.7326/0003-4819-156-6-201203200-00005.
36. Lewis JR, Zhu K, Prince RL. Adverse events from calcium supplementation: relationship to errors in myocardial infarction self-reporting in randomized controlled trials of calcium supplementation. J Bone Miner Res. 2012;27:719–22. doi:10.1002/jbmr.1484.
37. Manson JE, Bassuk SS. Calcium supplements: do they help or harm? Menopause. 2014;21:106–8. doi:10.1097/GME.0b013e31829be090.
38. Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ. 2010;341:c3691.
39. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356:1809–22. doi:10.1056/NEJMoa067312.
40. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet. 1996;348:1535–41.
41. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med. 2001;344:333–40. doi:10.1056/NEJM200102013440503.
42. Sato Y, Kanoko T, Satoh K, Iwamoto J. The prevention of hip fracture with risedronate and ergocalciferol plus calcium supplementation in elderly women with Alzheimer disease: a randomized controlled trial. Arch Intern Med. 2005;165:1737–42. doi:10.1001/archinte.165.15.1737.
43. Adachi JD, Saag KG, Delmas PD, Liberman UA, Emkey RD, Seeman E, et al. Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. Arthritis Rheum. 2001;44:202–11. doi:10.1002/1529-0131(200101)44:1<202::AID-ANR27>3.0.CO;2-W.
44. Kothawala P, Badamgarav E, Ryu S, Miller RM, Halbert RJ. Systematic review and meta-analysis of real-world adherence to drug therapy for osteoporosis. Mayo Clin Proc. 2007;82:1493–501. doi:10.1016/S0025-6196(11)61093-8.
45. Siris ES, Harris ST, Rosen CJ, Barr CE, Arvesen JN, Abbott TA, et al. Adherence to bisphosphonate

therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. Mayo Clin Proc. 2006; 81:1013–22. doi:10.4065/81.8.1013.
46. Namasivayam AM, Steele CM. Malnutrition and Dysphagia in long-term care: a systematic review. J Nutr Gerontol Geriatr. 2015;34:1–21. doi:10.1080/21551197.2014.1002656.
47. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA. 1998;280:2077–82. doi:10.1001/jama.280.24.2077.
48. Masud T, McClung M, Geusens P. Reducing hip fracture risk with risedronate in elderly women with established osteoporosis. Clin Interv Aging. 2009;4:445–9. doi:10.2147/CIA.S8200.
49. Serrano AJ, Begona L, Anitua E, Cobos R, Orive G. Systematic review and meta-analysis of the efficacy and safety of alendronate and zoledronate for the treatment of postmenopausal osteoporosis. Gynecol Endocrinol. 2013;29:1005–14. doi:10.3109/09513590.2013.813468.
50. Chesnut III CH, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res. 2004;19:1241–9. doi:10.1359/JBMR.040325.
51. McCloskey EV, Beneton M, Charlesworth D, Kayan K, DeTakats D, Dey A, et al. Clodronate reduces the incidence of fractures in community-dwelling elderly women unselected for osteoporosis: results of a double-blind, placebo-controlled randomized study. J Bone Miner Res. 2007;22:135–41. doi:10.1359/jbmr.061008.
52. Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med. 2007;357:1799–809. doi:10.1056/NEJMoa074941.
53. Prieto-Alhambra D, Judge A, Arden NK, Cooper C, Lyles KW, Javaid MK. Fracture prevention in patients with cognitive impairment presenting with a hip fracture: secondary analysis of data from the HORIZON Recurrent Fracture Trial. Osteoporos Int. 2014;25:77–83. doi:10.1007/s00198-013-2420-8.
54. Center JR, Bliuc D, Nguyen ND, Nguyen TV, Eisman JA. Osteoporosis medication and reduced mortality risk in elderly women and men. J Clin Endocrinol Metab. 2011;96:1006–14. doi:10.1210/jc.2010-2730.
55. Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int. 2000;11:83–91. 00110083.198 [pii].
56. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA. 1999;282:1344–52. doi:10.1001/jama.282.14.1344.
57. Lee S, Glendenning P, Inderjeeth CA. Efficacy, side effects and route of administration are more important than frequency of dosing of anti-osteoporosis treatments in determining patient adherence: a critical review of published articles from 1970 to 2009. Osteoporos Int. 2011;22:741–53. doi:10.1007/s00198-010-1335-x.
58. Rackoff P. Efficacy and safety of risedronate 150 mg once a month in the treatment of postmenopausal osteoporosis. Clin Interv Aging. 2009;4:207–14. doi:10.1016/j.bone.2007.09.001.
59. Brown JP, Kendler DL, McClung MR, Emkey RD, Adachi JD, Bolognese MA, et al. The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. Calcif Tissue Int. 2002;71:103–11. doi:10.1007/s00223-002-2011-8.
60. Schnitzer T, Bone HG, Crepaldi G, Adami S, McClung M, Kiel D, et al. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. Alendronate Once-Weekly Study Group. Aging (Milano). 2000;12:1–12.
61. Brown JP, Morin S, Leslie W, Papaioannou A, Cheung AM, Davison KS, et al. Bisphosphonates for treatment of osteoporosis: expected benefits, potential harms, and drug holidays. Can Fam Physician. 2014;60:324–33.
62. Khan AA, Rios LP, Sándor GKB, Khan N, Peters E, Rahman MO, et al. Bisphosphonate-associated osteonecrosis of the jaw in Ontario: a survey of oral and maxillofacial surgeons. J Rheumatol. 2011;38:1396–402. doi:10.3899/jrheum.100221.
63. Dell RM, Adams AL, Greene DF, Funahashi TT, Silverman SL, Eisemon EO, et al. Incidence of atypical nontraumatic diaphyseal fractures of the femur. J Bone Miner Res. 2012;27:2544–50. doi:10.1002/jbmr.1719.
64. Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA. 2003;290:1729–38. doi:10.1001/jama.290.13.1729.
65. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002;288:321–33. doi:10.1001/jama.288.3.321.
66. Cranney A, Tugwell P, Zytaruk N, Robinson V, Weaver B, Adachi J, et al. Meta-analyses of therapies for postmenopausal osteoporosis. IV. Meta-analysis of raloxifene for the prevention and treatment of postmenopausal osteoporosis. Endocr Rev. 2002;23:524–8. doi:10.1210/er.2001-4002.

67. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA. 1999;282:637–45. joc90496 [pii].
68. Silverman SL, Chines AA, Kendler DL, Kung AWC, Teglbjærg CS, Felsenberg D, et al. Sustained efficacy and safety of bazedoxifene in preventing fractures in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled study. Osteoporos Int. 2012;23:351–63. doi:10.1007/s00198-011-1691-1.
69. Palacios S, Silverman SL, de Villiers TJ, Levine AB, Goemaere S, Brown JP, et al. A 7-year randomized, placebo-controlled trial assessing the long-term efficacy and safety of bazedoxifene in postmenopausal women with osteoporosis. Menopause. 2015;22:806–13. doi:10.1097/GME.0000000000000419.
70. Cummings SR, Ensrud K, Delmas PD, LaCroix AZ, Vukicevic S, Reid DM, et al. Lasofoxifene in postmenopausal women with osteoporosis. N Engl J Med. 2010;362:686–96. doi:10.1056/NEJMoa0808692.
71. Reginster JY, Felsenberg D, Boonen S, Diez-Perez A, Rizzoli R, Brandi ML, et al. Effects of long-term strontium ranelate treatment on the risk of nonvertebral and vertebral fractures in postmenopausal osteoporosis: results of a five-year, randomized, placebo-controlled trial. Arthritis Rheum. 2008;58:1687–95. doi:10.1002/art.23461.
72. Seeman E, Vellas B, Benhamou C, Aquino JP, Semler J, Kaufman JM, et al. Strontium ranelate reduces the risk of vertebral and nonvertebral fractures in women eighty years of age and older. J Bone Miner Res. 2006;21:1113–20. doi:10.1359/jbmr.060404.
73. Reginster JY, Seeman E, De Vernejoul MC, Adami S, Compston J, Phenekos C, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab. 2005;90:2816–22. doi:10.1210/jc.2004-1774.
74. CHMP. Protelos and Osseor Article-20 procedure: CHMP scientific conclusions and PRAC assessment report. Eur Med Agency. 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Protelos_and_Osseor/Opinion_provided_by_Committee_for_Medicinal_Products_for_Human_Use/WC500162132.pdf. Accessed 15 Feb 2015.
75. European Medicines Agency. Protelos-H-C-560-PSU-31: EPAR—Assessment Report—Periodic safety update report. 2013. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000560/WC500147168.pdf.
76. European Medicines Agency. Protelos-H-C-560-A20–34: EPAR—Assessment Report—Article 20. 2012. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000560/WC500131789.pdf.
77. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361:756–65. doi:10.1056/NEJMoa0809493.
78. Bone HG, Chapurlat R, Brandi ML, Brown JP, Czerwiński E, Krieg MA, et al. The effect of three or six years of denosumab exposure in women with postmenopausal osteoporosis: results from the FREEDOM extension. J Clin Endocrinol Metab. 2013;98:4483–92. doi:10.1210/jc.2013-1597.
79. Papapoulos S, Roux C, Bone HG, Dakin P, Czerwinski E, Frey D, Kendler D, Lewiecki EM, Malouf J, Mellstrom D, Reginster JY, Resche H, Daizadeh NS, Wang A, Gavin M, Wagman RB, Brandi M. Denosumab treatment in postmenopausal women with osteoporosis for up to 9 years: results through year 6 of the FREEDOM extension study. Osteoporos Int. 2015;26:S37–9.
80. Brown JP, Prince RL, Deal C, Recker RR, Kiel DP, de Gregorio LH, et al. Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. J Bone Miner Res. 2009;24:153–61. doi:10.1359/jbmr.080901.
81. Kendler DL, Roux C, Benhamou CL, Brown JP, Lillestol M, Siddhanti S, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. J Bone Miner Res. 2010;25:72–81. doi:10.1359/jbmr.090716.
82. Brown JP, Roux C, Ho PR, Bolognese MA, Hall J, Bone HG, et al. Denosumab significantly increases bone mineral density and reduces bone turnover compared with monthly oral ibandronate and risedronate in postmenopausal women who remained at higher risk for fracture despite previous suboptimal treatment with an oral bis. Osteoporos Int. 2014;25:1953–61. doi:10.1007/s00198-014-2692-7.
83. Parthan A, Kruse M, Yurgin N, Huang J, Viswanathan HN, Taylor D. Cost effectiveness of denosumab versus oral bisphosphonates for postmenopausal osteoporosis in the US. Appl Health Econ Health Policy. 2013;11:485–97. doi:10.1007/s40258-013-0047-8.
84. Chau D, Becker DL, Coombes ME, Ioannidis G, Adachi JD, Goeree R. Cost-effectiveness of denosumab in the treatment of postmenopausal osteoporosis in Canada. J Med Econ. 2012;15 Suppl 1:3–14. doi:10.3111/13696998.2012.737393.
85. Ström O, Jönsson B, Kanis JA. Intervention thresholds for denosumab in the UK using a FRAX®-based cost-effectiveness analysis. Osteoporos Int. 2013;24:1491–502. doi:10.1007/s00198-012-2115-6.
86. Lexicomp. Lexicomp drug database. 2015. http://www.wolterskluwercdi.com/lexicomp-online/.
87. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1–34) on fractures and bone mineral den-

sity in postmenopausal women with osteoporosis. N Engl J Med. 2001;344:1434–41. doi:10.1056/NEJM200105103441904.
88. Boonen S, Marin F, Mellstrom D, Xie L, Desaiah D, Krege JH, et al. Safety and efficacy of teriparatide in elderly women with established osteoporosis: bone anabolic therapy from a geriatric perspective. J Am GeriatrSoc.2006;54:782–9.doi:10.1111/j.1532-5415.2006.00695.x.
89. Sikon A, Batur P. Profile of teriparatide in the management of postmenopausal osteoporosis. Int J Womens Health. 2010;2:37–44. doi:10.2147/IJWH.S4919.
90. Harper KD, Krege JH, Marcus R, Mitlak BH. Osteosarcoma and teriparatide? J Bone Miner Res. 2007;22:334. doi:10.1359/jbmr.061111.
91. Nevitt MC, Chen P, Dore RK, Reginster JY, Kiel DP, Zanchetta JR, et al. Reduced risk of back pain following teriparatide treatment: a meta-analysis. Osteoporos Int. 2006;17:273–80. doi:10.1007/s00198-005-2013-2.
92. Nevitt MC, Chen P, Kiel DP, Reginster JY, Dore RK, Zanchetta JR, et al. Reduction in the risk of developing back pain persists at least 30 months after discontinuation of teriparatide treatment: a meta-analysis. Osteoporos Int. 2006;17:1630–7. doi:10.1007/s00198-006-0177-z.
93. Boonen S, Marin F, Obermayer-Pietsch B, Simões ME, Barker C, Glass EV, et al. Effects of previous antiresorptive therapy on the bone mineral density response to two years of teriparatide treatment in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2008;93:852–60. doi:10.1210/jc.2007-0711.
94. Black DM, Greenspan SL, Ensrud KE, Palermo L, McGowan JA, Lang TF, et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. N Engl J Med. 2003;349:1207–15. doi:10.1097/01.OGX.0000115856.54444.D6.
95. Tsai JN, Uihlein AV, Lee H, Kumbhani R, Siwila-Sackman E, McKay EA, et al. Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. Lancet. 2013;382:50–6. doi:10.1016/S0140-6736(13)60856-9.
96. Black DM, Bilezikian JP, Ensrud KE, Greenspan SL, Palermo L, Hue T, et al. One year of alendronate after one year of parathyroid hormone (1–84) for osteoporosis. N Engl J Med. 2005;353:555–65. doi:10.1097/01.ogx.0000193859.78235.fe.
97. Saag KG, Shane E, Boonen S, Marín F, Donley DW, Taylor KA, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. N Engl J Med. 2007;357:2028–39. doi:10.1097/01.ogx.0000310357.43258.f1.
98. Greenspan SL, Bone HG, Ettinger MP, Hanley DA, Lindsay R, Zanchetta JR, et al. Effect of recombinant human parathyroid hormone (1–84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis. A randomized trial. Ann Intern Med. 2007;146:326–39.
99. Appelman-Dijkstra NM, Papapoulos SE. Novel approaches to the treatment of osteoporosis. Best Pract Res Clin Endocrinol Metab. 2014;28:843–57. doi:10.1016/j.beem.2014.07.003.
100. Papapoulos SE. Anabolic bone therapies in 2014: new bone-forming treatments for osteoporosis. Nat Rev Endocrinol. 2015;11:69–70. doi:10.1038/nrendo.2014.214.

Fracture Liaison Services

13

Paul J. Mitchell

The Need for Fracture Liaison Services

Fracture Begets Fracture

For more than three decades it has been known that a considerable proportion of older people who fracture their hip have suffered prior fragility fractures. In 1980, Gallagher and colleagues described the fracture history of people presenting with hip fractures in Rochester, Minnesota during the period 1965–1974 [1]. Sixty eight percent of women and 59 % of men had a history of at least one other fracture in addition to their hip fracture. More recent studies from Australia [2], the United Kingdom [3] and the United States [4] reported similar findings, with approximately half of hip fracture patients having prior history of a clinically apparent fracture.

A corollary to these retrospective observations follows from meta-analyses, which considered future fracture risk among people experiencing new, or incident, fractures [5, 6]. People who have suffered one fragility fracture are at double the risk of suffering future fractures, as compared to age-matched fracture-free peers. The '*osteoporotic career*' illustrated in Fig. 13.1 – an expression originally coined by Marsh and subsequently referred to by a growing number of organizations worldwide [7–10] – is familiar to people living with osteoporosis and their healthcare team. A minority of older people endure a cycle of fragility fractures throughout their latter decades [11].

An International Care Gap

Since the 1990s, a broad range of treatments have been licensed to improve bone mineral density (BMD) and, in the majority of cases, prevent fragility fractures, including hip and vertebral fractures [12–24]. These treatments can be administered as daily, weekly or monthly tablets, or as daily, quarterly, 6-monthly or annual injections. Expiry of patent protection relating to a number of the bisphosphonate drugs has led to widespread availability of low cost generic products throughout the world.

Given that about half of hip fracture patients effectively provide advance notice that they will fracture their hip in the future – by presenting with an incident fragility fracture in the present – it is all the more surprising, and disappointing, that the majority of fragility fracture sufferers do not receive appropriate secondary preventive care [7–10, 25–30]. A lack of clarity

P.J. Mitchell, BSc (Hons), C.Chem., MRSC
Synthesis Medical NZ Ltd, Franklin, Pukekohe 2120, New Zealand

School of Medicine, University of Notre Dame Australia, Sydney Campus, Darlinghurst, NSW, Australia
e-mail: paul.mitchell@synthesismedical.com

G. Duque, D.P. Kiel (eds.), *Osteoporosis in Older Persons: Advances in Pathophysiology and Therapeutic Approaches*, DOI 10.1007/978-3-319-25976-5_13

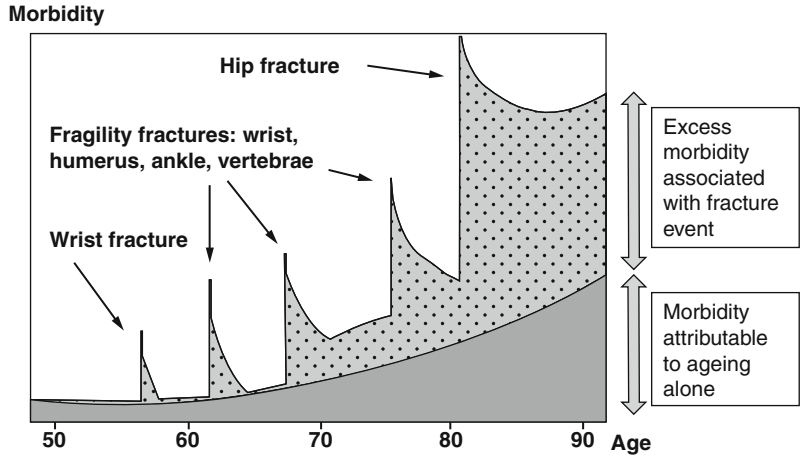


Fig. 13.1 The 'osteoporotic career': fragility fractures through the life span (Adapted from Kanis and Johnell [102]. Reproduced with kind permission of Springer International Publishing AG)

regarding where clinical responsibility lays for delivery of this care seems to be the primary source of inertia. A UK study, which evaluated behaviours of orthopaedic surgeons and general practitioners (GPs) in response to patients who suffered fragility fractures, identified where continuity of care was breaking down [31]. Whilst both surgeons and GPs agreed in principle that fragility fracture patients should undergo assessment for osteoporosis, each group relied on the other to deliver secondary prevention. This failure to take ownership for the secondary prevention of future fractures served to trigger the development of the first Fracture Liaison Services (FLS) in several countries [32–35], which were designed to reliably respond to the first fracture with a determined effort to prevent second and subsequent fractures. In addition to assessing and, where appropriate, treating osteoporosis, FLS ensure that interventions to reduce falls risk are deployed.

The Fracture Liaison Service Model of Care

FLS Case Studies

The purpose of an FLS is to ensure that all men and women above a specific age who suffer fragility fractures:

- Undergo assessment for treatment of osteoporosis, and initiate treatment where needed.
- Undergo assessment for falls risk and receive evidence-based interventions as required.

Some of the first high-performing FLS were developed in Australia [35], Canada [33], the United Kingdom [32] and the United States [34]. Summaries of the service structures and outcomes achieved by these FLS are provided below:

- Australia: The Minimal Trauma Fracture Liaison (MTFL) service at Concord Repatriation General Hospital in Sydney was established in 2005. The MTFL service provides care for non-frail fragility fracture patients, while frail patients are managed by the orthogeriatric service based at the same hospital. Delivered primarily by a first year advanced physician trainee, the impact of the MTFL service on fracture rates was evaluated. As compared to fracture patients who declined the consultation freely offered by the service, refracture rates were 80 % lower for MTFL patients [35]. A formal cost-effectiveness analysis concluded that the incremental costs per quality adjusted life year (QALY) gained for the MTFL was approximately one-third of the accepted maximum willingness to pay cost of AU$50,000 for one QALY gained [36].

- Canada: The Osteoporosis Exemplary Care Program (OECP) was established in St. Michael's Hospital in Toronto in 2002. In the first year of operations, 96 % of the 430 fracture patients managed by the OECP received appropriate care [33]. Formal cost-effectiveness analysis of the OECP reported that a hospital which employs an osteoporosis coordinator to manage 500 fracture patients per year will reduce subsequent hip fracture rates by 9 % in the first year [37]. A sensitivity analysis concluded that there was a 90 % probability that hiring a coordinator would cost less than CN$25,000 per hip fracture prevented, and that a coordinator could manage just 350 patients per year to remain cost-effective.
- United Kingdom: The Glasgow FLS was established in the university teaching hospitals in Glasgow in 1999 and 2000 [32]. During the first 18 months, 4600 fracture patients were seen by the FLS nurse specialists. Nearly three-quarters were considered for bone density testing, and among those tested 82 % were found to have low bone mass (i.e. osteopenia or osteoporosis). The Glasgow FLS expanded considerably during the first decade of operations [38]:
  - 1999: West Glasgow FLS
  - 1 centre: population 250,000: 1500 fractures per year
  - 2002: Pan-Greater Glasgow FLS
  - 3 centres: population 1 million: 6500 fractures per year
  - 2009: Pan-Greater Glasgow and Clyde FLS
  - 5 centres: population 1.4 million: 9000 fractures per year

  In 2011, a formal cost-effectiveness analysis of the Glasgow FLS was published [39]. This study concluded that 18 fractures were prevented, including 11 hip fractures, and £21,000 GBP was saved per 1000 patients managed by the Glasgow FLS versus 'usual care' in the UK.
- United States: In the late 1990s, Kaiser Permanente developed the Healthy Bones Program [34], facilitated by Kaiser's state-of-the-art electronic medical record systems, HealthConnect®. The Healthy Bones Program is delivered primarily by Care Managers and Nurse Practitioners. All fragility fracture patients presenting to Kaiser medical facilities receive secondary preventive care. A systematic approach to primary fracture prevention is also offered to women aged 65 years and over and men aged 70 years and over [40]. Actuarial analysis was conducted to assess the impact of the Healthy Bones Program on hip fracture rates [34]. In 2006, observed hip fracture rates in Kaiser Southern California were 37 % lower than the expected rate.

Publications on FLS have appeared from a growing number of other countries, including France [41], Ireland [42], Northern Ireland [43], Singapore [44], Spain [45], Switzerland [46] and The Netherlands [47]. Furthermore, the International Osteoporosis Foundation (IOF) Capture the Fracture® Program (see below) has created a 'map of best practice' which showcases FLS from all regions of the world [48].

An emerging body of evidence suggests that osteoporosis treatment is associated with reduced mortality [23, 49–52]. In 2014, for the first time, in addition to a beneficial effect on fracture rates, care delivered by an FLS was shown to reduce mortality of fracture patients. Investigators from the Netherlands recruited consecutive patients presenting to a university hospital with an FLS (FLS Group, n = 1412) and a general hospital without an FLS (No FLS Group, n = 1910) [53]. The results were analysed according to the intention-to-treat principle. Among the FLS Group, 67.8 % agreed to the FLS evaluation (the 'shows'). The 32.2 % of FLS Group patients who rejected the FLS assessment (the 'no shows') were older and had sustained more hip fractures. The subsequent non-vertebral fracture risk was lower for the FLS Group as compared to the No FLS Group, and increased over time. A 16 % lower risk of repeat fracture was evident at 12 months, which was not statistically significant. From 15 months onwards the risk was 28 % lower, increasing to 56 % lower by 24 months, both results achieving statistical significance. In terms of mortality – after correction for age, sex and baseline fracture location –

35 % fewer patients died in the FLS Group as compared to the No FLS Group. Notably, mortality reduction was significantly higher for women compared to men. If these findings prove to be reproducible by other FLS, in addition to reducing refracture rates and saving money, the case could be made that FLS save lives.

Systematic Review of FLS

The most recent of several systematic reviews on FLS sought to determine how service structure relates to outcomes of care [54–56]. Ganda and colleagues classified FLS according to the intensity of service provided, as Type A through to Type D as indicated below [56]:

- Type A – 3i FLS model:
  - Identification of fragility fracture patients and provision of education on osteoporosis and fracture risk to the patient.
  - Investigation, commonly including BMD testing.
  - Initiation of osteoporosis treatment where appropriate.
- Type B – 2i FLS model:
  - Identification.
  - Investigation.
  - Leaves the initiation of treatment for fragility fracture patients to the primary care provider (PCP).
- Type C – 1i FLS model:
  - Identification.
  - PCP is alerted that the patient has suffered a fracture and that further assessment is needed.
  - Leaves the investigation and initiation of treatment to the PCP.
- Type D – 'Zero i' FLS model:
  - Only provides osteoporosis and fracture risk education to the fracture patient.
  - PCP is neither alerted nor educated on the need for secondary fracture prevention measures.

The proportion of fracture patients that underwent BMD testing and received osteoporosis treatment is shown in Table 13.1. Clearly, the intensity of service provision determines the rates for investigation and initiation of treatment.

Table 13.1 Intensity of FLS service provision and outcomes of care

Model	BMD testing (%)	Osteoporosis treatment (%)
Type A: 3i FLS model	79	46
Type B: 2i FLS model	60	41
Type C: 1i FLS model	43	23
Type D: Zero i FLS model	–	8

Adapted from Ganda et al. [56]. Reproduced with kind permission of Springer International Publishing AG

Currently, there is a lack of consensus regarding what the 'ideal' osteoporosis treatment rate should be for fragility fracture patients. The National Institute for Health and Clinical Excellence (NICE) in the United Kingdom first published guidance on secondary fracture prevention for postmenopausal women in 2005 [57]. NICE estimated the proportion of women with new fragility fractures aged 50 years and over that could be treated according to their guidance, based on the following assumptions:

- Approximately 50 % of fragility fractures occur in women over the age of 75 years, and 25 % each in women aged 65–74 years and 50–64 years.
- The proportion of women with new fragility fractures who are treated with bisphosphonates was 100 % in the age group over 75 years, 60 % in the age group 65–74 years and 20 % in the age group 50–64 years.

While estimates informed by absolute fracture risk assessment, rather than BMD and age alone, are likely to provide a better basis for ascertaining what the 'ideal' treatment rate should be, it is likely to be in the range 50–70 %. Given that the majority of local, regional and national audits summarized on the IOF Capture the Fracture®

Program website report treatment rates of less than 20 % [28], the current situation globally is far from optimal.

Standards for FLS

During 2013–14, clinical or quality standards for FLS have been published [58–60]. These standards provide a quality framework which serves to illustrate what a high-performing FLS will deliver. Summaries of these documents are provided below:

- International Osteoporosis Foundation: The IOF Capture the Fracture® Program Best Practice Framework (BPF) is based on 13 globally endorsed clinical standards for FLS [58]. The BPF is structured to evaluate five 'domains' of an FLS, which relate to care of four fragility fracture groups (hip fracture, other inpatient fractures, outpatient fracture, vertebral fracture) and an organizational domain.
- Osteoporosis Canada: *Quality Standards for Fracture Liaison Services in Canada* describe seven key standards for FLS to deliver [59]. The quality standards are in compliance with the 2010 Osteoporosis Canada Guidelines [61] and the IOF BPF [58]. As of November 2014, the quality standards had been endorsed by the Canadian Orthopaedic Association, the Canadian Orthopaedic Nurses Association, Bone and Joint Canada and the Canadian Rheumatology Association.
- National Osteoporosis Society (UK): In December 2014, the National Osteoporosis Society in the United Kingdom published a draft clinical standard for FLS for public consultation [62]. These standards are based in the so-called '5IQ' approach, which incorporates a standard relating to long-term management:
  - Identification: Finding fracture patients.
  - Investigation: Fracture and falls risk assessment.
  - Information: Educating patients on their fracture and falls risk.
  - Intervention: Drug treatments and non-pharmacological options.
  - Integration: Provision of long-term management plans to general practitioners and other health care professionals.
  - Quality: Ongoing audit of the FLS, continuing professional development and peer review.

The emergence of these standards provides established FLS throughout the world an opportunity to benchmark their performance against best practice. Recent efforts in New Zealand to drive nationwide adoption of FLS have benefitted from the IOF BPF [63–65]. For healthcare professionals and administrators who are developing new FLS, quality standards provide a helpful illustration of 'what success looks like' and so facilitates design of a service which aims to deliver best practice from the outset.

International and National FLS Initiatives

During the current decade a number of major initiatives intended to drive widespread implementation of FLS at the international and national levels have been developed and implemented:

- International initiatives:
  - International Osteoporosis Foundation: The IOF Capture the Fracture® Program aims to support implementation of FLS throughout the world. Key components of the Program include the Best Practice Framework clinical standards for FLS discussed above [58], a comprehensive website with a suite of FLS resources [28] and a 'map of best practice' which enables sharing of best practice between FLS [48].
  - American Society for Bone and Mineral Research Task Force on Secondary Fracture Prevention: The ASBMR Task Force published a comprehensive report on the practicalities of FLS implementation [66, 67]. Input from 65 leading healthcare professionals from 36 countries reinforced the

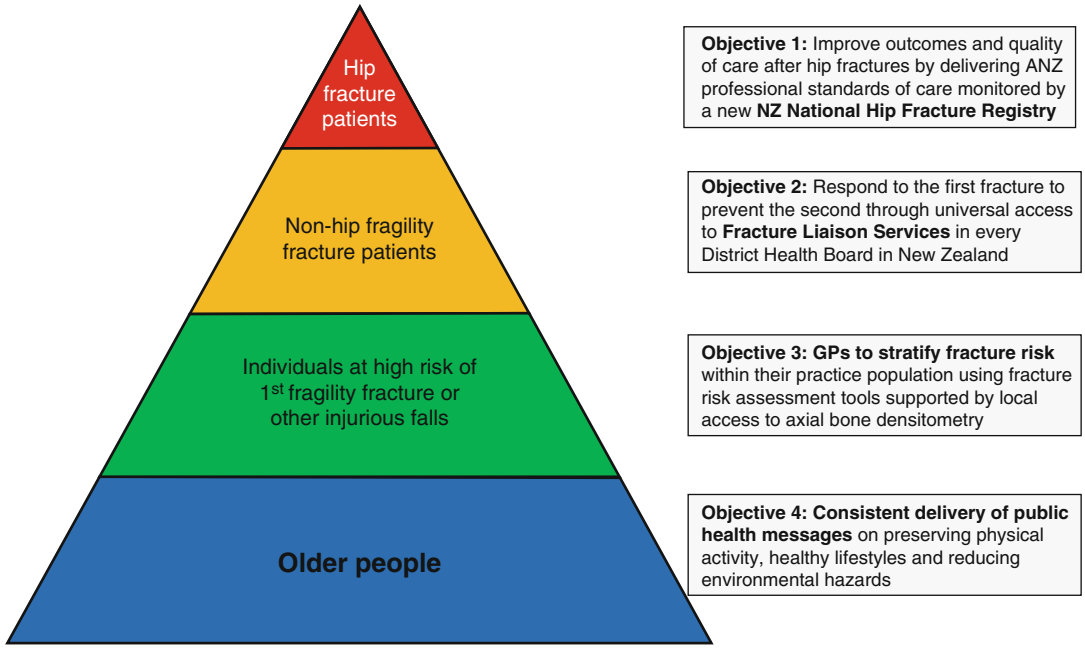


Fig. 13.2 BoneCare 2020: a systematic approach to hip fracture care and prevention for New Zealand (Reproduced with kind permission of Osteoporosis New Zealand)

global relevance of FLS as a mechanism to eliminate the post-fracture care gap.
  - Australian and New Zealand Bone and Mineral Society: In 2015, the ANZBMS published a position paper on secondary fracture prevention, which called for widespread implementation of FLS in both countries [68].
- National initiatives:
  - Canada: Since 2011, Osteoporosis Canada (OC) has led calls for nationwide implementation of FLS [69, 70]. In 2013, OC published *Make the FIRST break the LAST with FLS* [8], which provided policymakers, healthcare professionals and administrators with a comprehensive suite of tools to support FLS implementation and model the economic impact of fragility fractures.
  - New Zealand: In 2012, Osteoporosis New Zealand (ONZ) published *Bone Care 2020: A systematic approach to hip fracture care and prevention for New Zealand* [9]. The key components of the strategy included establishment of a NZ Hip Fracture Registry, to enable nationwide benchmarking of Australian and New Zealand professional standards of acute hip fracture care [71], and implementation of FLS in all District Health Boards (DHBs) as illustrated in Fig. 13.2. In 2013, the Ministry of Health set an expectation that all DHBs implement an FLS [64].
  - United Kingdom: Almost one half of localities in the UK have established an FLS [72–74]. The multisector initiatives which have underpinned this progress are described in detail elsewhere [75]. Osteoporosis and falls management after hip fracture have improved dramatically as a result of the National Hip Fracture Database [76] and (in England) a Department of Health funded financial incentive which links delivery of professionally-defined standards of care [77] to reimbursement at the level of the individual patient [78].
  - United States: The National Bone Health Alliance (NBHA) is a public-private partnership launched in 2010 that brings together the expertise and resources of its member organizations to collectively: promote bone health and prevent disease;

Fig. 13.3 NBHA cast mountain (thanks to NBHA for permission to reproduce)

improve diagnosis and treatment of bone disease; and enhance bone research, surveillance and evaluation [79]. NBHA is leading three major programs to improve secondary fracture prevention in the United States:

- Fracture Prevention CENTRAL: The Fracture Prevention CENTRAL website provides a comprehensive suite of resources to support implementation of FLS [10]. An associated webinar series shares experience from established high-performing FLS with health professionals and administrators who are developing services.
- 2Million2Many: The 2Million2Many disease awareness campaign aims to drive awareness among the public that a fragility fracture is a sentinel event which should lead to osteoporosis assessment [80]. The 'Cast Mountain' installation shown in Fig. 13.3 has been displayed at medical conferences to highlight the 5500 fractures which occur every day among people aged 50 years and over in the United States.

Practical Steps to Implement an FLS

This section aims to provide readers with practical guidance on key steps in the implementation of a FLS. This material has been adapted from the corresponding section of the recently published Fracture Liaison Service Resource Pack (with kind permission of Osteoporosis New Zealand) [65]. The international and national initiatives mentioned above are also recommended reading for health professionals and administrators who are at the beginning of FLS development for their institution or health system.

Multi-disciplinary Stakeholder Group

The first step in implementation of a high-performing FLS is to establish a multi-disciplinary

stakeholder group. The group should include representation from all groups that will be impacted by the FLS, which is likely to include:

- The 'Lead Clinician in Osteoporosis' for the institution or health system (usually an endocrinologist, rheumatologist, geriatrician or orthopaedic surgeon)
- A senior orthopaedic Surgeon with an interest hip/fragility fracture surgery
- A senior geriatrician or ortho-geriatrician
- A senior radiologist or nuclear medicine specialist
- Relevant specialist nurses, physiotherapists and other Allied Healthcare Professionals
- Information Technology personnel responsible for development/installation of a FLS database
- Representatives from local hospital and primary care medicines management teams
- Representatives from local primary care-based service commissioning/business management groups
- Representatives from local family medicine/general practice groups
- A representative from the local public health organization
- A patient representative from a local/national osteoporosis society

Quality Improvement Methodology

The next step is to utilise a quality improvement methodology, such as Plan-Do-Study-Act (PDSA), which has been applied to FLS development [81]. This methodology will facilitate initial FLS design and a structured approach to continuous quality improvement:

- Plan
  - Conduct baseline audit to quantify the secondary fracture prevention care gap
    - Quantify the number of patients aged over 50 years who attend with fragility fracture
    - Determine what proportion of patients aged over 50 years receive secondary prevention post-fracture
    - Review any data from previous local audits of fragility fracture care
  - Design prototype service to close the care gap
    - Agree the scope of the FLS and objectives
    - Identify a reliable process for identification of fracture patients
    - Agree protocols for wards and fracture clinics
  - Ensure algorithms and protocols are agreed with all stakeholder groups before FLS clinics are initiated
  - Agree all documentation and communication mechanisms within hospital and with family medicine doctors/general practitioners
  - Develop a FLS business plan with all costs included
  - Engage with institution/health system management and/or healthcare commissioners to fund prototype FLS phase
- Do
  - Implement prototype FLS model of care
  - Collect audit data throughout prototype phase
- Study
  - Analyse improvement in provision of secondary preventive care from audit
  - Refine prototype FLS model of care to improve performance
- Act
  - Implement changes and monitor performance improvement
  - Agree long-term funding of FLS with institutional/health system management
  - Repeat PDSA cycle through continuous ongoing audit and review

Operational Issues

As described previously, the primary purpose of a FLS is to identify fracture patients and provide them with information on why osteoporosis is of significance to them, to ensure that appropriate investigations are undertaken to determine future fracture risk, and to initiate osteoporosis treatment, where warranted, and ensure that interventions to reduce falls risk are deployed where appropriate.

Identification of Fracture Patients

Whilst information technology has impacted dramatically on healthcare in general in the last 15 years, and so will often now render case-finding of fracture patients a comparatively simple task, published approaches to fracture patient case-finding by FLS merit consideration. These include:

- For patients managed as inpatients:
  - Regular visits by the Fracture Liaison Nurse (FLN) to the orthopaedic wards with orthopaedic ward staff maintaining a list of fracture admissions in between FLN visits [32]
  - Attendance by the FLN at daily trauma team meetings [82]
  - A care pathway/protocol for direct referral from orthogeriatric services
  - IT systems such as the Emergency Department weekly fracture report at the Royal Newcastle Centre and John Hunter Hospital in New South Wales [83], Kaiser Permanente's HealthConnect® [84] or FITOS® (Fracture Identification Tool for Orthopaedic Surgeons, RioMed Limited, UK) [85]
- For patients managed as outpatients:
  - Routine attendance by the FLN at fracture clinics [32, 86]
  - Face-to-face interaction with a medical registrar [87]
  - 'Link-nurses' – Provision of a daily register of new fracture patients by fracture clinic nurses [32]
  - IT systems such as the Emergency Department weekly fracture report at the Royal Newcastle Centre and John Hunter Hospital in New South Wales [83], Kaiser Permanente's HealthConnect® [84] or FITOS® (Fracture Identification Tool for Orthopaedic Surgeons, RioMed Limited, UK) [85]

Vertebral fractures are the most common fracture caused by osteoporosis, yet frequently do not come to clinical attention [88]. Reasons for this include [89]:

- The nature of the clinical presentation of vertebral fracture
- Vertebral fractures are often overlooked on X-Rays
- Vertebral fracture can be overruled by a diagnosis with a poor prognosis
- The clinical relevance of vertebral fracture may be overlooked

As illustrated in Table 13.2, a consequence of this issue is that only a small proportion of patients managed by FLS have suffered vertebral fractures [32, 33, 46, 81, 83, 90–92].

Several approaches have been undertaken to improve opportunistic identification of vertebral fractures:

- Vertebral Fracture Assessment (VFA): VFA technology is available on most modern bone densitometers. Dutch investigators undertook VFA when patients underwent DXA scan [93]. Just over a quarter of patients (26 %) had a vertebral fracture, of which 68 % were previously unrecognized.
- Digitalized chest radiographs: Analysis of digitalized chest radiographs stored on the Taipei Veterans General Hospital Radiology

Table 13.2 Vertebral fractures make up a small proportion of fractures identified by FLS

Country	FLS	Vertebral fractures (%)	Reference
Australia	Royal Newcastle	1.6	Giles et al. [83]
Canada	St. Michael's, Toronto	1.7	Bogoch et al. [33]
Netherlands	Eindhoven	5.4	Blonk et al. [90]
Switzerland	University Hospitals of Geneva	5.5	Chevalley et al. [46]
UK	Cambridge	0.1	Premaor et al. [91]
UK	Glasgow	2	McLellan et al. [32]
UK	Ipswich	1.8	Clunie and Stephenson [92]
USA	University of Wisconsin	6.1	Harrington et al. [81]

Reproduced with kind permission of Optasia Medical Ltd.

Information System in Taiwan showed the prevalence of unrecognized vertebral fracture to be 18.2 % [94].

- Computed Tomography (CT): Reformatting data from CT examinations of the chest or abdomen provided investigators in New Zealand with a means to identify vertebral fractures [95]. Amongst 175 consecutive patients aged over 65 years who had undergone CT, the prevalence of vertebral fractures was 13 %. The majority (77 %) of these fractures were previously unknown.
- Magnetic Resonance Imaging (MRI): MRI scans used for detection of breast cancer by Italian investigators provided a means to case-find vertebral fractures [96]. Vertebral fractures were identified in 9 % of patients, of which less than 12 % were previously known.

Once FLS have eliminated the secondary prevention care gap for patients presenting with clinically obvious fragility fractures, the approaches above could be integrated into FLS protocols to improve identification rates for vertebral fractures.

Investigation and Initiation of Interventions by FLS

The approach taken to investigation of fracture patients and initiation of interventions to reduce secondary fracture risk will vary between countries, as these aspects of care will be described in national clinical guidelines. For FLS established in countries without specific clinical guidelines examples from Australia [97], Canada [61], the UK [98, 99] and the United States [100] could inform practice and provide a basis for development of country-specific guidance.

As has been reported for hypertension and hyperlipidaemia, adherence and persistence with osteoporosis treatments routinely diminishes to 50 % within 1 year of initiation [101]. This issue has been recognized in the UK clinical standard for FLS within the '5IQ' approach discussed previously [62]. Provision of long-term management plans to family medicine doctors/general practitioners and other health care professionals is essential if the impact of FLS on secondary fracture rates is to be optimised.

References

1. Gallagher JC, Melton LJ, Riggs BL, Bergstrath E. Epidemiology of fractures of the proximal femur in Rochester, Minnesota. Clin Orthop Relat Res. 1980;(150):163–71. PubMed Epub 1980/07/01. eng.
2. Port L, Center J, Briffa NK, Nguyen T, Cumming R, Eisman J. Osteoporotic fracture: missed opportunity for intervention. Osteoporos Int. 2003;14(9):780–4. PubMed Epub 2003/08/09. eng.
3. McLellan A, Reid D, Forbes K, Reid R, Campbell C, Gregori A, et al. Effectiveness of strategies for the secondary prevention of osteoporotic fractures in Scotland (CEPS 99/03). Glasgow, Scotland: NHS Quality Improvement Scotland; 2004.
4. Edwards BJ, Bunta AD, Simonelli C, Bolander M, Fitzpatrick LA. Prior fractures are common in patients with subsequent hip fractures. Clin Orthop Relat Res. 2007;461:226–30. PubMed Epub 2007/04/07. eng.
5. Klotzbuecher CM, Ross PD, Landsman PB, Abbott 3rd TA, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res. 2000;15(4):721–39. PubMed Epub 2000/04/26. eng.
6. Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas P, et al. A meta-analysis of previous fracture and subsequent fracture risk. Bone. 2004;35(2):375–82. PubMed Epub 2004/07/23. eng.
7. Capture the fracture: a global campaign to break the fragility fracture cycle. Nyon: International Osteoporosis Foundation; 2012.
8. Make the FIRST break the LAST with Fracture Liaison Services. Osteoporosis Canada; 2013.
9. Bone care 2020: a systematic approach to hip fracture care and prevention for New Zealand. Wellington: Osteoporosis New Zealand; 2012.
10. National Bone Health Alliance. Fracture prevention CENTRAL 2014, 18 Aug 2014. Available from: http://www.nbha.org/fpc.
11. Cooper C, Mitchell P, Kanis JA. Breaking the fragility fracture cycle. Osteoporos Int. 2011;22(7):2049–50. PubMed Epub 2011/05/25. eng.
12. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet. 1996;348(9041):1535–41. PubMed Epub 1996/12/07. eng.
13. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple

Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA. 1999;282(7):637–45. PubMed Epub 1999/10/12. eng.
14. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA. 1999;282(14):1344–52. PubMed Epub 1999/10/20. eng.
15. Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int. 2000;11(1):83–91. PubMed Epub 2000/02/09. eng.
16. Torgerson DJ, Bell-Syer SE. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. JAMA. 2001;285(22):2891–7. PubMed Epub 2001/06/13. eng.
17. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med. 2001;344(5):333–40. PubMed Epub 2001/02/15. eng.
18. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344(19):1434–41. PubMed Epub 2001/05/11. eng.
19. Chesnut IC, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res. 2004;19(8):1241–9. PubMed Epub 2004/07/03. eng.
20. Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med. 2004;350(5):459–68. PubMed Epub 2004/01/30. eng.
21. Reginster JY, Seeman E, De Vernejoul MC, Adami S, Compston J, Phenekos C, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metabol. 2005;90(5):2816–22. PubMed Epub 2005/02/25. eng.
22. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356(18):1809–22. PubMed Epub 2007/05/04. eng.
23. Lyles KW, Colon-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med. 2007;357(18):1799–809. PubMed Epub 2007/09/20. eng.
24. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361(8):756–65. PubMed Epub 2009/08/13. eng.
25. Elliot-Gibson V, Bogoch ER, Jamal SA, Beaton DE. Practice patterns in the diagnosis and treatment of osteoporosis after a fragility fracture: a systematic review. Osteoporos Int. 2004;15(10):767–78. PubMed Epub 2004/07/20. eng.
26. Giangregorio L, Papaioannou A, Cranney A, Zytaruk N, Adachi JD. Fragility fractures and the osteoporosis care gap: an international phenomenon. Semin Arthritis Rheum. 2006;35(5):293–305. PubMed Epub 2006/04/18. eng.
27. National Osteoporosis Society. Protecting fragile bones: a strategy to reduce the impact of osteoporosis and fragility fractures in England/Scotland/Wales/Northern Ireland. 2009 May–Jun 2009. Report No.
28. International Osteoporosis Foundation. Capture the fracture: break the worldwide fragility fracture cycle 2014. 18 Aug 2014. Available from: http://www.capturethefracture.org/.
29. The state of health care quality report 2014. Washington, DC: National Committee for Quality Assurance; 2014.
30. Health and Social Care Information Centre. Quality and outcomes framework – prevalence, achievements and exceptions report: England, 2013-14. Leeds; 2014.
31. Chami G, Jeys L, Freudmann M, Connor L, Siddiqi M. Are osteoporotic fractures being adequately investigated? A questionnaire of GP & orthopaedic surgeons. BMC Family Pract. 2006;7:7. PubMed Pubmed Central PMCID: 1388220, Epub 2006/02/09. eng.
32. McLellan AR, Gallacher SJ, Fraser M, McQuillian C. The fracture liaison service: success of a program for the evaluation and management of patients with osteoporotic fracture. Osteoporos Int. 2003;14(12):1028–34. PubMed Epub 2003/11/06. eng.
33. Bogoch ER, Elliot-Gibson V, Beaton DE, Jamal SA, Josse RG, Murray TM. Effective initiation of osteoporosis diagnosis and treatment for patients with a fragility fracture in an orthopaedic environment. J Bone Joint Surg Am. 2006;88(1):25–34. PubMed Epub 2006/01/05. eng.
34. Dell R, Greene D, Schelkun SR, Williams K. Osteoporosis disease management: the role of the orthopaedic surgeon. J Bone Joint Surg Am. 2008;90 Suppl 4:188–94. PubMed Epub 2008/11/15. eng.
35. Lih A, Nandapalan H, Kim M, Yap C, Lee P, Ganda K, et al. Targeted intervention reduces refracture rates in patients with incident non-vertebral osteoporotic fractures: a 4-year prospective controlled study. Osteoporos Int. 2011;22(3):849–58. PubMed Epub 2010/11/26. eng.
36. Cooper MS, Palmer AJ, Seibel MJ. Cost-effectiveness of the Concord Minimal Trauma

Fracture Liaison service, a prospective, controlled fracture prevention study. Osteoporos Int. 2012;23(1):97–107. PubMed Epub 2011/09/29. eng.
37. Sander B, Elliot-Gibson V, Beaton DE, Bogoch ER, Maetzel A. A coordinator program in post-fracture osteoporosis management improves outcomes and saves costs. J Bone Joint Surg Am. 2008;90(6):1197–205. PubMed Epub 2008/06/04. eng.
38. McLellan AR, editor. Putting FLS into context: patients, professionals and policymakers. National osteoporosis society FLS education programme 2010 October 2010; Bristol/London/Newcastle/Cardiff/Manchester/Birmingham: National Osteoporosis Society.
39. McLellan AR, Wolowacz SE, Zimovetz EA, Beard SM, Lock S, McCrink L, et al. Fracture liaison services for the evaluation and management of patients with osteoporotic fracture: a cost-effectiveness evaluation based on data collected over 8 years of service provision. Osteoporos Int. 2011;22(7):2083–98. PubMed Epub 2011/05/25. eng.
40. Dell R. Fracture prevention in Kaiser Permanente Southern California. Osteoporos Int. 2011;22 Suppl 3:457–60. PubMed Epub 2011/08/24. eng.
41. Boudou L, Gerbay B, Chopin F, Ollagnier E, Collet P, Thomas T. Management of osteoporosis in fracture liaison service associated with long-term adherence to treatment. Osteoporos Int. 2011;22(7):2099–106. PubMed Epub 2011/04/30. eng.
42. Ahmed M, Durcan L, O'Beirne J, Quinlan J, Pillay I. Fracture liaison service in a non-regional orthopaedic clinic – a cost-effective service. Ir Med J. 2012;105(1):24, 6–7. PubMed.
43. Wallace I, Callachand F, Elliott J, Gardiner P. An evaluation of an enhanced fracture liaison service as the optimal model for secondary prevention of osteoporosis. JRSM Short Rep. 2011;2(2):8. PubMed Pubmed Central PMCID: 3046558, Epub 2011/03/04. eng.
44. Chandran M, Tan MZ, Cheen M, Tan SB, Leong M, Lau TC. Secondary prevention of osteoporotic fractures – an "OPTIMAL" model of care from Singapore. Osteoporos Int. 2013;24(11):2809–17. PubMed.
45. Carpintero P, Gil-Garay E, Hernandez-Vaquero D, Ferrer H, Munuera L. Interventions to improve inpatient osteoporosis management following first osteoporotic fracture: the PREVENT project. Arch Orthop Trauma Surg. 2009;129(2):245–50. PubMed Epub 2009/01/07. eng.
46. Chevalley T, Hoffmeyer P, Bonjour JP, Rizzoli R. An osteoporosis clinical pathway for the medical management of patients with low-trauma fracture. Osteoporos Int. 2002;13(6):450–5. PubMed Epub 2002/07/11. eng.
47. Huntjens KM, van Geel TC, Geusens PP, Winkens B, Willems P, van den Bergh J, et al. Impact of guideline implementation by a fracture nurse on subsequent fractures and mortality in patients presenting with non-vertebral fractures. Injury. 2011;42 Suppl 4:S39–43. PubMed Epub 2011/10/05. eng.
48. International Osteoporosis Foundation. Map of best practice 2014. 23 Dec 2014. Available from: http://capturethefracture.org/map-of-best-practice.
49. Bolland MJ, Grey AB, Gamble GD, Reid IR. Effect of osteoporosis treatment on mortality: a meta-analysis. J Clin Endocrinol Metabol. 2010;95(3):1174–81. PubMed Epub 2010/01/19. eng.
50. Center JR, Bliuc D, Nguyen ND, Nguyen TV, Eisman JA. Osteoporosis medication and reduced mortality risk in elderly women and men. J Clin Endocrinol Metabol. 2011;96(4):1006–14. PubMed Epub 2011/02/04. eng.
51. Beaupre LA, Morrish DW, Hanley DA, Maksymowych WP, Bell NR, Juby AG, et al. Oral bisphosphonates are associated with reduced mortality after hip fracture. Osteoporos Int. 2011;22(3):983–91. PubMed Epub 2010/11/06. eng.
52. Sambrook PN, Cameron ID, Chen JS, March LM, Simpson JM, Cumming RG, et al. Oral bisphosphonates are associated with reduced mortality in frail older people: a prospective five-year study. Osteoporos Int. 2011;22(9):2551–6. PubMed Epub 2010/10/21. eng.
53. Huntjens KM, van Geel TA, van den Bergh JP, van Helden S, Willems P, Winkens B, et al. Fracture liaison service: impact on subsequent nonvertebral fracture incidence and mortality. J Bone Joint Surg Am. 2014;96(4):e29. PubMed.
54. Little EA, Eccles MP. A systematic review of the effectiveness of interventions to improve post-fracture investigation and management of patients at risk of osteoporosis. Implement Sci. 2010;5:80. PubMed Pubmed Central PMCID: 2988064, Epub 2010/10/26.eng.
55. Sale JE, Beaton D, Posen J, Elliot-Gibson V, Bogoch E. Systematic review on interventions to improve osteoporosis investigation and treatment in fragility fracture patients. Osteoporos Int. 2011;22(7):2067–82. PubMed.
56. Ganda K, Puech M, Chen JS, Speerin R, Bleasel J, Center JR, et al. Models of care for the secondary prevention of osteoporotic fractures: a systematic review and meta-analysis. Osteoporos Int. 2013;24(2):393–406. PubMed Epub 2012/07/26. Eng.
57. National Institute for Health and Clinical Excellence. Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women, Technology appraisal guidance, vol. 87. London: National Institute for Clinical Excellence (NICE); 2005.
58. Akesson K, Marsh D, Mitchell PJ, McLellan AR, Stenmark J, Pierroz DD, et al. Capture the fracture: a best practice framework and global campaign to break the fragility fracture cycle. Osteoporos Int. 2013;24(8):2135–52. Epub 2013/04/16.
59. Osteoporosis Canada. Quality standards for fracture liaison services in Canada. Toronto: Osteoporosis Canada; 2014.

60. Gittoes N, McLellan AR, Cooper A, Dockery F, Davenport G, Goodwin V, et al. Effective secondary prevention of fragility fractures: clinical standards for fracture liaison services (draft for consultation). Camerton: National Osteoporosis Society; 2014.
61. Papaioannou A, Morin S, Cheung AM, Atkinson S, Brown JP, Feldman S, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ. 2010;182(17):1864–73. PubMed Pubmed Central PMCID: 2988535.
62. Gittoes N, McLellan AR, Cooper A, Dockery F, Davenport G, Goodwin V, et al. Effective secondary prevention of fragility fractures: clinical standards for fracture liaison services. Camerton: National Osteoporosis Society; 2014.
63. Health Quality and Safety Commission. Topic 6: why hip fracture prevention and care matters. Wellington; 2013, 18 Aug 2014. Available from: http://www.hqsc.govt.nz/our-programmes/reducing-harm-from-falls/10-topics/topic-6/.
64. Mitchell PJ, Cornish J, Milsom S, Hayman L, Seibel MJ, Close J, et al. BoneCare 2020: a systematic approach to hip fracture care and prevention for New Zealand. 3rd fragility fracture network congress 2014, 4–6 Sept 2014, Madrid; 2014.
65. Osteoporosis New Zealand. Fracture liaison services resource pack. Wellington: Osteoporosis New Zealand; 2014.
66. Eisman JA, Bogoch ER, Dell R, Harrington JT, McKinney Jr RE, McLellan A, et al. Making the first fracture the last fracture: ASBMR task force report on secondary fracture prevention. J Bone Miner Res. 2012;27(10):2039–46. PubMed Epub 2012/07/28. eng.
67. Eisman JA, Bogoch ER, Dell R, Harrington JT, McKinney RE Jr, McLellan A, et al. Appendix A to 'making the first fracture the last fracture': ASBMR task force report on secondary fracture prevention 2012. 1 Nov 2012. Available from: http://onlinelibrary.wiley.com/doi/10.1002/jbmr.1698/suppinfo.
68. Mitchell PJ, Ganda K, Seibel MJ. Australian and New Zealand Bone and Mineral Society Position Paper on Secondary Fracture Prevention Programs: A Call to Action. Australian and New Zealand Bone and Mineral Society; (In press: 2015).
69. Osteoporosis: towards a fracture free future. Toronto: Osteoporosis Canada; 2011.
70. Osteoporosis Canada. Osteoporosis patient bill of rights 2011. Available from: http://www.osteoporosis.ca/osteoporosis-and-you/copn/patient-bill-of-rights/.
71. Australian and New Zealand Hip Fracture Registry (ANZHFR) Steering Group. Australian and New Zealand guideline for hip fracture care: improving outcomes in hip fracture management of adults. Sydney: Australian and New Zealand Hip Fracture Registry Steering Group; 2014.
72. Clinical Effectiveness and Evaluation Unit. Falling standards, broken promises: report of the national audit of falls and bone health in older people 2010. Royal College of Physicians; 2011.
73. All wales audit of secondary prevention of osteoporotic fractures 2012. Aberystwyth: All Wales Osteoporosis Advisory Group; 2012.
74. The National Falls Programme in association with WorksOut as part of the Delivery Framework for Adult Rehabilitation in Scotland. Up and about or falling short? A report of the findings of a mapping of services for falls prevention and management and fracture prevention in older people in Scotland. Edinburgh: The Scottish Government; 2012.
75. Mitchell PJ. Fracture liaison services in the United Kingdom. Curr Osteoporos Rep. 2013;11(4):377–84. PubMed.
76. National hip fracture database (NHFD) extended report 2014. London: Royal College of Physicians; 2014.
77. British Geriatrics Society. The care of patients with fragility fracture. British Orthopaedic Association; 2007.
78. British Geriatrics Society. Best practice tariff for hip fracture – making ends meet 2010. 15 Mar 2012. Available from: http://www.bgs.org.uk/index.php?option=com_content&view=article&id=700:tariffhipfracture&catid=47:fallsandbones&Itemid=307.
79. National Bone Health Alliance. National bone health alliance: strong bones America Washington D.C. 2013. 17 Jan 2013. Available from: http://www.nbha.org/.
80. National Bone Health Alliance. 2Million2Many 2014, 18 Aug 2014. Available from: http://www.2million2many.org/.
81. Harrington JT, Barash HL, Day S, Lease J. Redesigning the care of fragility fracture patients to improve osteoporosis management: a health care improvement project. Arthritis Rheum. 2005;53(2):198–204. PubMed Epub 2005/04/09. eng.
82. Stephenson S. Developing an orthopaedic elderly care liaison service. J Orthop Nursing. 2003;7(3):150–5.
83. Giles M, Van Der Kallen J, Parker V, Cooper K, Gill K, Ross L, et al. A team approach: implementing a model of care for preventing osteoporosis related fractures. Osteoporos Int. 2011;22(8):2321–8. PubMed Epub 2010/11/04. eng.
84. Kaiser Permanente. Connectivity: comprehensive health information at your fingertips 2015. Cited 18 Feb 2015. Available from: http://share.kaiserpermanente.org/total-health/connectivity/.
85. Riomed Limited. FITOS = Fracture identification tool for orthopaedic surgeons Eastleigh, UK; 2015. Cited 18 Feb 2015. Available from: http://www.riomed.com/fitos.html.
86. Vaile J, Sullivan L, Bennett C, Bleasel J. First fracture project: addressing the osteoporosis care gap. Intern Med J. 2007;37(10):717–20. PubMed Epub 2007/09/27. eng.
87. Kuo I, Ong C, Simmons L, Bliuc D, Eisman J, Center J. Successful direct intervention for osteoporosis in patients with minimal trauma fractures.

Osteoporos Int. 2007;18(12):1633–9. PubMed Epub 2007/07/03. eng.
88. Delmas PD, van de Langerijt L, Watts NB, Eastell R, Genant H, Grauer A, et al. Underdiagnosis of vertebral fractures is a worldwide problem: the IMPACT study. J Bone Miner Res. 2005;20(4):557–63. PubMed Epub 2005/03/15. eng.
89. Lems WF. Clinical relevance of vertebral fractures. Ann Rheum Dis. 2007;66(1):2–4. PubMed Pubmed Central PMCID: 1798393, Epub 2006/12/21. eng.
90. Blonk MC, Erdtsieck RJ, Wernekinck MG, Schoon EJ. The fracture and osteoporosis clinic: 1-year results and 3-month compliance. Bone. 2007;40(6): 1643–9. PubMed Epub 2007/04/17. eng.
91. Premaor MO, Pilbrow L, Tonkin C, Adams M, Parker RA, Compston J. Low rates of treatment in postmenopausal women with a history of low trauma fractures: results of audit in a Fracture Liaison Service. QJM. 2010;103(1):33–40. PubMed Epub 2009/10/30. eng.
92. Clunie G, Stephenson S. Implementing and running a fracture liaison service: an integrated clinical service providing a comprehensive bone health assessment at the point of fracture management. J Orthop Nursing. 2008;12:156–62. Epub 21-11-2008.
93. Jager PL, Slart RH, Webber CL, Adachi JD, Papaioannou AL, Gulenchyn KY. Combined vertebral fracture assessment and bone mineral density measurement: a patient-friendly new tool with an important impact on the Canadian Risk Fracture Classification. Can Assoc Radiol J. 2010;61(4):194–200. PubMed Epub 2010/03/05. eng.
94. Chang HT, Chen CK, Chen CW, Lin MH, Peng LN, Chang CY, et al. Unrecognized vertebral body fractures (VBFs) in chest radiographic reports in Taiwan: a hospital-based study. Arch Gerontol Geriatr. 2012;55(2):301–4. PubMed Epub 2011/10/08. eng.
95. Chan PL, Reddy T, Milne D, Bolland MJ. Incidental vertebral fractures on computed tomography. N Z Med J. 2012;125(1350):45–50. PubMed Epub 2012/03/03. eng.
96. Bazzocchi A, Spinnato P, Garzillo G, Ciccarese F, Albisinni U, Mignani S, et al. Detection of incidental vertebral fractures in breast imaging: the potential role of MR localisers. Eur Radiol. 2012;22(12):2617–23. PubMed.
97. Osteoporosis Australia. Detection, prevention and treatment of osteoporosis. Melbourne: Royal Australian College of General Practitioners; 2010.
98. Denosumab for the prevention of osteoporotic fractures in postmenopausal women: NICE technology appraisal guidance 204. London: National Institute for Health and Clinical Excellence; 2010.
99. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. NICE technology appraisal guidance 161 (amended). London: National Institute for Health and Clinical Excellence; 2011.
100. Clinician's guide to prevention and treatment of osteoporosis. Washington, DC: National Osteoporosis Foundation; 2013.
101. Seeman E, Compston J, Adachi J, Brandi ML, Cooper C, Dawson-Hughes B, et al. Non-compliance: the Achilles' heel of anti-fracture efficacy. Osteoporos Int. 2007;18(6):711–9. PubMed Epub 2007/01/25. eng.
102. Kanis JA, Johnell O. The burden of osteoporosis. J Endocrinol Invest. 1999;22(8):583–8.

Treatment of Osteoporosis in Long-Term Care

14

Gustavo Duque, Pushpa Suriyaarachchi, Piumali Gunawardene, and Oddom Demontiero

Introduction

Severe disability, end stages of chronic diseases, poor social/familial support, and severe cognitive impairment, are considered as major determinants of admission of older people into long-term care institutions (LTCI) [1], as these conditions make elderly patients unable to cope with their life in the community thus requiring a higher amount of assistance in their activities of daily living [1]. Therefore, LTCI offer a set of care measures that attempt to improve their patients' quality of life and provide relief to caregivers and families.

Osteoporosis is one of the major health problems among LTC residents. It is considered one of the major "Geriatric Syndromes" (See Chap. 7) not only because its incidence increases with age but also because it predisposes to the occurrence of fractures and disability. Despite evidence that osteoporosis is highly prevalent in LTCI; it remains underdiagnosed and undertreated [2–8]. It is unfortunate because the higher prevalence of osteoporotic fractures [4, 8] has a significant impact on quality of care [9, 10] and, most importantly, on patient quality of life and mortality [9]. Even if awareness on the importance of osteoporosis in LTCI has grown in recent years, the effectiveness of the current treatments, although strongly validated in non-institutionalized seniors, has not been established in the LTCI population [11–13]. In this chapter, we will review the current considerations that should be made concerning the treatment of osteoporosis in LTCI. A comprehensive review of the literature is made, followed by a series of recommendations for the treatment of osteoporosis in LTCI, taking into account the unique aspects of this particular population.

The Particular Characteristics of the LTC Environment

Nursing homes play a pivotal role in caring for the frail population of older adults. In some countries, long-term care is differentiated according to the level of care required by their residents. Whereas low level of care institutions sometimes

G. Duque, MD, PhD, FRACP (✉)
Australian Institute for Musculoskeletal Science, The University of Melbourne and Western Health, St. Albans, VIC 3021, Australia
e-mail: gduque@unimelb.edu.au

P. Suriyaarachchi, MD, MBBS, FAFRM(RACP)
Department of Rehabilitation Medicine, Nepean Hospital, Penrith, NSW 2750, Australia
e-mail: Pushpa.Suriyaarachchi@health.nsw.gov.au

P. Gunawardene, MBBS, FRACP
O. Demontiero, MBBS, FRACP
Department of Geriatric Medicine, Nepean Hospital, Penrith, NSW 2750, Australia
e-mail: Piumali.gunawardene@health.nsw.gov.au; Oddom.demontiero@health.nsw.gov.au

G. Duque, D.P. Kiel (eds.), *Osteoporosis in Older Persons: Advances in Pathophysiology and Therapeutic Approaches*, DOI 10.1007/978-3-319-25976-5_14

Table 14.1 Risk factors for osteoporotic fractures

General population
Low bone strength (by either DXA or ultrasound)
Female gender[a]
Older age[a]
Maternal history of fracture
History of previous fractures[a]
Previous hyperthyroidism
Diabetes mellitus
Psychotropic medication use
Greater caffeine use
Postural instability[a]
Institutionalized older persons (all the previous list, plus)
Male residents[a]
Low serum vitamin D[a]
Bowel or bladder incontinence[a]
Cognitive impairment[a]
Use of anxiolytics[a]
Poorer balance[a]
Ambulatory[a]
High serum phosphate[a]

Adapted from Chen et al. [52]
[a]Higher hazard ratio in institutionalized older persons *vs.* community dwelling individuals

refer to "hostels" and high level of care as "nursing homes", for the purposes of this Chapter we will use the generic term of LTCI for both types of institutions. While the risk factors for osteoporosis may differ from a high and low level of care [12], the prevalence and relevance of risk factors for osteoporosis in these populations is similar (Table 14.1).

Although results vary among different countries and health systems, the prevalence of osteoporosis in LTCI – mostly determined using bone mineral density (BMD) criteria – ranges from 50 % of men to 80–85 % in women [14–16]. In a prospective cohort of white female nursing home residents (n = 1427) over 18 months [16], a total of 223 osteoporotic fractures occurred among 180 women. Low BMD and transfer dependence were the most significant risk factors for fractures. In addition, among residents dependent on transfer, those with a BMD below the median had more than a threefold increase in fracture risk when compared with other transfer-dependent residents. These and other subsequent reports [17–20] have highlighted the importance of dependence in transfer as a risk factor for osteoporosis in this population, independently of BMD. In some cases, transfer dependence was secondary to previous osteoporotic fractures with a history of previous fractures being highly predictive of subsequent fractures [21, 22].

In addition, osteoporotic fractures in LTCI have a significant economic impact. Costs associated with fractures include (but are not limited to) higher levels of medical and nursing care, use of analgesics, higher involvement of allied health professionals, and complex management of medical complications associated with fractures. Overall, these costs surpass the cost of treating osteoporosis in a population of LTCI at high risk of fractures. For instance, a study of nursing home residents in Maryland found that in the month following a fracture, those who experienced fractures were hospitalized more than 15 times as often as those who did not [23]. This significant burden on the health system also has an important impact on medical expenditures and health budgets, representing 28.2 % of total expenditures for the treatment of osteoporotic fractures in the American population [23, 24].

How to Diagnose Osteoporosis in LTCI

The diagnosis of osteoporosis in community-dwelling populations is usually made after a minimal trauma fracture occurs and/or after BMD quantification shows low bone mass (more than 2.5 SD below the value for young normals). Based on these criteria, clinicians identify those subjects who are at high risk of first or subsequent osteoporotic fractures. In settings where BMD is not available, the use of other risk factors such as history of fracture could provide enough evidence to recommend treatment, independently of BMD results [25–27]. This concept is particularly relevant for LTCI for several reasons,

because BMD testing may not be practical owing to the difficulty in mobilizing patients for transport to a facility with BMD equipment due to logistics, or mobility and behavioral problems that interfere with BMD testing. In addition, the performance of a BMD test has not been shown to modify physicians' therapeutic decision-making in the treatment of osteoporosis in residents of LTCI. Gupta and Aronow [28] reported that only 49 % of 136 post- menopausal women in a nursing home population had BMD measurements. Of these 66 women, 31 (47 %) had osteoporosis, 21 (32 %) had osteopenic BMD, and 14 (21 %) had normal BMD. Most importantly, only 55 % of patients with documented osteoporosis were treated. Other studies have reported a similar situation [5, 29]. This evidence illustrates the underuse of both diagnostic and therapeutic approaches for osteoporotic patients in LTCI, even in residents with low BMD or previous history of minimal trauma fractures, the critical population in which osteoporosis treatment might be considered.

The reasons why health care providers largely ignore the diagnosis or treatment of osteoporosis in the LTC setting are poorly understood. However, some studies have attempted to elucidate the thought process of the clinician when deciding about osteoporosis assessment and treatment in residents of LTCI. Colon-Emeric et al. [8] found that factors associated with initiation of any bone protection (medication or hip protectors) in institutionalized populations included female gender and rural/suburban location. In contrast, residents with esophagitis, peptic ulcer disease, and alcohol abuse were less likely to receive treatment. In a recent study by the same group [30], the authors use a cluster-randomized, single-blind, controlled trial of a multimodal quality improvement intervention. Nursing homes (n = 67) with > or =10 residents with a diagnosis of osteoporosis or recent hip fracture (n = 606) were randomized to receive an early or delayed intervention consisting of audit and feedback, educational modules, teleconferences, and academic detailing. Prescription of osteoporosis therapies before and after the intervention period was measured. Despite these interventions, no significant improvements were observed in any of the quality indicators (use of treatment and/or hip protectors). Only a direct physician contact by an academic detailer was significantly associated with prescription of osteoporosis pharmacotherapy or hip protectors in multivariable models, thus suggesting that close guidance and clear guidelines could constitute effective interventions to increase awareness of the importance of the diagnosis and treatment of osteoporosis in this high-risk population.

Looking for an alternative approach to the assessment of BMD and/or risk of fractures in institutionalized patients, Elliot et al. used ultrasound to quantify bilateral calcaneal BMD in 49 institutionalized women aged 68–100 years and correlated these measures with their serum vitamin D levels [31]. Using this more mobile diagnostic method, which does not rely on ionizing radiation, the authors found that osteoporosis was highly prevalent (59 %) and poorly documented in the patient's medical record. Overall, although ultrasound has a number of limitations as a diagnostic method for osteoporosis, which includes operator's experience and variability between different machines, it could be a good alternative to DXA for the diagnosis and, in some cases, the follow-up of patients with osteoporosis in LTCI.

In summary, osteoporosis is clearly underdiagnosed and undertreated in LTCI [32]. Considering the implications that osteoporotic fractures have on morbidity and mortality, it is pivotal to establish a unified approach to identify patients at risk and to treat them appropriately. Usual risk algorithms could have the risk of overdiagnosing risk in this population [25], therefore, from a diagnostic point of view, and in absence of risk algorithms specific for LTCI residents, diagnosis of osteoporosis should be based on a combination of risk factors, previous history of minimal trauma fractures, clinical findings (kyphosis, clinical fractures), radiological findings, and height reduction. The therapeutic decision-making process will be reviewed further in this chapter.

Who Should Be Treated?

Two consensus conferences, one in Canada [33], and one in Australia [12] are concordant in their conclusions that osteoporosis in LTCI should be identified and treated. The question remains as to who should be treated and under what criteria?

Indeed, prevention of osteoporotic fractures is considered a quality indicator for nursing home care in several countries. In the United States, a national panel of nursing home experts developed a set of specific care processes associated with better outcomes for general medical conditions, including osteoporosis [32]. A ballot-based selecting process included rating validity (process associated with improved outcomes), feasibility of measurement (with charts or interviews), feasibility of implementation (given staffing resources in average community LTCI), and importance (expected benefit and prevalence in LTCI). Among the 114-quality indicators identified during this exercise, seven were specifically suggested for osteoporosis (Table 14.2).

However, the evidence suggests that despite being an indicator of poor care, osteoporotic fractures are still highly prevalent in LTCI while the number of high-risk patients receiving any osteoporosis treatment is very low [34]. Studies in several populations of prescribers have identified the most important factors that prevent the use of osteoporosis treatment in LTCI:

Length of Treatment Versus Patient Life Expectancy and/or Prognosis – The mean survival time of institutionalized elderly residents varies from site to site based on the complexity of the concurrent diseases, quality of care, and mean age. In Australian nursing homes, the

Table 14.2 Quality indicators for osteoporosis care in LTCI in USA

Topic	NH indicator	Note
On admission to the NH	All female residents should be offered both calcium and vitamin D and weight-bearing exercises within 1 month	Exclude if advanced dementia or poor prognosis Feasibility of measurement questionable
Mobilization	IF a NH resident is bedfast, then mobilization should be attempted unless there is a contraindication	Feasibility of measurement questionable
Calcium/vitamin D for osteoporosis	IF a NH resident has osteoporosis, then calcium and vitamin D supplements should be prescribed within 1 month of admission of a new diagnosis of osteoporosis	Exclude if advanced dementia or poor prognosis
Treatment of new osteoporosis	IF a NH resident is newly diagnosed with osteoporosis, then he or she should be offered pharmacologic treatment within 3 months of diagnosis	Exclude if advanced dementia or poor prognosis
Calcium/vitamin D for corticosteroid use	IF a NH resident is taking corticosteroids for more than 1 month, then the resident should also be offered calcium and vitamin D	
Identifying secondary osteoporosis	IF a NH resident has a new diagnosis of osteoporosis, then, during the initial evaluation period, medications should be reviewed as possibly contributing to osteoporosis	Exclude if advanced dementia or poor prognosis
Exercise therapy for new fracture	IF an ambulatory NH resident has an osteoporotic fracture diagnosed, then some form of physical therapy should be prescribed within 1 month	Exclude if advanced dementia or poor prognosis

Adapted from Ref. [32]

average length of stay is about 2.5 years [35], which closely corresponds with Canadian reports [36]. Within this period, residents of LTCI at high risk of falls and fractures will very likely suffer at least one osteoporotic fracture during their stay. Considering that most current osteoporosis treatments have an effect on fracture prevention within 6–8 months and that the number needed to treat decreases with age [37], it is important to re-emphasize the importance of initiation of osteoporosis treatment (both preventive and therapeutic) in this high-risk population, which should have a significant impact on fracture reduction in the LTCI setting independent of the resident's expected length of stay.

Adherence – Adherence to osteoporosis medications is an important problem in ambulatory elderly patients [38, 39]. Approximately 20–30 % of patients abandon their treatment within 6–12 months after beginning therapy [38, 39]. Reasons associated with non-adherence include side effects of medication, fear of side effects or other health risks, and not knowing the results of BMD test results. In LTCI, this should not represent a problem, because administration of medications is closely supervised by nursing staff and, in some cases, regularly followed up by pharmacists. No data is available regarding adherence with osteoporotic treatments in LTCI. However, re-evaluation of drug therapy should be done periodically, especially when LTC residents refuse to take their medications, or when nurses have to crush or modify the dosage form for the resident to take his medications. In addition, development of parenteral presentations for osteoporosis treatments (intravenous and subcutaneous) is expected to improve adherence in this population [40].

Tolerability – Tolerability to osteoporosis treatment is usually good. To decrease constipation and flatulence associated with calcium, it is suggested to start with 500 mg of elemental calcium once a day for 1–2 weeks, and then increase to 500 mg of elemental calcium twice per day and then three times per day [41]. Vitamin D has not been associated with side effects or toxicities [41–44]. However, and despite good tolerability and low risk of side effects, adherence to vitamin D and calcium in LTCI remains low. In a study performed at a major LTCI in USA, Hamid et al. [44] reported that most of the residents were not supplemented adequately with calcium and vitamin D, despite the fact that vitamin D deficiency was documented in their blood tests.

Oral bisphosphonates, although used less frequently lately, are usually well tolerated if specific administration requirements are followed. These requirements include fasting, taking with a full glass of water, remaining in an upright position, and not taking any medications or food concomitantly. However, erosive esophagitis can develop, particularly if administration requirements are not followed properly. Overall, oral bisphosphonates should be avoided in patients with esophageal strictures, achalasia, or untreated symptomatic acid reflux [45]. Indeed, with the more frequent use of parenteral, better-tolerated treatments for osteoporosis, their use is becoming popular in LTCI. While subcutaneous injection of Denosumab is easy and usually innocuous, administration of IV bisphosphonates is easy in settings where infusions are a common practice.

With the exception of initial flu-like symptoms, which occur in a minority of patients, both Denosumab and Zoledronic Acid are well tolerated. Indications for treatment and side effects in the long term, are reviewed in a later section of this Chapter.

Pharmacoeconomics – Preventing and treating osteoporosis in LTCI may represent an economic burden on their already limited budgets if the cost of medications and the time needed to administer the medications by nurses are the only factors taken into consideration. From a different perspective, vertebral, or more importantly, hip fractures, represent an enormous burden for institutions and society because of factors such as use of analgesic treatments, functional and cognitive deterioration, and use of more nursing staff. Not only does fracture occurrence indicate poor quality of management [32], but also it results in greater financial losses. Some reports suggest that preventing and treating osteoporosis to prevent hip fractures in LTCI is cost effective when used in a

Table 14.3 Falls prevention, recommendations

On admission to LTCI, an evidence based screen for fall risk should be under taken with clear links to intervention
Risk assessment should be repeated every 6 months or in the event of a fall
Evidence of screening and delivery of evidence based falls prevention strategies should be included as part of LTCI facilities accreditation processes
Medication should be reviewed by a pharmacist in association with the General Practitioner annually to identify medication-related problems and ensure appropriate prescribing
Psychotropic medications should specifically be reviewed in relation to falls risk. Benzodiazepines should be actively avoided in older people
Multifactorial comprehensive assessment linked to tailored intervention should be routine practice in LTCI
Exercise as part of a multi-factorial intervention is recommended. Exercise must challenge balance and be under taken at least twice weekly (caregivers should be encouraged to assist)
Environmental assessment, which assesses the safe interaction of a resident with their environment, should be part of a multi-factorial intervention
Hip protectors may be used as part of a multi factorial intervention, although their efficacy has not been well established, the actual types of pads have not been well characterized as to efficacy, and adherence may be challenging
Use of physical, mechanical and chemical restraint is not recommended as a falls prevention strategy

high-risk population and when all the aforementioned considerations are made [46, 47].

Polypharmacy or Appropriate Use of Medication – Polypharmacy is highly prevalent in LTCI [48]. Physicians working in LTCI should periodically review the indications of the medications prescribed to their patients at and after admission. The physician in collaboration with the pharmacist and other members of the team should perform a regular systematic medication review. Additionally, a list of medical problems should be included in the patient's chart to document any new active medical problem. Although there has been a prevailing advocacy of "deprescribing" medications after admissions to LTCI [49], if the patient is at high risk of fracture (as per risk factors mentioned above and in Table 14.3), and if there is a clear indication, osteoporosis treatment should be maintained in LTCI residents. In fact, discontinuation of osteoporosis treatment in LTCI residents may have important health consequences. There is no evidence that continuation of osteoporosis treatment in LTCI has a deleterious effect or potential interactions with other medications. In addition, it is well documented that discontinuation of vitamin D, calcium, and even bisphosphonates is followed by changes in bone markers that suggest an increase in bone resorption, which will affect bone mass and predispose to fractures [50]. Overall, and unless clear contraindications are present, there is wide agreement that the benefits of preventing a fracture in high-risk patients surpass the considerations for discontinuation of treatment [12, 33].

Assessment of Osteoporosis and Fracture Risk in LTCI

General Guidelines

- Comorbidities, risk factors, and life expectancy should be considered before initiating treatment.
- All patients admitted in LTCI should be evaluated for both falls and non-fall-related risk of fractures. Interventions targeting identified risk factors should be implemented (Table 14.3). A plan of action regarding discontinuation of medications that can induce falls should be implemented.
- Bed-ridden residents unable to mobilize should be excluded from pharmacologic treatment of osteoporosis. However, considering that they are still at risk for fractures that occur with transfer from bed to chair or even lifting, adequate nutrition and care with lifting and transferring should always be considered.
- The resident's opinion and/or that of the responsible party for health care decisions must be always considered (advantages and disadvantages) regarding treatment option for osteoporosis.

Screening

- Even though BMD screening for all residents 65 years and older has been recommended,

logistical considerations often preclude the health care team from implementing this in clinical practice. Considering the age and functionality of patients admitted to LTCI, it is often impossible to perform a BMD test. If possible, residents with risk factors should be assessed for osteoporosis using either DXA or ultrasound.

- Two risk assessment tools have been proposed to facilitate the identification of fracture risk in community dwelling individuals. The FRAX [25] and the Garvan [51] fracture risk assessment tools have become pivotal in closing the care gap in osteoporosis. However, these tools have been validated in predominantly community dwelling populations; their applicability to residents of LTCI, who have a different risk profile to community populations, remains unknown.
- In their analysis of the FREE study data Chen et al. have developed and validated [52] an algorithm to identify fracture risk in nursing home residents. This algorithm integrates easily assessed clinical risk factors to predict the risk of fractures in frail older people (Table 14.3), which is a population that closely correspond to the average resident at LTCI.

Laboratory Tests

- There is no evidence to indicate that biochemical bone markers are useful in this type of setting.
- It is suggested that secondary causes of both osteoporosis and falls risk should be ruled out with the following tests on admission: serum calcium, vitamin D, PTH, thyroid stimulating hormone (TSH), serum creatinine in all residents, also including testosterone measurements in men [53].

Treatment of Osteoporosis in LTCI

Indications for Starting Treatment

- Patients with high absolute risk factors for fractures (as per risk algorithms), even though BMD is unknown or not done because of logistical problems.
- Osteoporosis detected by densitometry.
- A previous history of minimal trauma (fragility) fractures.
- Residents who suffer new minimal trauma fractures on site.

Non-pharmacological Interventions

Some studies have demonstrated that non-pharmacological interventions are effective for reducing the number of fractures in elderly individuals [54–56]. Increasing dietary calcium and assuring appropriate physical activity [57] and sun exposure is highly feasible at LTCI. Although some studies have reported contradictory results in LTCI residents, the use of hip protectors has been shown to prevent hip fractures and improving the quality of life in this population [54]. However, compliance has been an issue in most of those studies, even when patients and staff are educated on the subject and after free distribution of hip protectors amongst residents [55]. In addition, it is not well documented which hip protector is the best to use.

Pharmacological Interventions

Calcium and Vitamin D (Table 14.4)

Calcium and vitamin D supplements should be prescribed in institutionalized elderly residents if they are not able to attain the recommended daily allowance from foods to decrease or prevent the risk of osteoporotic fractures, including hip fractures [12, 41, 43, 56, 58]. Levels of vitamin D deficiency in LTCI residents is potentiated by their low level of sun exposure [59, 60], however, it is extremely difficult to correct serum vitamin D by simply exposing residents to sunlight [61] therefore supplementation is still needed. As an additional benefit of supplementing vitamin D in LTCI residents, there is evidence that vitamin D supplementation at a dose of 800 IU/day reduces the risk of falls through improvements in muscle strength [62]. Preparations of vitamin D can be used from 10,000 IU a week or 50,000 IU every

month. In LTCI, this can decrease nursing time in terms of medication administrations without affecting its efficacy or toxicity [41].

Adequate calcium nutrition should be part of a preventive strategy in osteoporosis management. A total elemental calcium intake of 1500 mg/day is recommended for nursing home residents. There are many preparations or forms of calcium supplementation available on the market. These preparations may vary in the type of salt, the amount of elementary calcium, the costs, and the absorption rates. Calcium carbonate is the most frequently used calcium supplement because it contains 40 % of element calcium and is the least expensive. Calcium carbonate requires an acidic environment for best absorption; it should be taken with meals for optimal absorption. Elderly patients may have decreased gastric secretion, and many are simultaneously taking acid-reducing medications.

Calcium citrate may be an alternative for some patients. It contains 24 % of elemental calcium per tablet, but it does not need an acidic environment to be absorbed. However, it is more expensive than calcium carbonate. Dosage should be divided throughout the day to facilitate adherence, because the tablets size is quite large, making it difficult for some patients to swallow. Liquid formulations are available, but the taste may be a problem for some patients. Chewable preparations are also available as well as combination preparation with vitamin D. A common side effect of calcium is constipation. It can be decreased by slowly titrating the dose from once daily for a few weeks to twice then three times daily. Finally, calcium supplement can decrease the absorption of some medications that are frequently used in the LTCI setting (i.e. quinolones, tetracycline, levothyroxine, etc.). Managing this drug interaction can be done by spacing the time of administration of calcium by at least 2 h.

Table 14.4 Vitamin D and calcium supplementation recommendations [41, 43, 60, 71]

Vitamin D
Supplementation should be universal
Optimal 25(OH)D concentration should be >75 nmol/L in this high risk population
Dose equivalent to 1000 IU/day (25 mcg/day) necessary to achieve this target
Acceptability likely to be higher with monthly dosing
Sunlight exposure should be encouraged
Calcium
General endorsement of calcium supplements is not appropriate
Long term compliance with calcium is very poor
Anti-fracture efficacy of calcium supplements is marginal
Calcium supplement alone may increase the risk of cardiovascular disease
Increased dietary calcium should be encouraged in place of calcium supplements

Anti-resorptives (Tables 14.5 and 14.6)

Anti-resorptives currently used in clinical practice include oral (alendronate, risedronate and ibandronate) and intravenous bisphosphonate (zoledronate) and subcutaneous Denosumab. Other anti-resorptives such as estrogens and selective estrogen receptors modulators are not

Table 14.5 Pharmacological prevention of fractures in LTCI residents vs. community-dwelling older persons

Agent	Dose	Evidence in LTCI/frail older subjects
Cholecalciferol	800 IU/day (oral)	Yes (Fx prevention)
Alendronate	70 mg/weekly (oral)	Yes (only BMD)
Risedronate	35 mg/weekly or 150 mg/monthly (oral)	No
Zoledronate	5 mg/annually (IV)	Yes (only BMD)
Teriparatide	40 μg/day (SC)	No
Denosumab	60 mg every 6 months (SC)	No
Strontium Ranelate	2 g/day (oral)	No

Adapted from Duque et al. [12]

Table 14.6 Anti-resorptives recommendations

Put on calcium/vit D (see Table 14.4)
Parenteral anti-resorptives (Zoledronic acid or Denosumab) should be considered as first choice in LTCI
If oral bisphosphonate is started, recognize practical issues preventing successful uptake of the medication including:
Swallowing/upper GI side effects/compliance in patients
Correct oral dosing is variable due to logistics and practical considerations
Recommend education of nursing staff by pharmacists on oral BP dosing
Check 25(OH)D, Ca, and eGFR before using Zoledronic acid or Denosumab
Fracture occurring on anti-resorptive therapy
Consider using teriparatide if fracture occurs after 12 months on BP therapy
Side effects of anti-resorptive therapy
Oral BPs should not be used in patients with dysphagia or disordered swallowing
Acute phase reaction post IV BP or SC Denosumab can be managed with paracetamol
ONJ is rare (between 1 in 10,000 and <1 in 100,000), good dental care is recommended
Atypical femoral fractures are unlikely to be of concern in this group with the low total duration of BP therapy
Treatment should be reviewed after 5 years

recommended due to either side effects or lack of superiority against other most effective medications.

Bisphosphonates are the most commonly used medications for fracture prevention in the general population. The evidence supporting the use of oral bisphosphonates in institutionalized older persons is limited to just one randomized controlled study, which demonstrated the utility of alendronate in improving BMD in nursing home residents [63]. A particular limitation of oral bisphosphonates in the LTCI environment is the fact that adherence may be affected by the administrative burden on both nursing staff and patients due to complex directions for administration, difficult administration to patients with cognitive impairment, and a high prevalence of swallowing problems among residents [64]. In this setting, intravenous bisphosphonates represent a useful alternative to oral bisphosphonates due to the lack of gastrointestinal side effects, prolonged dose intervals (1 year) and 100 % adherence over 12 month intervals or longer if less frequent dosing is favored. In fact, a recent study by Greenspan et al. [65] tested the effect of a single dose of zoledronic acid in 165 frail older women (65 year and older) living in nursing homes and assisted-living facilities. Although not powered to determine an effect on fracture reduction, one dose of zoledronic acid improved BMD over 2 years, an effect that is expected to reduce fracture risk in this population.

In terms of Denosumab, no studies have been performed testing the effect of this compound on either BMD or fracture reduction in LTCI. Nevertheless, Denosumab has demonstrated a significant anti-fracture efficacy in the older (older than 75) subgroup of participants in the FREEDOM Study [66]. As additional benefits of this anti-resorptive, Denosumab is administered subcutaneously thus saving staff time, it has a lower incidence of immediate side effects (i.e. less flu-like symptoms), and better biosafety in patients with low renal function [67], which constitute a significant majority of residents at LTCI.

The number of potential side effects associated with anti-resorptives is a common concern of physicians when deciding on an osteoporosis treatment. Assuring that the serum levels of vitamin D are above 50 nmol/L and that serum calcium is within normal levels will prevent some of the immediate side effects of these medications [68]. In terms of long-term side effects (usually occurring after several years of treatment), osteonecrosis of the jaw (ONJ) and atypical fractures are the potential side effects of most concern. Although there are no reports on the prevalence of ONJ in nursing home patients treated with anti-resorptives, a recent international consensus conference [69] concluded that the risk of ONJ associated with oral bisphosphonate therapy for osteoporosis was low and that routine pretreatment dental assessment should only be performed in patients at high risk (i.e. cancer patients receiving IV bisphosphonates) and is not a cost-benefit option for all patients treated for osteoporosis. In addition, a recent task force organized by the

American Society for Bone and Mineral Research [70] concluded that although the relative risk of patients with atypical fractures taking anti-resorptives is high, the absolute risk of atypical fractures in patients on anti-resorptives is low. Considering that this side effect is associated with the prolonged use of anti-resorptives, it is very unlikely that a LTCI resident newly started on anti-resorptives would present this side effect. Nevertheless, in patients admitted at LTCI who are already taking these medications for long-term (longer than 5 years), some warning signs should be identified (i.e. groin pain, increased cortical thickness in the X-rays). In that case, the Task Force suggested that anti-resorptives should be re-evaluated, if the clinician is concerned, then the medication should be ceased, in which case the risk of an atypical fracture may decline. Even in the absence of symptoms, most providers are re-assessing patients after 5 years of oral bisphosphonates and discontinuing them if the risk at that time if their risk for fracture is not high (no fractures while on treatment, BMD T-score higher than −2.5, no prevalent fractures).

Other Treatments

One anabolic treatment (teriparatide) and one other treatment (strontium ranelate) are available for fracture prevention (Table 14.7). In terms of strontium, a systematic review by Inderjeeth et al. [71] on the efficacy and safety of pharmacological agents in managing osteoporosis in the old–old (75 year and older) concluded that there was good evidence for the benefit of current treatments in reducing vertebral fractures, but that data were limited for non-vertebral and hip fracture reduction. Strontium ranelate is the only agent to date that has demonstrated a reduction in non-vertebral and hip fracture events in a high-risk elderly female population, but no studies have assessed the effect of strontium ranelate in a LCTI population. Recently, strontium has been associated with higher incidence of cardiovascular and cerebrovascular disease. Therefore its use in this population should be prudently considered.

In the case of teriparatide, this anabolic medication is administered subcutaneously on a daily basis. Although no studies have assessed the effect of Teriparatide in RACFs, there are several issues that may limit its use in this population [38]. These limitations include the administration route, which increases the nursing time, and the high cost of the medication. In general, teriparatide should not be considered as a first-line treatment for fracture prevention, and even less so in the LTCI population.

Table 14.7 Other treatments

Strontium ranelate is not considered as an alternative first-line treatment option due to cardiovascular risk
Teriparatide should not be considered first line and should only be considered in special circumstances

Conclusion

Prevention of osteoporotic fractures in older persons living in LTCI should involve active identification of risk, which should include those risk factors that are particular to this population, identification of secondary causes of falls and fractures, active interventions to prevent falls, and early initiation of both non-pharmacological and pharmacological interventions to treat osteoporosis and prevent fractures in this high-risk population. All these interventions, which are highly effective, have demonstrated their cost-effectiveness and their beneficial impact on residents' quality of life, independence, and survival.

References

1. Luppa M, Luck T, Weyerer S, König HH, Brähler E, Riedel-Heller SG. Prediction of institutionalization in the elderly. A systematic review. Age Ageing. 2010; 39:31–82.
2. Martinez-Reig M, Ahmad L, Duque G. The orthogeriatrics model of care: systematic review of predictors of institutionalization and mortality in post-hip fracture patients and evidence for interventions. J Am Med Dir Assoc. 2012;13:770–7.
3. Kruavit A, Chailurkit LO, Thakkinstian A, Sriphrapradang C, Rajatanavin R. Prevalence of vitamin D insufficiency and low bone mineral density in elderly Thai nursing home residents. BMC Geriatr. 2012;12:49.

4. Rodondi A, Chevalley T, Rizzoli R. Prevalence of vertebral fracture in oldest old nursing home residents. Osteoporos Int. 2012;23:2601–6.
5. Gloth 3rd FM, Simonson W. Osteoporosis is underdiagnosed in skilled nursing facilities: a large-scale heel BMD screening study. J Am Med Dir Assoc. 2008;9:190–3.
6. Wright RM. Use of osteoporosis medications in older nursing facility residents. J Am Med Dir Assoc. 2007;8:453–7.
7. Ooms ME, Vlasman P, Lips P, et al. The incidence of hip fractures in independent and institutionalized elderly people. Osteoporos Int. 1994;4:6–10.
8. Colon-Emeric C, Lyles KW, Levine DA, et al. Prevalence and predictors of osteoporosis treatment in nursing home residents with known osteoporosis or recent fracture. Osteoporos Int. 2007;18:553–9.
9. Hindmarsh D, Loh M, Finch CF, Hayen A, Close JC. Effect of comorbidity on relative survival following hospitalisation for fall-related hip fracture in older people. Australas J Ageing. 2014;33:E1–7.
10. Abimanyi-Ochom J, Watts JJ, Borgström F, Nicholson GC, Shore-Lorenti C, Stuart AL, Zhang Y, Iuliano S, Seeman E, Prince R, March L, Cross M, Winzenberg T, Laslett LL, Duque G, Ebeling PR, Sanders KM. Changes in quality of life associated with fragility fractures: Australian arm of the International Cost and Utility Related to Osteoporotic Fractures Study (AusICUROS). Osteoporos Int. 2015;26:1781–90.
11. Cheng HY. Evidence-based prescribing of antiresorptive therapy for female nursing home residents with osteoporosis: how good is the evidence? J Am Geriatr Soc. 2006;54:375–6.
12. Duque G, Close JJ, de Jager JP, Ebeling PR, Inderjeeth C, Lord S, McLachlan AJ, Reid IR, Troen BR, Sambrook PN. Treatment for osteoporosis in Australian residential aged care facilities: consensus recommendations for fracture prevention. Med J Aust. 2010;193:173–9.
13. Parikh S, Avorn J, Solomon DH. Pharmacological management of osteoporosis in nursing home populations: a systematic review. J Am Geriatr Soc. 2009; 57:327–34.
14. Kucukler FK, Simsek Y, Turk AÇ, Arduc A, Guler S. Osteoporosis and silent vertebral fractures in nursing home resident elderly men in Turkey. J Clin Densitom. 2015. pii: S1094-6950(15)00120-1. doi:10.1016/j.jocd.2015.05.064.
15. Doherty DA, Sanders KM, Kotowicz MA, Prince RL. Lifetime and five-year age-specific risks of first and subsequent osteoporotic fractures in postmenopausal women. Osteoporos Int. 2001;12:16–23.
16. Chandler JM, Zimmerman SI, Girman CJ, et al. Low bone mineral density and risk of fracture in white female nursing home residents. JAMA. 2000;284: 972–7.
17. Greenspan SL, Myers ER, Kiel DP, et al. Fall direction, bone mineral density, and function: risk factors for hip fracture in frail nursing home elderly. Am J Med. 1998;104:539–45.
18. Gloth 3rd FM. Osteoporosis in long term care. Part 1 of 2: recognizing bone and beyond. Director. 2004;12:175–6, 179–80.
19. Broe KE, Hannan MT, Kiely DK, et al. Predicting fractures using bone mineral density: a prospective study of long-term care residents. Osteoporos Int. 2000;11:765–71.
20. Zimmerman SI, Girman CJ, Buie VC, et al. The prevalence of osteoporosis in nursing home residents. Osteoporos Int. 1999;9:151–7.
21. Nakamura K, Takahashi S, Oyama M, Oshiki R, Kobayashi R, Saito T, Yoshizawa Y, Tsuchiya Y. Prior nonhip limb fracture predicts subsequent hip fracture in institutionalized elderly people. Osteoporos Int. 2010;21:1411–6.
22. Girman CJ, Chandler JM, Zimmerman SI, Martin AR, Hawkes W, Hebel JR, Sloane PD, Magaziner J. Prediction of fracture in nursing home residents. J Am Geriatr Soc. 2002;50:1341–7.
23. Zimmerman S, Chandler JM, Hawkes W, et al. Effect of fracture on the health care use of nursing home residents. Arch Intern Med. 2002;162:1502–8.
24. Ray NF, Chan JK, Thamer M, et al. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the National Osteoporosis Foundation. J Bone Miner Res. 1997; 12:24–35.
25. McClung MR. To FRAX or not to FRAX. J Bone Miner Res. 2012;27:1240–2.
26. Hajjar RR, Kamel HK. Osteoporosis for the home care physician. Part 1: etiology and current diagnostic strategies. J Am Med Dir Assoc. 2004;5:192–6.
27. Schousboe JT, Ensrud KE, Nyman JA, et al. Universal bone densitometry screening combined with alendronate therapy for those diagnosed with osteoporosis is highly cost-effective for elderly women. J Am Geriatr Soc. 2005;53:1697–704.
28. Gupta G, Aronow WS. Underuse of procedures for diagnosing osteoporosis and of therapies for osteoporosis in older nursing home residents. J Am Med Dir Assoc. 2003;4:200–2.
29. Dugard MN, Jones TJ, Davie MW. Uptake of treatment for osteoporosis and compliance after bone density measurement in the community. J Epidemiol Community Health. 2010;64:518–22.
30. Colón-Emeric CS, Lyles KW, House P, Levine DA, Schenck AP, Allison J, Gorospe J, Fermazin M, Oliver K, Curtis JR, Weissman N, Xie A, Saag KG. Randomized trial to improve fracture prevention in nursing home residents. Am J Med. 2007;120:886–92.
31. Elliott ME, Binkley NC, Carnes M, et al. Fracture risks for women in long-term care: high prevalence of calcaneal osteoporosis and hypovitaminosis D. Pharmacotherapy. 2003;23:702–10.
32. Saliba D, Solomon D, Rubenstein L, et al. Quality indicators for the management of medical conditions in nursing home residents. J Am Med Dir Assoc. 2004;5:297–309.
33. Duque G, Mallet L, Roberts A, et al. Quebec Symposium for the Treatment of Osteoporosis in

Long-Term Care. To treat or not to treat, that is the question: proceedings of the Quebec Symposium for the Treatment of Osteoporosis in Long- term Care Institutions, Saint-Hyacinthe, Quebec, November 5, 2004. J Am Med Dir Assoc. 2006;7:435–41.
34. Kamel HK. Underutilization of calcium and vitamin D supplements in an academic long- term care facility. J Am Med Dir Assoc. 2004;5:98–100.
35. Residential Aged Care in Australia. http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=10737422896. Last visited 22 July 2015.
36. Bergman H, Montambault J. Services d'hébergement. In: Arcand M, Hébert R, editors. Précis pratique de gériatrie. 2nd ed. St-Hyacinthe/Paris: Edisem/Maloine; 1997.
37. Reginster JY. Antifracture efficacy of currently available therapies for postmenopausal osteoporosis. Drugs. 2011;71:65–78.
38. Papaioannou A, Kennedy CC, Dolovich L, et al. Patient adherence to osteoporosis medications. Problems, consequences and management strategies. Drugs Aging. 2007;24:35–55.
39. Caro JJ, Ishak KJ, Huybrechts KF, et al. The impact of compliance with osteoporosis therapy on fracture rates in actual practice. Osteoporos Int. 2004;15:1003–8.
40. Zarowitz BJ, Cheng LI, Allen C, O'Shea T, Stolshek B. Osteoporosis prevalence and characteristics of treated and untreated nursing home residents with osteoporosis. J Am Med Dir Assoc. 2015;16:341–8.
41. Demontiero O, Herrmann M, Duque G. Supplementation with vitamin D and calcium in long-term care residents. J Am Med Dir Assoc. 2011;12:190–4.
42. Hathcock JN, Shao A, Vieth R, et al. Risk assessment for vitamin D. Am J Clin Nutr. 2007;85:6–18.
43. Rolland Y, de Souto Barreto P, Abellan Van Kan G, Annweiler C, Beauchet O, Bischoff-Ferrari H, Berrut G, Blain H, Bonnefoy M, Cesari M, Duque G, Ferry M, Guerin O, Hanon O, Lesourd B, Morley J, Raynaud-Simon A, Ruault G, Souberbielle JC, Vellas B, French Group of Geriatrics and Nutrition. Vitamin D supplementation in older adults: searching for specific guidelines in nursing homes. J Nutr Health Aging. 2013;17:402–12.
44. Hamid Z, Riggs A, Spencer T, et al. Vitamin D deficiency in residents of academic long-term care facilities despite having been prescribed vitamin D. J Am Med Dir Assoc. 2007;8:71–5.
45. Jachna CM, Shireman TI, Whittle J, et al. Differing patterns of antiresorptive pharmacotherapy in nursing facility residents and community dwellers. J Am Geriatr Soc. 2005;53:1275–81.
46. Parikh S, Mogun H, Avorn J, Solomon DH. Osteoporosis medication use in nursing home patients with fractures in 1 US state. Arch Intern Med. 2008;168:1111–5.
47. Fleurence RL, Iglesias CP, Johnson JM. The cost effectiveness of bisphosphonates for the prevention and treatment of osteoporosis: a structured review of the literature. Pharmacoeconomics. 2007;25:913–33.
48. Jokanovic N, Tan EC, Dooley MJ, Kirkpatrick CM, Bell JS. Prevalence and factors associated with polypharmacy in long-term care facilities: a systematic review. J Am Med Dir Assoc. 2015;16:535.e1–12. doi:10.1016/j.jamda.2015.03.003. Epub 2015 Apr 11.
49. Scott IA, Hilmer SN, Reeve E, Potter K, Le Couteur D, Rigby D, Gnjidic D, Del Mar CB, Roughead EE, Page A, Jansen J, Martin JH. Reducing inappropriate polypharmacy: the process of deprescribing. JAMA Intern Med. 2015;175:827–34.
50. Deane A, Constancio L, Fogelman I, et al. The impact of vitamin D status on changes in bone mineral density during treatment with bisphosphonates and after discontinuation following long- term use in postmenopausal osteoporosis. BMC Musculoskelet Disord. 2007;8:3.
51. Nguyen ND, Frost SA, Center JR, et al. Development of prognostic nomograms for individualizing 5-year and 10-year fracture risks. Osteoporos Int. 2008;19:1431–44.
52. Chen JS, Sambrook PN, Simpson JM, et al. A selection strategy was developed for fracture reduction programs in frail older people. J Clin Epidemiol. 2010;63:679–85.
53. Johnson K, Suriyaarachchi P, Kakkat M, Boersma D, Gunawardene P, Demontiero O, Tannenbaum C, Duque G. Yield and cost-effectiveness of laboratory testing to identify metabolic contributors to falls and fractures in older persons. Arch Osteoporos. 2015;10:226.
54. Singh S, Sun H, Anis AH. Cost-effectiveness of hip protectors in the prevention of osteoporosis related hip fractures in elderly nursing home residents. J Rheumatol. 2004;31:1607–13.
55. Cameron ID, Kurrle SE, Quine S, Sambrook PN, March L, Chan DK, Lockwood K, Cook B, Schaafsma FF. Improving adherence with the use of hip protectors among older people living in nursing care facilities: a cluster randomized trial. J Am Med Dir Assoc. 2011;12:50–7.
56. Abizanda P, López MD, García VP, Estrella Jde D, da Silva González Á, Vilardell NB, Torres KA. Effects of an Oral Nutritional Supplementation Plus Physical Exercise Intervention on the Physical Function, Nutritional Status, and Quality of Life in Frail Institutionalized Older Adults: The ACTIVNES Study. J Am Med Dir Assoc. 2015;16:439.e9–16. doi:10.1016/j.jamda.2015.02.005.
57. Silva RB, Eslick GD, Duque G. Exercise for falls and fracture prevention in long term care facilities: a systematic review and meta-analysis. J Am Med Dir Assoc. 2013;14:685–9.
58. Mocanu V, Vieth R. Three-year follow-up of serum 25-hydroxyvitamin D, parathyroid hormone, and bone mineral density in nursing home residents who had received 12 months of daily bread fortification with 125 μg of vitamin D_3. Nutr J. 2013;12:137.
59. Verhoeven V, Vanpuyenbroeck K, Lopez-Hartmann M, Wens J, Remmen R. Walk on the sunny side of life – epidemiology of hypovitaminosis D and mental

health in elderly nursing home residents. J Nutr Health Aging. 2012;16:417–20.
60. Drinka PJ, Krause PF, Nest LJ, Goodman BM. Determinants of vitamin D levels in nursing home residents. J Am Med Dir Assoc. 2007;8:76–9.
61. Durvasula S, Sambrook PN, Cameron ID. Factors influencing adherence with therapeutic sunlight exposure in older people in intermediate care facilities. Arch Gerontol Geriatr. 2012;54:e234–41.
62. Bischoff-Ferrari HA, Orav EJ, Dawson-Hughes B. Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: a 3-year randomized controlled trial. Arch Intern Med. 2006;166:424–30.
63. Greenspan SL, Schneider DL, McClung MR, et al. Alendronate improves bone mineral density in elderly women with osteoporosis residing in long-term care facilities. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2002;136:742–6.
64. McHorney CA, Schousboe JT, Cline RR, et al. The impact of osteoporosis medication beliefs and side-effect experiences on non-adherence to oral bisphosphonates. Curr Med Res Opin. 2007;23:3137–52.
65. Greenspan SL, Perera S, Ferchak MA, Nace DA, Resnick NM. Efficacy and safety of single-dose zoledronic Acid for osteoporosis in frail elderly women: a randomized clinical trial. JAMA Intern Med. 2015;175:913–21.
66. Boonen S, Adachi JD, Man Z, Cummings SR, Lippuner K, Törring O, Gallagher JC, Farrerons J, Wang A, Franchimont N, San Martin J, Grauer A, McClung M. Treatment with denosumab reduces the incidence of new vertebral and hip fractures in postmenopausal women at high risk. J Clin Endocrinol Metab. 2011;96:1727–36.
67. Diab DL, Watts NB. Denosumab in osteoporosis. Expert Opin Drug Saf. 2014;13:247–53.
68. Reid IR. Short-term and long-term effects of osteoporosis therapies. Nat Rev Endocrinol. 2015;11:418–28.
69. Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F, Reid IR, Ruggiero SL, Taguchi A, Tetradis S, Watts NB, Brandi ML, Peters E, Guise T, Eastell R, Cheung AM, Morin SN, Masri B, Cooper C, Morgan SL, Obermayer-Pietsch B, Langdahl BL, Al Dabagh R, Davison KS, Kendler DL, Sándor GK, Josse RG, Bhandari M, El Rabbany M, Pierroz DD, Sulimani R, Saunders DP, Brown JP, Compston J, International Task Force on Osteonecrosis of the Jaw. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res. 2015;30:3–23.
70. Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung AM, Cosman F, Curtis JR, Dell R, Dempster DW, Ebeling PR, Einhorn TA, Genant HK, Geusens P, Klaushofer K, Lane JM, McKiernan F, McKinney R, Ng A, Nieves J, O'Keefe R, Papapoulos S, Howe TS, van der Meulen MC, Weinstein RS, Whyte MP. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2014;29:1–23.
71. Inderjeeth CA, Foo AC, Lai MM, Glendenning P. Efficacy and safety of pharmacological agents in managing osteoporosis in the old old: review of the evidence. Bone. 2009;44:744–51.

Fracture Care in the Elderly

15

Jay M. Zampini and Christopher M. Bono

Introduction

As life expectancy around the globe continues to increase [1], the prevalence of osteoporosis is expected to increase along with fractures. Osteoporosis insidiously converts bone, the primary organ of support and mobility, from rigid beams to veritable "empty eggshells" that can fail under physiologic conditions of daily living. Fractures do not occur simply as a result of poor bone quality but of the interaction between the strength of the bone and its ability to withstand the forces that are exerted on the bone. These forces are a function of muscular strength, balance, dexterity, cognitive function, and falls. These issues, coupled with severe medical comorbidity, can increase the risk of surgical intervention [2, 3]. Postoperative morbidity and mortality can also be increased, however, by delaying treatment [4–6]. The concept that elderly and osteoporotic patients have unique care requirements has been given considerable attention in recent years and has led to the development of distinct areas of study and treatment in orthopaedics, traumatology, and spinal surgery [7–9]. Additionally, several mechanical, biologic, and technical advances have made the treatment of osteoporosis related injuries safer and more successful and will be discussed in detail. The purpose of this chapter is to review the impact of osteoporosis on the manner in which fractures occur, are stabilized, and heal with attention to fractures that occur commonly and are likely to be encountered in clinical practice.

Mechanism of Bone Injury

Fractures occur when an applied force, the product of mass and acceleration, exceeds the capacity of the bone to absorb and transmit that force. Fractures can be described by a number of important attributes. These include the number of fragments, or comminution, the degree of separation of fragments, or displacement, angulation in the cardinal anatomic planes, and involvement of an articular surface. Bone fractures differently in patients with osteoporosis than in patients with adequate bone density. Whereas bone with adequate mineral density typically fractures following high-energy events such as a fall from a height or motor vehicle collision (a force applied by a massive object or at high acceleration), fractures in osteoporotic bone can occur following low-energy trauma

J.M. Zampini, MD • C.M. Bono, MD (✉)
Division of Spine Surgery,
Department of Orthopaedic Surgery,
Harvard Medical School,
Brigham and Women's Hospital,
75 Francis Street, Boston,
MA 02115, USA
e-mail: jzampini@partners.org; bonocm@me.com

G. Duque, D.P. Kiel (eds.), *Osteoporosis in Older Persons: Advances in Pathophysiology and Therapeutic Approaches*, DOI 10.1007/978-3-319-25976-5_15

such as a fall from the standing position or even from participating in activities of daily living and exercise (a physiologic mass at low acceleration). The clinical manifestation of this difference is the observation of less comminuted, more displaced fractures in young healthy bone compared to more comminuted, less displaced fractures in osteoporotic bone. A specific example of this is the proximal weight-bearing region (plateau) of the proximal tibia. In patients with adequate bone mineral density, a large portion of a tibial plateau will split off following a forceful impact with the femoral condyles. In the osteoporotic patient, the femoral condyle will crush the subchondral cancellous bone of the tibial plateau, leading to depression of the articular surface into the void created by the crumbled bone (Fig. 15.1).

The mechanism of injury for spinal fractures similarly varies with bone mineral density. Young vertebral bodies can sustain tremendous axial compressive loads because of the trabecular support beams with numerous cross-connections. A vertebral body of adequate bone mineral density can be compared to an unopened beverage can. Provided one had excellent balance, one could support his or her weight on the can without damaging it. A substantial force applied to the can could burst it, in much the same way that a substantial force applied to a normal vertebra causes the vertebra to burst and fragments to displace widely. If the can were emptied of beverage, the same maneuver would cause the can to collapse and be crushed. In the osteoporotic spine, the vertebral body is "emptied" of trabecular support and cross connections, rendering it capable of being crushed under physiologic forces or minor trauma. The morphology of an osteoporotic fracture typically shows central depression the endplates of lumbar vertebrae and wedge shaped deformity of thoracic vertebrae (Fig. 15.2). Further information regarding specific fracture patterns and the differences between normal and osteoporotic bone will be discussed below.

A final morphologic difference between fractures in osteoporotic bone and bone of adequate

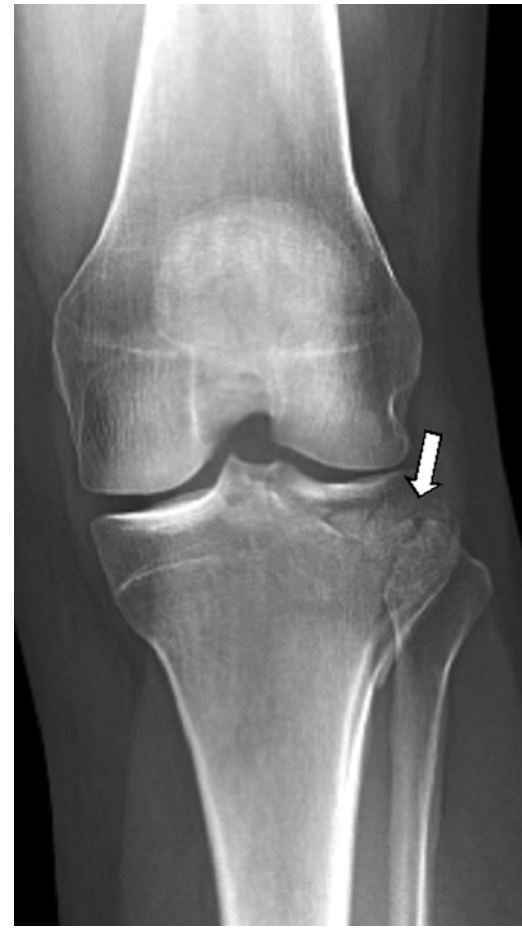


Fig. 15.1 A tibial plateau fracture in patients with osteoporosis results in depression of the articular surface and compaction of the underlying cancellous bone (*arrow*)

mineral density has been reported to result from prolonged treatment of osteoporosis with the bisphosphonate class of antiresorptive agents. Initially, reports of subtrochanteric fractures of the femur, usually associated with high-energy trauma, were sporadically reported to have occurred following a low-energy event [10–13]. Analyses of these reports ultimately revealed a relative risk of such atypical fractures that increased with longer duration of bisphosphonate use, with the American Society of Bone and Mineral Research reporting an incidence of 78 fractures per 100,000 patients after 8 years of medication usage compared to 2 fractures per

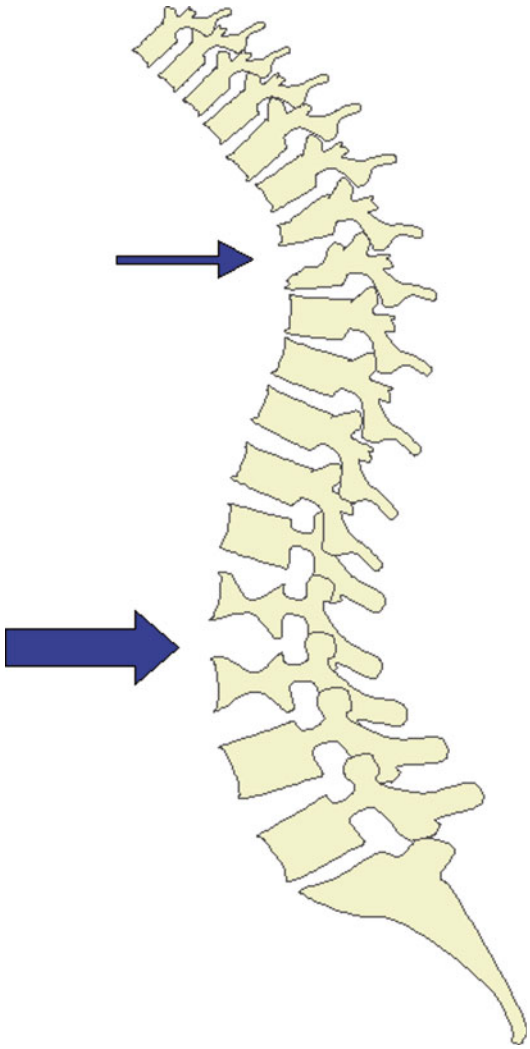


Fig. 15.2 Wedge fractures are more common in the thoracic spine (*small arrow*), while central depression fractures are more frequent in the lumbar spine (*large arrow*). These patterns are likely the result of the mechanical alignment of the spine in these regions

100,000 patients using bisphosphonates for 2 years [11]. An atypical femur fracture is associated with a prodrome of pain before the fracture. The radiographic appearance of a fracture line emanates from the lateral cortex and progresses medially; there is thickening or "beaking" of the bone at the fracture site (Fig. 15.3). Additionally, atypical fractures of the pelvis [14] and ulna [15] have been reported.

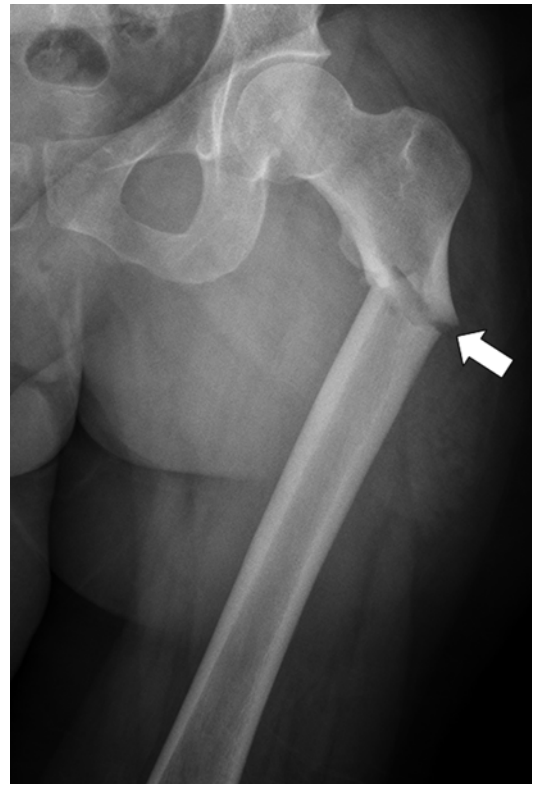


Fig. 15.3 An atypical femur fracture is identified by thickening, or "beaking," of the bone at the fracture site (*arrow*)

Fixation Challenges in Osteoporotic Bone

The clinical importance of the prior discussion of fracture morphology and mechanism, aside from assisting in communication between healthcare providers, is to determine the optimal method of definitive fracture treatment. A general goal of fracture care is to restore and maintain anatomic alignment during fracture healing. Manipulation of bone fragments at the time of surgery is often required to reduce fracture displacement and angulation. Once anatomic alignment has been achieved, it is typically held in place with metallic implants such as screws, plates, and rods. This inherently mechanical process is akin to anchoring an object into a household wall. A screw placed into a wooden stud would achieve excellent purchase, or hold, capable of supporting a

heavy object without fail (Fig. 15.4a). A screw placed only into plaster with no other support, however, would lose purchase as the head is advanced to the wall and the threads turned, crumbling the brittle plaster and allowing the screw to be pulled from the wall with minimal effort (Fig. 15.4b). Screw fixation in osteoporotic bone can result in that same disconcerting feel that nothing is holding, and, without taking proper measures, can lead to early failure of fracture stabilization [16, 17].

To overcome these challenges, several solutions have been engineered to provide better fixation in suboptimal situations. Since the primary device of fracture fixation is the screw, much attention has been given to improve this common and ancient simple machine. In some circumstances, screws with a larger ratio of external thread diameter to internal shaft diameter can be used to apply the force of fixation over a larger bone surface area. Devices have also been designed to gain fixation by placing multiple screws into the bone, each of which would individually have insufficient purchase. The multiplicity of points of fixation, often coupled with the ability to lock the screws rigidly to the plate, provides better stabilization of fractures in weakened bone [18]. Another example of screw

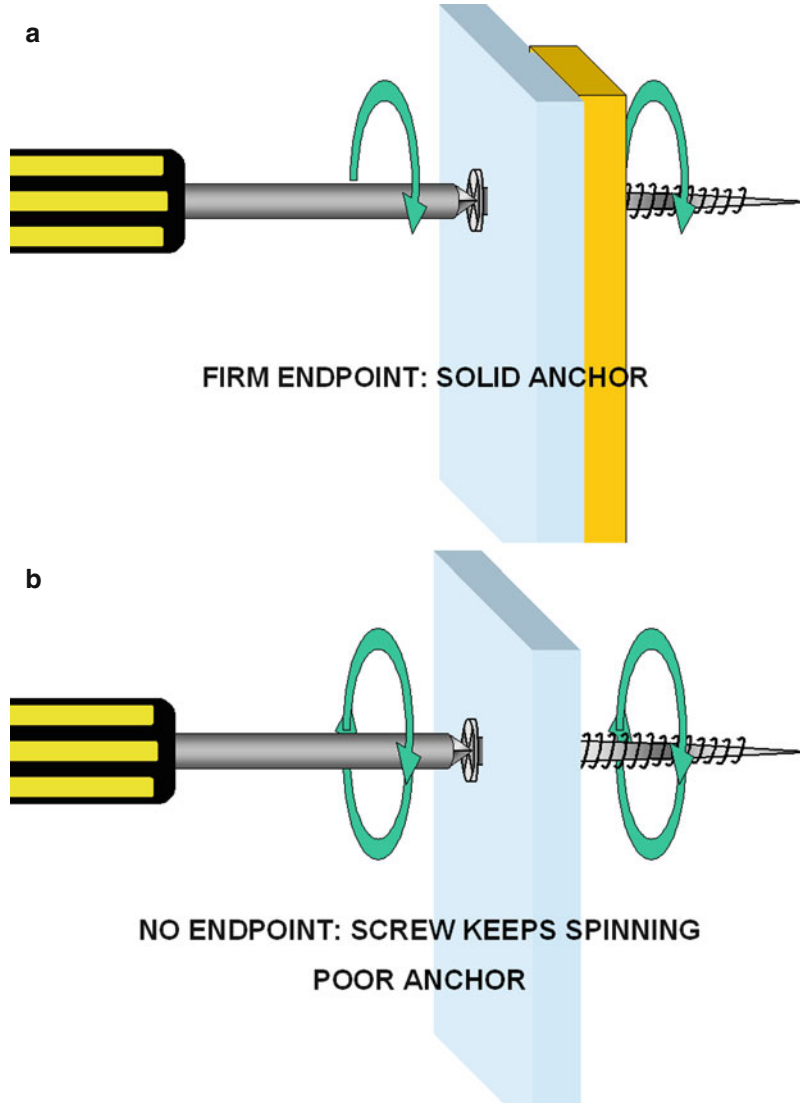


Fig. 15.4 In normal bone, a screw achieves excellent purchase with a firm endpoint. Using the described analogy of inserting a screw in to a plaster wall, this would be analogous to "catching" the beam (**a**). In contrast, inserting screws into osteoporotic bone yields no endpoint, analogous to "missing" the beam (**b**). The screw can be turned indefinitely with no endpoint as it spins in place

engineering is the design of some screws with a threaded cap that can be applied to the tip of the screw and allow the device to function more like a nut and bolt, gaining strength by pressing firmly against the stronger cortical bone surface instead of relying on thread purchase in weakened trabecular bone. Finally, additional screw purchase can be gained by augmenting the bone with polymethylmethacrylate (PMMA) bone cement. PMMA begins as viscous fluid that can be injected into bone to interdigitate into the spaces between bone trabeculae. The fluid polymerizes into a hard solid (the nonmedical variety of this substance is acrylic). Screw purchase is gained by dispersing the force of fixation over the much larger surface area gained by the interdigitation of cement and bone [19]. This concept is applied in vertebroplasty and kyphoplasty, methods of vertebral augmentation for osteoporotic compression fractures, and will be discussed in further detail below.

Changing the location of the fixation device can also aid in its ability to stabilize a fracture. Intramedullary nails, though not initially developed for osteoporotic bone, are inserted into the medullary cavity of long bones, such as the femur, tibia, and humerus. In contrast to plates, intramedullary devices are located closer to the weightbearing axis of the bone (Fig. 15.5). This allows the fracture ends of the bone to bear more of the load than would be allowed by a plate. Sliding hip screws rely on a similar principle in that they allow the broad cancellous surfaces of an intertrochanteric fracture to sustain the majority of the load. The primary function of the implant, therefore, is to keep the fragments aligned but not to bear load.

Finally, there are methods of treating fractures that do not rely on screw-based implants or fracture reduction. For example, most surgeons consider an arthroplasty (that is, joint replacement) to be the treatment of choice for elderly patients

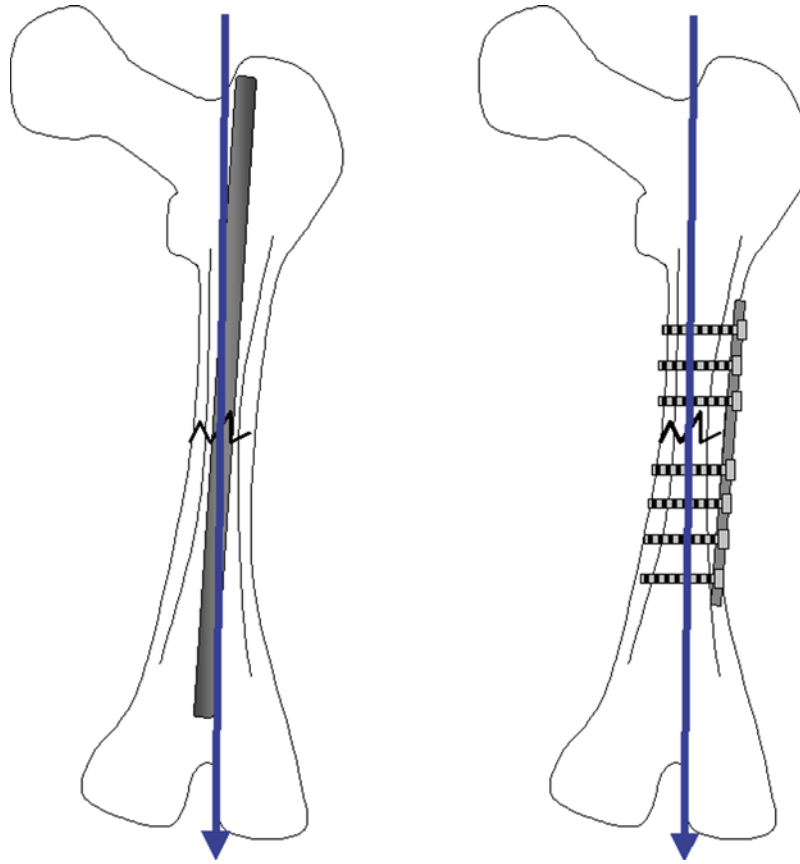


Fig. 15.5 An An intramedullary nail is better aligned with the weight-bearing axis of a bone (*left*), which may have advantages in osteoporotic patients. Plates and screws lie farther away from the weight-bearing axis (*right*)

with femoral neck fractures of the hip [20] and certain fractures of the proximal humerus [21]. Such a treatment circumvents the need to reduce and stabilize a fracture and provide an optimal environment for fracture healing, as it involves removal and replacement of the fractured segment of bone. Furthermore, the prosthesis is usually secured to the bone with PMMA cement, which is preferred over so-called press-fit fixation, in the setting of osteoporotic bone. Such a fixation method does not directly rely on bone density as much as screw, plate, or rod fixation.

Timing of Fracture Treatment in the Elderly

The optimal time for surgical treatment of fractures in older patients has been a matter of continuous debate, although the issues have, in many ways, stayed the same [22]. Factors that influence the decision include the anatomic structure injured, the effect of the fracture on mobilization and ambulation, and the overall medical condition of the patient.

In general, and despite the opinion occasionally rendered through social media [23], the goals of fracture fixation are to provide the patient with optimal ability to mobilize from recumbency, ambulate, and participate in activities of daily living. This is best understood through clinical examples. Hip fracture is perhaps the paradigm of injury that impairs these three functions. Nonoperative management leaves patients recumbent, placing them at high risk for pressure ulcers, thromboembolic events, and pulmonary decompensation. Furthermore, nonoperative treatment has been shown to result in a higher mortality rate [24]. Early surgical treatment would, therefore, minimize the time during which a patient would be completely incapacitated and unable to mobilize from bed [4–6]. This factor must be counterbalanced with a careful consideration of the patient's medical history, current medical condition, and ability to improve the current medical condition. These assessments will typically result in surgery that can be optimally performed within two [4] to four days [25] of injury. The current recommendation is to perform surgery for hip fractures as early as medically allowable and ideally within 48 h of injury [26]. Ongoing studies to evaluate the feasibility of accelerated surgical care within a mean of approximately 6 h following diagnosis [27], underscore the observation that patients are often in optimal condition at the time of presentation to the hospital and tend to decline during the hospitalization.

Vertebral fractures represent another commonly encountered group of injuries that can have detrimental effect on quality of life, pulmonary function, and the ability to perform activities of daily living. While hip fractures have immediately negative effects, vertebral compression fractures are more insidious but result in a six- to ninefold increase in 1 year mortality similar to that of hip fractures [28]. The traditional treatment of vertebral compression fractures (VCF) has included oral analgesic medications, advising the avoidance of painful activities, and counseling the patient that the fracture will heal in time and that pain will soon subside [29]. Nearly two-thirds of patients with symptomatic VCF actually will experience enough pain relief within 6 weeks to return to pre-fracture level of activities and thereby avoid the risks of prolonged inactivity. In contradistinction, persistently painful fractures can lead to physical deconditioning, emotional and psychological distress, and dependence on pain medications. The development of percutaneous vertebral augmentation, also known as vertebroplasty and kyphoplasty, has introduced an alternative for these patients where none previously existed [30–33]. Whereas most studies report that the procedure effectively reduces pain and quickly, a more important effect attesting to the ability of the procedures to restore function, similar to that of hip fracture surgery, has been a reported reduction in mortality risk for patients treated with vertebral augmentation than with nonsurgical treatment [34, 35]. This is, of course, not without surgical risk, a thorough discussion of which is included below. The challenge with VCFs is determining which patients would benefit from nonsurgical care and which would benefit from early

performance of vertebral augmentation. No consensus has been reached regarding the optimal timing of vertebral augmentation as there has for hip fracture fixation. Patients confined to a bed or chair with severe pain appear to have the most to lose by waiting, similar to a hip fracture patient, and would therefore benefit from an early decision to perform vertebral augmentation. For patients able to mobilize but who complain of pain severe enough to limit other activities, a trial of nonoperative care for 4–6 weeks may be ample time to determine if pain relief will be adequate or if vertebral augmentation would be of benefit.

Bone Healing Challenges in Osteoporotic Bone

The rate and quality of bone healing is compromised in patients with osteoporosis compared to patients without osteoporosis. Animal studies have demonstrated this effect with femur fractures and fracture callus in standardized models of osteoporotic bone [36, 37]. Clinical studies have similarly shown delayed healing and poor rates of spinal fusion in elderly, osteoporotic patients [38]. The biologic basis for this has been reported to result from the reduced number and proliferative capacity of bone marrow mesenchymal stem cells (MSCs) that occurs with advanced age [39]. These findings highlight the importance of maintaining an optimal healing environment at the surgical site through meticulous surgical technique as well as biologic, pharmacologic, and electrophysiologic alteration of the healing site.

Surgical Solutions

The disadvantaged state of osteoporotic bone healing can be made worse through improper surgical technique. A fracture limits the endosteal blood supply to the bone by the disruption the internal architecture and vasculature of the bone. Modern techniques of fracture surgery emphasize the importance of maintaining blood supply to the fracture site through meticulous handling of the periosteum and surrounding muscular envelope. This leads to less devitalization of the bone's remaining blood supply and optimizes healing of the fracture and surgical site. A concrete application of this theory can be seen in the use of intramedullary fixation and percutaneously applied fixation plates. Both techniques involve external manipulation of the fracture, insertion of the device distant from the fracture site, and avoidance of direct access of the fracture site. Screws are also inserted percutaneously to the plate for fixation of the fracture (Fig. 15.6). In a similar method, instrumentation has been developed for the percutaneous insertion of pedicle screws and rods for instrumented stabilization of spinal fusion, thus avoiding the damage to the vasculature that occurs with open exposure of the spine for fusion.

Biologic Solutions

Healing and growth of any bone requires three elemental factors: source of cells capable of producing bone (ostengenecity), a stimulatory factor to induce the bone-producing cells to form bone (osteoinductivity), and a scaffold of material sufficient to guide the production of bone (osteoconductivity). Biologic optimization of bone healing can target any or all of these factors. In relation to the above discussion regarding the reduced number and function of MSCs in osteoporosis and advanced age, several products have been developed to either increase the concentration of a patient's native stem cells or to transplant allogeneic stem cells at the time of surgery. A patient's own MSCs can be harvested from bone marrow by aspiration of the iliac crest using a Jamshidi needle. Commercially available products such as BMAC (Harvest Technologies, Inc, Munich, Germany) process the bone marrow using sterile centrifugation and isolation of the buffy coat to achieve a reported eightfold increase in the concentration of MSCs [40, 41]. Similarly, osteogenic cell density can be increased at a fracture or spinal fusion site using commercially available allogeneic MSC products such as Cellentra VCBM (Biomet, Warsaw, IN), Trinity

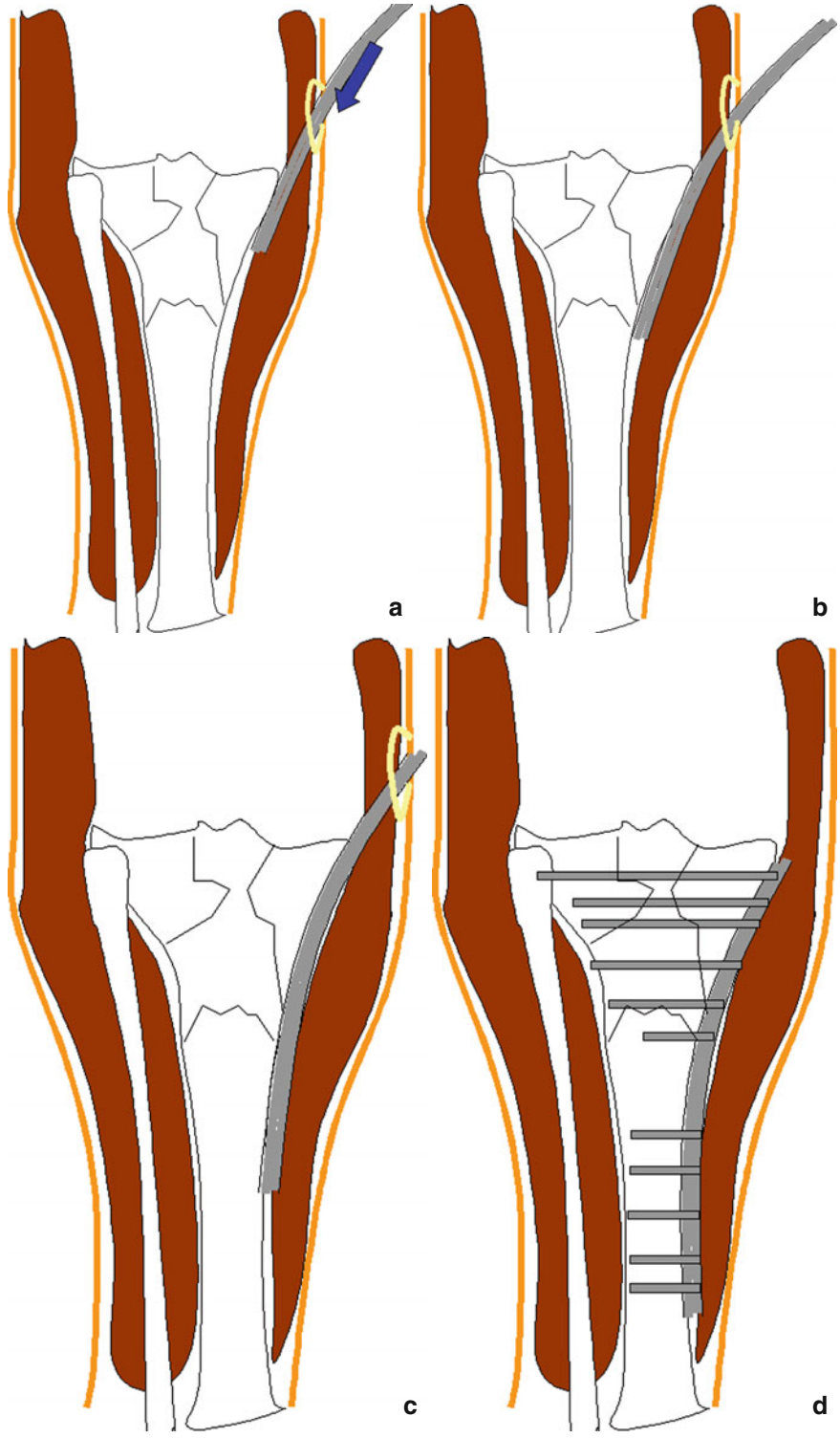


Fig. 15.6 If Suclosed reduction can be achieved, less invasive methods of plate fixation can be used in osteoporotic and elderly patients. In contrast to formal open fixation, these methods utilize smaller incision (*arrow*) in the skin through which a plate is introduced under the muscle (**a**). The plate is then slid along the periosteal surface (**b**) until it is in an acceptable position (**c**). The plate is then held in place with screws (**d**) that are inserted in a percutaneous manner using specialized alignment guides

Evolution (Orthofix, Lewisville, TX), and Osteocel (Nuvasive, San Diego, CA). These products provide the osteogenicity necessary for fracture and spinal fusion healing and have been shown to produce none of the immune reactions typical of other unmatched, potentially incompatible allogeneic tissue transplant [42, 43].

Osteogenic cells can be induced to form bone through the stimulatory effects of the so-called bone morphogenic proteins (BMPs), a group of compounds of the transforming growth factor-beta superfamily. Through recombinant DNA technology, BMP-2 is commercially available for implantation to augment fracture and spinal fusion healing and is marketed under the trade name Infuse (Medtronic, Memphis, TN). Another product, BMP-7, was previously marketed as OP-1 (Olympus Biotech, Center Valley, PA) but the production has ceased and the product is no longer available. BMPs have demonstrated positive effects on fracture healing in animal models as well as in human studies of open fractures and nonunions of the tibia [44, 45]. In the spine, BMP-2 has been studied extensively and has been reported to result in successful fusion in nearly all patients undergoing anterior lumbar fusion [46] and in 60–85 % of the more commonly performed posterolateral fusion [47–52]. While none of these studies were performed to determine explicitly the effect of BMP on healing of osteoporotic bone, data have been reported showing a positive effect on fracture healing [53, 54] and spinal fusion [55, 56] in experimental models of osteoporosis. While the use of recombinant human BMP sounds like a potential cure for all of the challenges encountered in bone healing in osteoporosis, recent attention has been turned to methodologic biases that were not initially reported in many of the human trials of BMP [57]. These flaws, caused in large part by faulty trial design, peer review, and financial conflict of interest, led to underreporting of the risk of complications of the use of BMP including bone resorbtion and implant displacement, urogenital events, infection, radiculitis, ectopic bone formation, and malignancy. Subsequent review of trial data revealed a risk of complications 10–50 times higher than that which was originally reported. Currently, the potential benefit of using BMP-2 must be weighed against the potential risk of complications for any individual patient.

Pharmacologic Solutions

Recent animal data have suggested that some pharamacological agents used to treat osteoporosis may also have a positive effect on fracture healing. The best example of this is parathyroid hormone (PTH). Under normal physiologic conditions, PTH functions to increase circulating calcium by inducing reabsorbtion of bone. In daily, pulsatile, supraphysiologic doses, the opposite effect has been observed, leading to a net increase in bone mineral density [58]. Through recombinant DNA technology, a truncated form of PTH is produced and marketed as teraparatide (Forteo, Eli Lilly and co., Indianapolis, IN). A systematic review of several case reports [59] and two randomized controlled trials [60, 61] have repeatedly shown that recombinant PTH in pulsatile doses can accelerate healing of fractures in patients with osteoporosis, particularly fractures of the wrist and pelvis. Additionally, recombinant PTH also appears to accelerate bone healing in spinal fusion in rat [62, 63] and rabbit models of osteoporosis [64]. These results should be approached with caution as studies in human patients have not yet shown the same effect. Also, the increase in bone density of the fusion mass and acceleration of fusion may not be accompanied by a commensurate increase in functional strength of the bone [65]. Further study is required before recombinant PTH should be applied widely to patients undergoing spinal fusion.

Bisphosphonates are antiresorptive medications that have been proposed for use to augment spinal fusion in osteoporotic patients. Early reports of bisphosphonate use in spinal fusion demonstrated clear detrimental effects [66, 67]. More recent reports have been mixed with some showing weaker bone strength following bisphosphonate use [68], some showing no difference in treatment and control groups

[69–71], and some suggesting improved healing [72]. At this time, the lack of consensus and wide variability between reported effects suggest that more information should be gathered before prescribing or continuing the use of bisphosphonates for osteoporotic patients undergoing spinal fusion. Bisphosphonate use in fracture healing, on the other hand, has not been shown to have a detrimental effect [73]. A recent meta-analysis of randomized controlled trials of bisphosphonate use following osteoporotic fractures reports that no detrimental effect exists but does not necessarily suggest that a beneficial effect exists either. At the very least, it does appear that there is no delay in healing imparted by the impairment of osteoclast function induced by the bisphosphonates.

Electrophysiologic Solutions

Bone has been observed to develop electrical potentials at areas of mechanical compression and tension [74]. This finding, coupled with the observation that bone shows a greater propensity to form new bone under compression (Wolff's law), has led to the development of electromagnetic devices designed to stimulate the production of bone in addition to what would be produced under physiologic conditions. These devices have been applied to fracture and spinal fusion healing. There is conflicting evidence, however, concerning the efficacy of electrical stimulation on spinal fusion or fracture healing. A recent systematic review found no consistent evidence to support or refute the use of electrical stimulation devices to enhance spinal fusion [75]. The use of bone growth stimulators appears to be more encouraging in extremity fractures, particularly of the tibial shaft [76, 77]. Perhaps this is a result of the targeted bone being located in a more subcutaneous location and therefore closer to the device compared to spinal fusion. Notwithstanding these observations, there are no data concerning the efficacy of electrical stimulation to enhance spinal fusion or fracture healing in elderly or osteoporotic patients.

Specific Injuries and Treatment in the Osteoporotic and Elderly Patient

Hip Fractures

As discussed above, hip fracture is perhaps the paradigmatic fracture in the osteoporotic patient and, although some of the surgical details have evolved, the general approach to treatment has not changed much in the past few decades. Hip fractures can be classified according to anatomic region and can be generally grouped into those fractures that occur within the joint capsule (Fig. 15.7) and those that occur outside the capsule (Fig. 15.8). The former category is comprised of the subcapital and femoral neck fractures and the latter the intertrochanteric fractures. The joint capsule is the most important distinction because it is the location of the blood vessels that supply the femoral neck and head. Compression or disruption of these vessels will compromise perfusion and potentially lead to impaired fracture healing and osteonecrosis of the femoral head. Minimally displaced or impacted fractures do not typically compromise the capsular vasculature and can be found to heal reliably with internal fixation through a minimally invasive procedure. This is best achieved using multiple parallel screws placed across the fracture site into the femoral neck and head (Fig. 15.9). The fracture fragments are compressed together by screws designed to allow thread purchase in the head fragment only and not across the fracture itself. This increases stability of the fragments and promotes healing through bone compression. The screws are placed through a small incision or stab incisions that incur little blood loss and minimal disruption of the soft tissue surrounding the fracture.

Treatment of displaced fractures is somewhat more controversial. Because fracture displacement can compress or disrupt the blood supply to the femoral head and neck, a decision must be made either to reduce the fracture to the anatomic position and perform internal fixation or to abandon the hope of fracture healing and perform prosthetic replacement of the proximal femur or

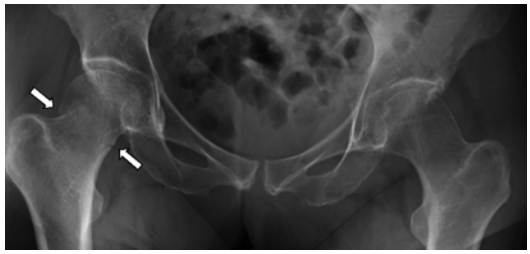


Fig. 15.7 Femoral neck fractures (*arrows*) occur within the hip capsule. Displaced femoral neck fractures can disrupt the capsule along with the blood supply to the femoral head

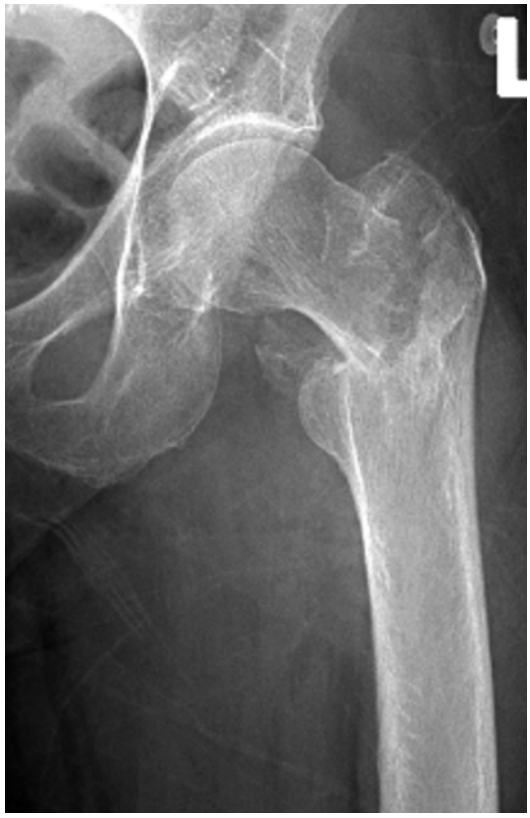


Fig. 15.8 Intertrochanteric fractures occur outside the hip capsule and do not typically disrupt the blood supply to the proximal femur. As a result, reduction and internal fixation routinely leads to adequate fracture healing

hip. The advantage of reduction and internal fixation is that it can be performed in a minimally invasive fashion as described above. This benefit must be weighed against the potential that the fracture may still not heal; widely displaced fractures are often found at the time of surgery to have

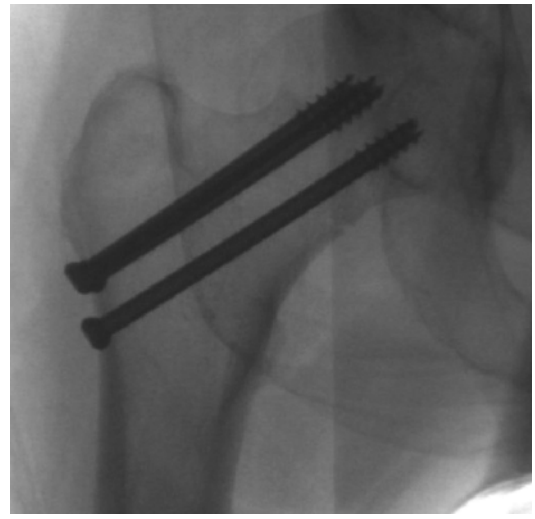


Fig. 15.9 Non-displaced or anatomically reduced femoral neck fractures can be stabilized with three lag screws and have a reasonable likelihood of healing

disrupted the vasculature as opposed to have simply compressed it. A fracture nonunion or hip osteonecrosis can lead to pain, ambulatory compromise, and further operations. Prosthetic replacement (Fig. 15.10) can eliminate these concerns and may result in a lower reoperation rate and better long-term hip function [20, 78, 79]. Although partial prosthetic replacement of the hip (hemiarthroplasty) has been performed successfully for decades, recent attention has been given to total hip replacement for hip fracture. With global life expectancy increasing, a patient treated at 65 years of age with a hemiarthroplasty may live with the prosthesis for an additional 20 years. During this period, the patient would be subjected to the possibility of degeneration of the acetabulum and pain resulting from the articulation with the prosthesis. Total hip arthroplasty replaces both the acetabulum and proximal femur and eliminates this possibility. The reported long term success with total hip arthroplasty for femoral neck fracture [20, 79] has led to a change in the treatment of femoral neck fractures with more surgeons favoring total hip arthroplasty at this time than in the past [80]. At this time, a preponderance of evidence suggests that healthy, high-functioning patients would be best served with a total hip arthroplasty; a patient with limited pre-injury

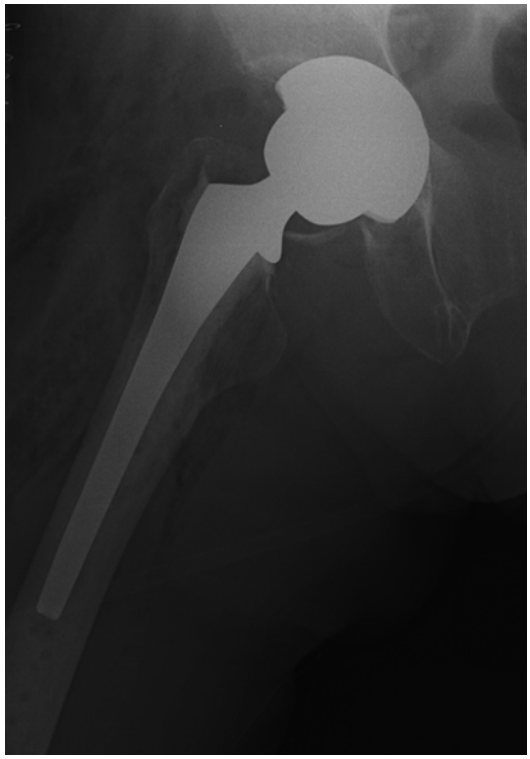


Fig. 15.10 Displaced femoral neck fractures have a poor likelihood of healing and are better treated with arthroplasty

mobility would benefit from hemiarthroplasty; a nonambulatory patient or patient with severe cognitive dysfunction would be best treated with reduction and internal fixation [78, 79].

Intertrochanteric fractures occur within the broad, cancellous, extracapsular region between the greater and lesser trochanters (Fig. 15.8). Displacement does not compromise the blood supply to the fracture site and these fractures therefore have a high rate of healing. Treatment of intertrochanteric fractures is less controversial than femoral neck fractures. Most surgeons agree that early internal fixation is optimal to prevent proximal femoral shortening, angulation, and deformity, and to more rapidly restore pre-injury ambulatory function than with nonoperative treatment. Perhaps the only source of debate is whether to use a sliding hip screw or an intramedullary nail. A sliding hip screw provides and maintains compression across the fracture site during fracture healing. The procedure has been used for decades and was once the primary method of intertrochanteric fracture fixation. The disadvantage of the technique is that splitting of the vastus lateralis is often required and is associated with high intraoperative blood loss. As a "minimally invasive" alternative, intramedullary devices were introduced for intertrochanteric fixation. The procedure, while more technically challenging, offered the potential advantages of less perceived blood loss as well as mechanically optimal positioning of the implant relative to the weight-bearing axis. Early reports of intramedullary nail fixation reported equivalent outcomes and complication rates with a lower rate of allogeneic blood transfusion [81]. More recent reports have that surgical complications, risk of blood loss, and systemic effects of surgery are equivalent [82, 83]. A preponderance of evidence appears to support the use of either device for fixation of intertrochanteric fractures, possibly with intramedullary nails serving more comminuted, unstable fractures better and with a lower risk of revision surgery.

Thoracic and Lumbar Fractures

The most common vertebral injury in patients with osteoporosis is the compression fracture (Fig. 15.2). These injuries can occur during normal physiologic functions such as coughing, sneezing, and turning in bed or with low-energy events such as grocery transport or vehicular encounter with the unpredictable roadway topography that characteristically follows a New England winter. Pain can be acute or insidious in onset and can have an impact that varies from mild nuisance to complete debilitation with significantly diminished quality and duration of life [28]. The long-term effects of vertebral compression fractures can be chronic pain, deformity (kyphosis), pulmonary compromise, and early gastrointestinal satiety [84, 85].

Traditional treatment of vertebral compression fractures focused on mitigation of symptoms and would often be met with a protracted course of pain management and activity modification, possibly with prolonged bed rest. Vertebral aug-

mentation is a family of techniques first developed in the 1980s as vertebroplasty for percutaneous stabilization of vertebral fractures [31]. The procedure is performed by inserting a large bore needle percutaneously and with radiographic guidance down the axis of the pedicle into the fractured vertebral body. PMMA is then injected as a viscous fluid through the needle into the vertebral body and is allowed to cure into a solid. By interdigitating into the trabeculae and fracture lines, the fracture, and thereby the pain generator, is stabilized. First-generation vertebroplasty techniques were found to result in PMMA extrusion from the vertebral body into the venous system and spinal canal in 20–70 % of cases [30, 33], a complication which can produce devastating consequences including pulmonary embolus, respiratory distress, and injury to the spinal cord and nerve roots. This complication led to the development of kyphoplasty, a modified form of vertebral augmentation during which an inflatable balloon tamp is inserted through the needle first and inflated to create a cavity into which the PMMA can be injected [33]. The balloon tamp provides for safer and more reproducible injection of the cement with less risk of extrusion and may allow for at least partial restoration the height of the vertebral body lost as a result of the compression fracture (Fig. 15.11). In practice, vertebral height restoration appears to be influenced more by the acuity of the fracture and fracture mobility more than the balloon; simply placing a patient prone on an operating table that fosters lordosis – or stated in another way, hyperextends the spine – will increase the vertebral height in a relatively acute fracture but not in a chronic, partially healed fracture. The creation of a cavity for injection of the PMMA is, however, a real advantage over early-generation vertebroplasty. Using a balloon tamp to create a cavity into which PMMA can be injected has been reported to reduce the occurrence of cement extrusion to approximately 9 % [33].

Vertebral augmentation is indicated for treatment of persistent pain from unhealed osteoporotic compression fractures. Since many VCFs

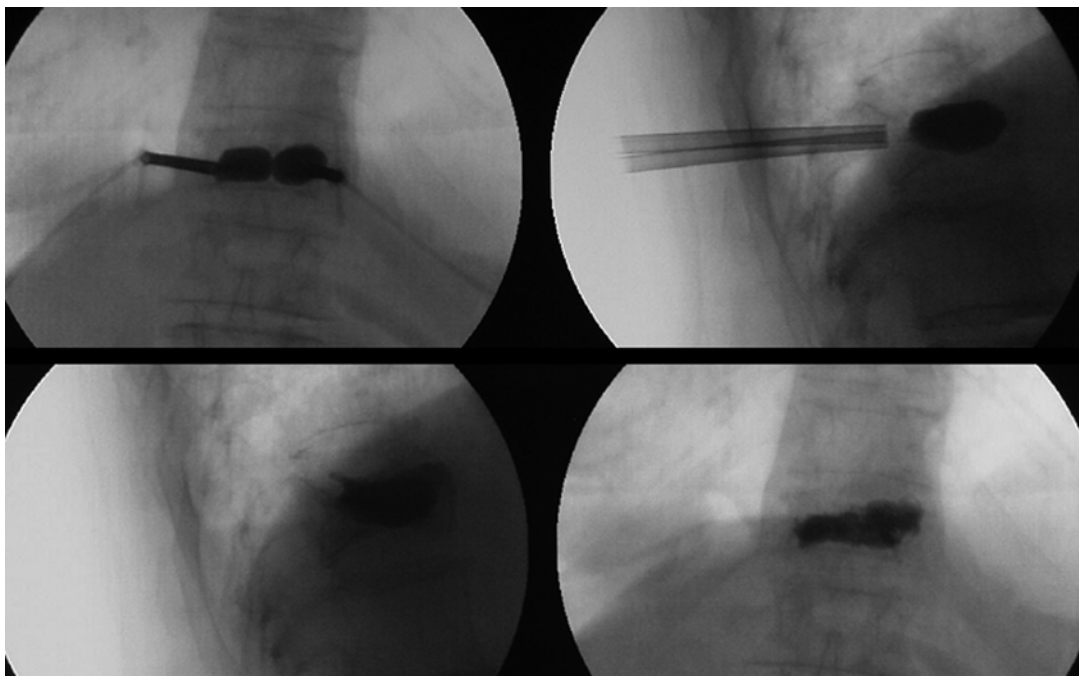


Fig. 15.11 A vertebral compression fracture can be treated with kyphoplasty. A balloon tamp is inserted and inflated to create a void and reduce fracture displacement (*top row*). The balloon is then deflated and removed and bone cement is injected to fill the void and stabilize the fracture

will be healed and discovered incidentally at the time of initial radiographic imaging, it is imperative to confirm that a newly discovered VCF is indeed acute or shows radiographic findings of abnormal bone activity consistent with painful conditions. This information is most often obtained by the magnetic resonance imaging (MRI) demonstration of increased signal on the STIR sequence or decreased signal on the T1 sequence, both of which are consistent with bone edema. Abnormal radiotracer uptake on a bone scan can provide similar information in patients unable to undergo MRI. In the authors' experience, fractures as old as 1–2 years can still have dramatic pain relief, provided that appropriate imaging findings confirm that the fracture has not healed and that edema is still present. Active spinal infection and uncorrectable coagulopathy are relative contraindications to vertebral augmentation. A burst fracture is also a contraindication to vertebral augmentation. These fractures are identified by the presence of fragments of the vertebral body displaced into the spinal canal (Fig. 15.12). In contrast to the simple compression fracture which, by definition, has an intact posterior wall of the vertebral body, displaced fracture fragments can compress and injure the spinal cord and cauda equina and can be displaced further by cement injection during vertebral augmentation [86, 87].

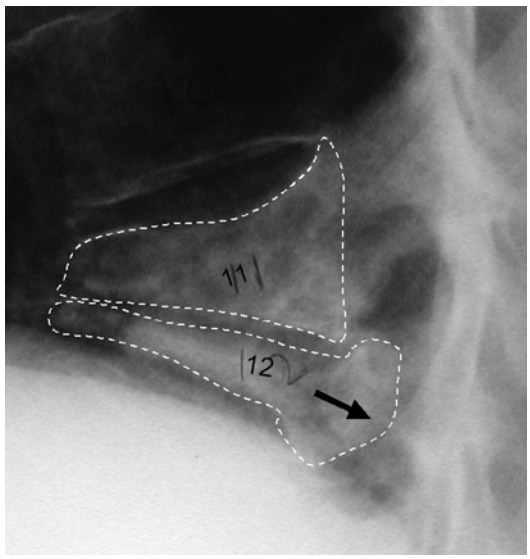


Fig. 15.12 A senile burst fracture (*bottom*, T12) can be distinguished from a simple compression fracture (*top*, T11) by the presence of posteriorly displaced vertebral body fragments that can impinge upon the spinal cord or cauda equina

Early reports of vertebral augmentation documented outcomes that rank among the most successful of any spine procedure. Rates of pain relief have been reported to reach 90–100 % with significant functional improvement as well [30, 88, 89]. These studies reported rapid relief of pain in patients treated with vertebral augmentation. After 6–12 months, patients treated with or without vertebral augmentation reported similar functional outcomes. These early reports, although describing nonrandomized patient cohorts, appear to corroborate the natural history of pain relief following VCF and suggest that vertebral augmentation can provide earlier achievement of optimal pain relief in the right patients.

Two randomized, sham-procedure controlled trials were reported in 2009 [90, 91] which have questioned the efficacy of vertebroplasty and led to considerable debate [92, 93]. Both trials reported equivalent pain relief in patients undergoing the actual vertebroplasty procedure as did patients undergoing a well designed sham procedure. These studies have provided the best evidence to date regarding vertebral augmentation and have changed the willingness of some primary care providers to refer VCF patients for evaluation for vertebroplasty [94]. The study authors have identified several limitations of the studies including patient enrollment that did not meet power requirements by the a priori analysis, skewed patient crossover from sham to vertebroplasty, possible treatment of fractures older than what has observed to show the best result with vertebral augmentation. Additional limitations of the study have been identified as well including the bias introduced by unwillingness of patients in the most severe pain to consent to randomization and a possibility that some of the treated fractures did not have adequate pretreatment imaging to confirm acuteness. Similar studies have not been performed to evaluate kyphoplasty as of yet. In total, it appears that suboptimal data have driven many of the decisions to perform vertebral augmentation and that even the most optimal information so far may be subop-

timal. Further high-quality evidence is required to present the final answer to this hotly debated question. The authors currently recommend vertebral augmentation only to patients presenting with severe functional impairment.

One final challenge in the treatment of osteoporotic VCF is the occurrence of subsequent fractures following initial fracture treatment. It has been suggested that vertebral augmentation can increase stresses at adjacent osteoporotic vertebrae and thereby increase the risk of adjacent fractures. While subsequent fractures undeniably occur in patients following vertebral augmentation, it is unclear if these fractures are sequellae of the procedure or of the natural history of severe osteoporosis. At this time, reports are mixed but appear to document that additional fractures will occur in 11–30 % of patients with symptomatic VCF regardless of the treatment of the index fracture [30, 95, 96]. When treating a patient with a VCF, it is imperative that systemic anti-osteoporosis therapy be administered to reduce the likelihood of another VCF, which may be overlooked by both the referring and consulting physicians.

Odontoid Fractures

The odontoid process, or dens, is the unique cranial projection from the vertebral body of C2 that serves as an axis around which the ring of C1 rotates. The odontoid process is held securely between the anterior arch of C1 and transverse ligament. It is found to be a point of stress concentration that is susceptible to unique fracture patterns because it is a narrow junction of bone between two relatively rigid spinal segments (namely, the occiput-C1 complex, and the subaxial spine, the mobility of which is typically diminished as a result of disc degeneration).

This arrangement predisposes the odontoid to a fracture pattern that occurs commonly in elderly osteoporotic individuals, whose ambulatory balance and ability to brace for a fall may be compromised. The usual mechanism is fall forward in which the patient's forehead strikes the ground or an item of furniture. The impact produces an extension moment that displaces the head, C1, and fragment of the odontoid process posteriorly (Fig. 15.13). Because the ratio of spinal canal

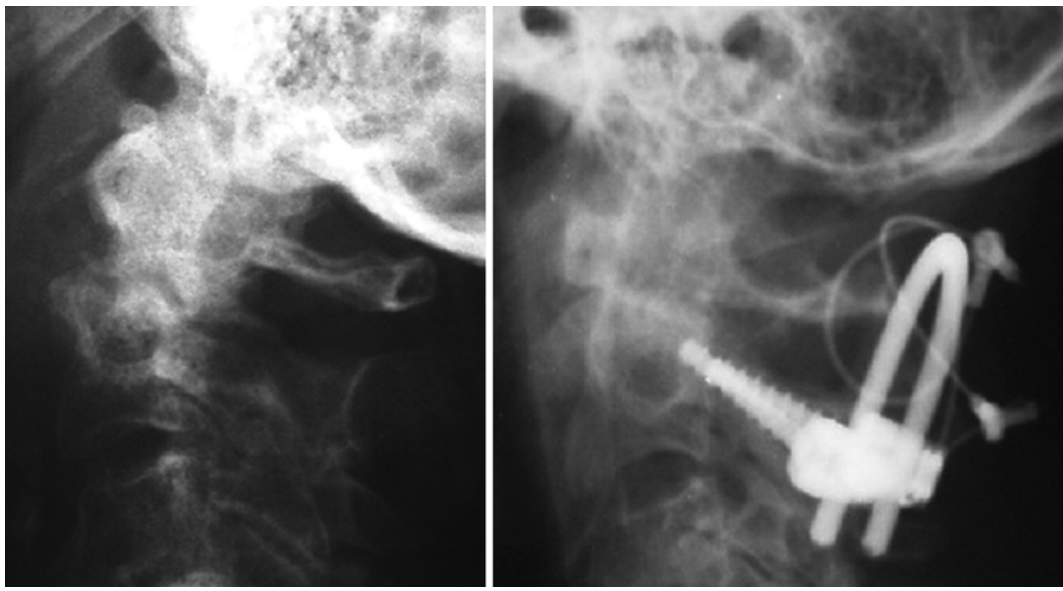


Fig. 15.13 Odontoid fractures are common in the elderly (*left*), often presenting with posterior displacement thats result from falling forward and striking the forehead or face. In some cases, stabilization is recommended, which can involve a posterior C1-C2 fusion with instrumentation (*right*)

diameter to spinal cord diameter is approximately three to one at this spinal level, even large amounts of displacement can be tolerated without neural compression. Thus, neurologic deficits infrequently result from odontoid fractures. There are wide differences among spine care providers in the approach to treatment of odontoid fractures in older and osteoporotic patients with consensus regarding the optimal method of treatment lacking [97]. Proponents of nonsurgical care would apply a hard or soft cervical orthosis collar for spinal immobilization until the fracture heals. Surgical treatment involves stabilization of the fracture either with transfixation of the fracture with screws placed from an anterior approach or fusion of C1-C2 from a posterior approach. Surgical treatment recently has been reported to have no more a deleterious impact on a patient mortality than nonsurgical treatment and may even prolong survival in certain age groups [98, 99]. Additionally, nonoperative treatment has been found to result in a higher rate of fracture nonunion (up to 22 %) [100]. Fracture nonunion does not appear to have a negative impact on patient outcome but does often lead to delayed surgery. Although further, high quality study of this fracture are required [97], current evidence appears to favor surgical treatment for odontoid fractures in younger (less than 75 years old), highly functional geriatric patients with fracture displacement or neurological deficit.

Distal Radius Fractures

As a result of the impairment of ambulatory function and reaction time that occur with increasing age, a fall on to an outstretched hand is a common occurrence that can lead to a distal radius fracture. The metaphyseal bone of the distal radius, like that of the vertebral body and hip, is affected more than the cortical or subchondral bone and fails upon loading. Along the osteoporosis time line, fractures of the distal radius occur earlier than hip fractures. They should be interpreted as an indicator of significant bone loss and a warning sign that a hip fracture may be imminent, particularly within the first month following the event [101]. Compared with the general population, patients who have sustained an osteoporotic distal radius fracture are at twice the risk for a subsequent hip fracture [102], and should thus be considered for systemic anti-osteoporosis therapy.

Treatment of distal radius fractures includes cast immobilization or surgical stabilization. Selection of the optimal treatment should be guided by the fracture pattern and the patient's functional demands. Nondisplaced fractures should be treated in a well-molded cast for approximately 6 weeks. Longer periods of immobilization can lead to worsened osteopenia and wrist stiffness. Treatment of displaced fractures is somewhat more controversial. A fall on to an outstretched hand typically produces a dorsally angulated fracture. Malunion with a small degree of dorsal angulation can be well tolerated. Greater amounts of angulation, however, can lead to improper function of the hand and wrist that would compromise patient independence and ability and should be reduced through fracture manipulation. Reduction into anatomic alignment can sometimes be maintained with a cast but will often fall back into malalignment as the comminuted fragments undergo remodeling during early fracture healing. These fractures are therefore typically treated with surgical stabilization. Fixation can be achieved by transfixing the fracture with percutaneously placed pins, an external fixator, or an internal fixation plate and screws. External fixation devices represent a method of fixation that avoids direct exposure of the fracture site, potentially limiting devitalization of the bone as discussed above. The technique has been shown to maintain an anatomic alignment superior to cast immobilization [103]. Regardless, even in cases of malunion, functional outcome has been shown to be acceptable [104]. A major objection to external fixation is the requirement that the devices span the carpus and immobilize the wrist during fracture healing. Internal fixation plates mitigate this risk by limiting fixation to the distal radius and allowing free motion of all wrist and hand joints. Low profile plates have been designed to be supported by the dense cortical and subchondral bone with screws that lock directly to the plate, thereby acting as a

fixed-angle device and avoiding the fixation challenges of the osteoporotic metaphysis [105]. Recently, advanced percutaneous pinning techniques have been developed to take advantage of the benefits of both the external fixation device (i.e. limited fracture manipulation and devitalization) and internal fixation (facilitating rapid restoration of joint mobility) [106].

A final method of stabilizing osteoporotic fractures of the distal radius involves mechanical augmentation of the metaphyseal bone with injectable cements in a manner similar to vertebral augmentation. Calcium phosphate cements marketed under the trade names Norian SRS and ChronOS Inject (DePuy-Synthes, Raynham, MA) have been reported to improve patient reported outcome and histological evidence of bone formation [107, 108]. The fracture stabilization provided by the injectable bone cement allows for earlier mobilization of the wrist compared with cast treatment alone. In summary, several surgical developments have allowed for successful fixation of severe distal radius fractures in the osteoporotic patient. These advances, however, must be considered as tools to assist fracture care only. Distal radius fractures in osteoporotic patients do not fare as well functionally as patients with normal bone mineral density and should be considered high risk for a complication of treatment [109].

Tibial Plateau Fractures

Proximal tibial fractures occur in the bone supporting the knee. Fractures that involve the articular surface of the proximal tibia are referred to as tibial plateau fractures. In osteoporotic patients, as discussed above, the fractures commonly present with depression of the articular surface into the trabecular bone of the proximal tibial metaphysis. This produces an incongruent articular surface which can lead to painful arthritis. Occult tibial plateau fractures have been recognized as a cause of chronic knee pain in the elderly [110, 111].

A primary goal of surgical treatment of tibial plateau fractures is restoration of the joint surface. When large fracture fragments are present, direct, open reduction and internal fixation is often the optimal method of treatment (Fig. 15.14). If only a portion of the joint surface is depressed with the cortical rim of the proximal tibia remaining intact, the fracture reduction can be performed using less invasive methods. Through a small incision, a window can be made in the cortex of the proximal tibia and a bone tamp inserted to push fracture fragments back into the normal anatomic position. Recently, techniques have been developed utilizing the balloon tamps initially designed for vertebral kyphoplasty [112]. The balloon tamp is inserted percutaneously and inflated under radiographic guidance to reduce the fracture fragments to the anatomic position. In osteoporotic bone, compression and reduction of the fracture fragments using any method can lead to large voids in the proximal tibia that must be filled to support the anatomic alignment. These gaps can be filled either with bone graft in a technique known as impaction or compaction grafting [113] or with PMMA bone cement. Bone grafting offers the advantage of being fully incorporated into the patient's bone but with the caveat that the reabsorption that occurs during remodeling can lead to recurrence of fracture displacement. Bone cement, on the other hand, will assume the exact shape of the void and interdigitate into the bony trabeculae. The nonresorbability can protect against recurrent fracture displacement but can lead to a tissue reaction with osteolysis at the border of the PMMA. The risks and benefits of both techniques, therefore, must be weighed with each individual patient during surgical planning.

Following fracture reduction, internal fixation is typically performed to support and maintain the anatomic alignment of fracture fragments. Percutaneously placed screws are often adequate for stabilization of tibial plateau fractures. Screw fixation in osteoporotic bone can be augmented using PMMA bone cement injected to fill fracture voids or independently for the augmentation of screw fixation as described above. The PMMA is injected as a fluid and then a screw is inserted, allowing the PMMA to cure and harden around the screws. This increases the strength of the

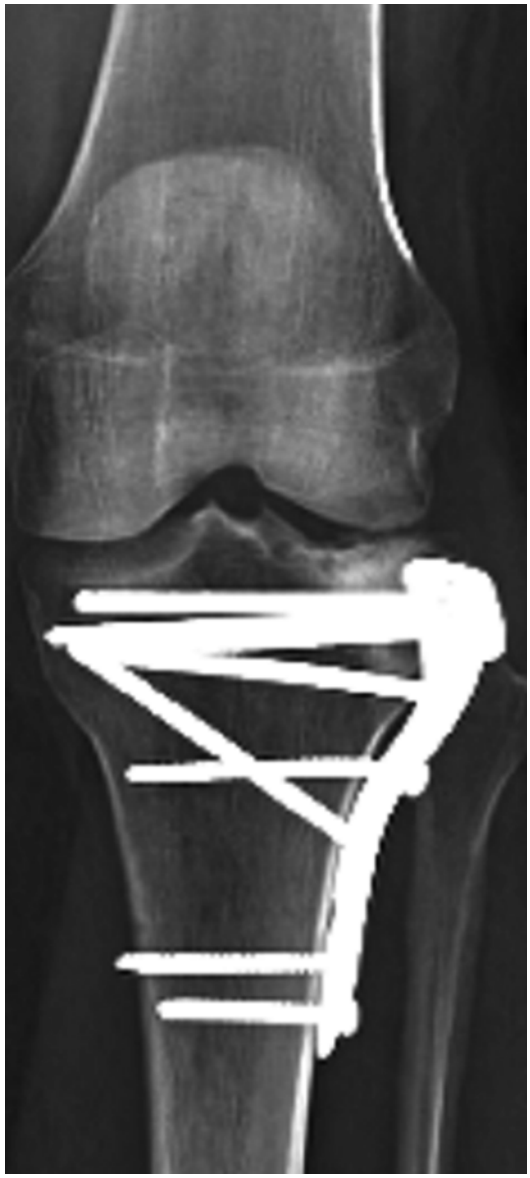


Fig. 15.14 Tibial plateau fractures are often stabilized with a plate and screws

screw fixation by providing a broader area of implant-bone interface. The interface can also be enhanced by utilizing a plate designed to accommodate multiple screws that thread into, or "lock," into the plate. The stability and strength are gained not simply from screw purchase into bone but from the fixation to the plate. Promising results using this device in osteoporotic bone have been reported [114]. Despite these techniques, fracture fixation in the elderly and osteoporotic still presents a challenge. Perhaps the greatest word of caution has been a report that internal fixation of tibial plateau fractures in the elderly is associated with a tenfold increase in fixation failure when compared to fracture fixation in younger, nonosteoporotic bone [115].

Conclusions

The treatment of fractures in elderly, osteoporotic patients presents formidable challenges as a result of the interplay between impaired bone healing, impaired bone fixation, and impaired general medical health. Over the past few decades, several advances have been made to improve internal fixation devices, bone and healing augmentation methods, and multidisciplinary care teams to improve the outcome of fracture treatment in the elderly. As the population ages, we must continue to strive for more effective methods of fracture prevention and care.

References

1. World Health Organization Global Health Observatory (GHO): Life Expectancy. http://www.who.int/gho/mortality_burden_disease/life_tables/situation_trends_text/en/. Accessed 20 Nov 2014.
2. Battacharyya T, Iorio R, Healy WL. Rate of and risk factors for acute inpatient mortality after orthopaedic surgery. J Bone Joint Surg Am. 2002;84:562–72.
3. Streubel PN, Ricci WM, Wong A, Gardner MJ. Mortality after distal femur fracture in elderly patients. Clin Orthop Relat Res. 2011;479:1188–96.
4. Zuckerman JD, Skovron ML, Koval KJ, et al. Postoperative complications and mortality associated with operative delay in older patients who have a fracture of the hip. J Bone Joint Surg Am. 1995;77-A:1551–6.
5. Hamlet WP, Lieberman JR, Freedman EL, et al. Influence of health status and the timing of surgery on mortality in hip fracture. Am J Orthop. 1997;26:621–7.
6. McGuire KJ, Bernstein J, Polsky D, Silber JH. The 2004 Marshall Urist Award: Delays until surgery after hip fracture increases mortality. Clin Orthop Relat Res. 2004;428:294–301.
7. Moore L, Turgeon AF, Sirois M-J, Lavoie A. Trauma centre outcome performance: a comparison of young adults and geriatric patients in an inclusive trauma system. Injury. 2012;43(9):1580–5.
8. Bielza Galindo R, Ortiz Espada A, Arias Munana E, et al. Opening of an acute orthogeriatric unit in a general hospital. Rev Esp Geriatr Gerontol. 2013;48(1):26–9.

9. Pape HC, Friess T, Liener U, et al. Development of geriatric trauma centers – an effort by the German Society for Trauma and Orthopaedics. Injury. 2014;45(10):1513–5.
10. Desai PA, Vyas PA, Lane JM. Atypical femoral fractures: a review of the literature. Curr Osteoporos Rep. 2013;11(3):179–87.
11. Shane E, Burr D, Abrahamsen B, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2014;29(1):1–23.
12. Shane E, Burr D, Ebeling PR, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2010; 25(11):2267–94.
13. Schilcher J, Koeppen V, Aspenberg P, Michaelsson K. Risk of atypical femoral fracture during and after bisphosphonate use. N Engl J Med. 2014;371(10): 974–6.
14. Patel V, Graves L, Lukert B. Pelvic fractures associated with long-term bisphosphonate therapy – case report. J Musculoskelet Neuronal Interact. 2013;13(2):251–4.
15. Tan SH, Saseendar S, Tan BH, et al. Ulnar fractures with bisphosphonate therapy: a systematic review of published case reports. Osteoporos Int. 2015;26: 421–9.
16. Goh JC, Shah KM, Bose K. Biomechanical study on femoral neck fracture fixation in relation to bone mineral density. Clin Biomech. 1995;10:304–8.
17. Spangler L, Cummings P, Tencer AF, et al. Biomechanical factors and failure of transcervical hip fracture repair. Injury. 2001;32:223–8.
18. Davis AT, Israel H, Cannada LK, Bledsoe JG. A biomechanical comparison of one-third tubular plates versus periarticular plates for fixation of osteoporotic distal fibula fractures. J Orthop Trauma. 2013;27(9):e201–7.
19. Wahnert D, Lange JH, Schulze M, et al. A laboratory investigation to assess the influence of cement augmentation of screw and plate fixation in a simulation of distal femoral fracture in osteoporotic and non-osteoporotic bone. Bone Joint J. 2013;95-B(10): 1406–9.
20. Keating JF, Grant A, Masson M, et al. Randomized comparison of reduction and fixation, bipolar hemiarthroplasty, and total hip arthroplasty. Treatment of displaced intracapsular hip fractures in healthy older patients. J Bone Joint Surg Am. 2006;88: 249–60.
21. Maier D, Jaeger M, Izadpanah K, et al. Proximal humeral fracture treatment in adults. J Bone Joint Surg Am. 2014;96(3):251–61.
22. [No authors listed]. Hip fractures in the elderly. Lancet. 1967;2(7505):34.
23. Orthopedia vs. anesthesia (orthopaedics, anaesthetics, conversation). YouTube. 2010. https://www.youtube.com/watch?v=3rTsvb2ef5k. Accessed 24 Nov 2014.
24. Hoerer D, Volpin G, Stein H. Results of early and delayed surgical fixation of hip fractures in the elderly: a comparative retrospective study. Bull Hosp Jt Dis. 1993;53:29–33.
25. Moran CG, Wenn RT, Sikand M, et al. Early mortality after hip fracture: is delay before surgery important? J Bone Joint Surg Am. 2005;87:483–9.
26. Koval KJ, Cooley MR. Clinical pathway after hip fracture. Disabil Rehabil. 2005;27:1053–60.
27. Hip Fracture Accelerated Surgical Treatment and Care Track (Hip ATTACK) Investigators. Accelerated care versus standard care among patients with hip fracture: the HIP ATTACK pilot trial. CMAJ. 2014;186(1):E52–60.
28. Cauley JA, Thompson DE, Ensrud KC, et al. Risk of mortality following clinical fractures. Osteoporos Int. 2001;11:556–61.
29. Rao RD, Singrakhia MD. Painful osteoporotic vertebral fracture. J Bone Joint Surg Am. 2003;85:2010–22.
30. Alvarez L, Alcaraz M, Perez-Hiqueras A, et al. Percutaneous vertebroplasty: functional improvement in patients with osteoporotic compression fractures. Spine. 2006;31:1113–8.
31. Deramond H, Depriester C, Galibert P, et al. Percutaneous vertebroplasty with polymethylmethacrylate. Technique, indications, and results. Radiol Clin North Am. 1998;36:533–46.
32. Barr JD, Barr MS, Lemley TJ, et al. Percutaneous vertebroplasty for pain relief and spinal stabilization. Spine. 2000;25:923–8.
33. Lieberman IH, Dudeny S, Reinhart MK, Bell G. Initial outcome and efficacy of 'kyphoplasty' in the treatment of painful osteoporotic vertebral compression fractures. Spine. 2001;26:1631–7.
34. Zampini JM, White AP, McGuire KJ. Comparsison of 5766 vertebral compression fractures treated with or without kyphoplasty. Clin Orthop Relat Res. 2010;468:1773–80.
35. Edidin AA, Ong KL, Lau E, Kurtz SM. Mortality risk for operated and nonoperated vertebarl fracture patients in the medicare population. J Bone Miner Res. 2011;26(7):1617–26.
36. Namkung-Matthai H, Appleyard R, Jansen J, et al. Osteoporosis influences the early period of fracture healing in a rat osteoporotic model. Bone. 2001;28: 80–6.
37. Meyer RA, Tsahakis PJ, Martin DE, et al. Age and ovariectomy impair both the normalization of mechanical properties and the accretion of mineral by the fracture callus in rats. J Orthop Res. 2001;19:428–35.
38. Simmons E, Kuhele J, Lee J, et al. Evaluation of metabolic bone disease as a risk factor for lumbar fusion. Spine J. 2002;2:99S.
39. Kucera T, Soukup T, Krs O, Urban K, Sponer P. Bone healing capacity in patients undergoing total hip arthroplasty. Acta Chir Orthop Traumatol Czech. 2012;79(1):52–8.
40. Jager M, Jelinek EM, Wess KM, et al. Bone marrow concentrate: a novel strategy for bone defect treatment. Curr Stem Cell Res Ther. 2009;4(1): 34–43.

41. Petri M, Namazian A, Wilke F, et al. Repair of segmental lone-bone defects by stem cell concentrate augmented scaffolds: a clinical and positron emission tomography-computed tomography analysis. Int Orthop. 2013;37:2231–7.
42. LeBlanc K, Tammik C, Rosendahl K, et al. HLA expression and immunologic properties of differentiated and undifferentiated mesenchymal stem cells. Exp Hematol. 2003;31(10):890–6.
43. Gomez-Barrena E, Rosset P, Muller I, et al. Bone regeneration: stem cell therapies and clinical studies in orthopaedics and traumatology. J Cell Mol Med. 2011;15(6):1266–86.
44. Friedlander GE, Perry CR, Cole JD, et al. Osteogenic protein-1 (bone morphogenetic protein-7) in the treatment of tibial nonunions. J Bone Joint Surg Am. 2001;83A:S151–8.
45. Govender S, Csimma C, Genant HK, et al. Recombinant human bone morphogeneetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. J Bone Joint Surg Am. 2002;84A:2123–34.
46. Burkus JK, Transfeldt EE, Kitchel SH, et al. Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2. Spine. 2002;27:2396–408.
47. Kanayama M, Hashimoto T, Shigenobu K, et al. A prospective randomized study of posterolateral lumbar fusion using osteogenic protein-1 (OP-1) versus local autograft with ceramic bone substitute: emphasis of surgical exploration and histologic assessment. Spine. 2006;31:1067–74.
48. Vaccaro AR, Patel T, Fischgrund J, et al. A 2-year follow-up pilot study evaluating the safety and efficacy of OP-1 putty (rhBMP-7) as an adjunct to iliac crest autograft in posterolateral lumbar fusions. Eur Spine J. 2005;14:623–9.
49. Vaccaro AR, Anderson DG, Patel L, et al. Comparison of OP-1 putty (rhBMP-7) to iliac crest autograft for posterolateral lumbar arthrodesis: a minimul 2-year follow-up pilot study. Spine. 2005;30:2709–16.
50. Boden SD, Kang J, Sandju HS, et al. Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans: a prospective, randomized clinical pilot trial: 2002 Volvo Award in clinical studies. Spine. 2002;27:2662–73.
51. Johnsson R, Stromqvist B, Aspenberg P. Randomized radiostereometric study comparing osteogenic protein-1 (BMP-7) and autograft bone in human nonistrumented posterolateral lumbar fusion: 2002 Volvo Award in clinical studies. Spine. 2002;27:2654–61.
52. Bono C, Lee C. Critical analysis of trends in fusion for degenerative disc disease over the last twenty years: influence of technique on fusion rate and clinical outcome. Spine J. 2002;2:47S–8.
53. Egerman M, Baltzer AW, Adamaszek S, et al. Direct adenoviral transfer of bone morphogenetic protein-2 cDNA enhances fracture healing in ostroporotic sheep. Hum Gene Ther. 2006;17:507–17.
54. Diwan AD, Leong A, Appleyard R, et al. Bone morphogenetic protein-7 accelerated fracture healing in osteoporotic rats. Indian J Orthop. 2013;47(6):540–6.
55. Park SB, Park SH, Kim NH, Chung CK. BMP-2 induced early bone formation in spine fusion using rat ovariectomy osteoporisis model. Spine J. 2013; 13(10):1273–80.
56. Zarrinkalam MR, Schultz CG, Ardern DW, et al. Recombinant human bone morphogenetic protein-type 2 (rhBMP-2) enhances local bone formation in the lumbar spine of osteoporotic sheep. J Orthop Res. 2013;31(9):1390–7.
57. Carragee EJ, Hurwitz EL, Weiner BK. A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned. Spine J. 2011;11(6): 471–91.
58. Fujita T, Inoue T, Morii H, et al. Effect of intermittent weekly dose of human parathyroid hormone (1-34) on osteoporosis: a randomized double-masked prospective study using three dose levels. Osteoporos Int. 1999;9(4):296–306.
59. Zhang D, Potty A, Vyas P, Lane J. The role of recombinant PTH in human fracture healing: a systematic review. J Orthop Trauma. 2014;28(1):57–62.
60. Aspenberg P, Genant HK, Johansson T, et al. Teriparatide for acceleration of fracture repair in humans: a prospective, randomized, double-blind study of 102 postmenopausal women with distal radius fractures. J Bone Miner Res. 2010;25(2):404–14.
61. Peichl P, Holzer LA, Maier R, Holzer G. Parathyroid hormone 1-84 accelerates fracture-healing in pubic bones of elderly osteoporotic women. J Bone Joint Surg Am. 2011;93:1583–7.
62. Sugiura T, Kashii M, Matsuo Y, et al. Intermittent administration of teriparatide enhances bone graft healing and adccelerates spinal fusion in rats with glucocorticoid-induced osteoporosis. Spine J 2015; 15(2): 298–306.
63. Qui Z, Wei L, Liu J, et al. Effect of intermittend PTH (1-34) on posterolateral spinal fusion with iliac crest bone graft in an ovariectomized rat mode. Osteoporos Int. 2013;24(10):2693–700.
64. Lehman Jr RA, Dmitriev AE, Cardoso MJ, et al. Effect of teriparatide [rPTH(1,340] and calcitonin on intertransverse process fusion in a rabbit model. Spine (Phila PA 1976). 2010;35(2):146–52.
65. Lina IA, Puvanesarajah V, Liauw JA, et al. Quantitative study of parathyroid hormone (1-34) and bone morphogenetic protein-2 on spinal fusion outcomes in a rabbit model of lumbar dorsolateral intertransverse process arthrodesis. Spine (Phila PA 1976). 2014;39(5):347–55.
66. Huang RC, Khan SN, Sandhu HS, et al. Alendronate inhibits spine fusion in a rat model. Spine. 2005; 30:2516–22.
67. Xue Q, Li H, Zou X, et al. The influence of alendronate treatment and bone graft volume on posterior lateral spine fusion in a porcine model. Spine. 2005; 30:1116–21.

68. Koo KH, Lee JH, Chang BS, Lee CK. Effects of alendronate on lumbar posterolateral fusion using hydroxyapatite in rabbits. Artif Organs. 2012;36(12): 1047–55.
69. Park SB, Park SH, Kang YK, Chung CK. The time-dependent effect of ibandronate on bone graft remodeling in an ovariectomized rat spinal arthrodesis model. Spine J. 2014;14(8):1748–57.
70. Park YS, Kim HS, Baek SW, et al. The effect of zolendronic acid on the volume of the fusion-mass in lumbar spinal fusion. Clin Orthop Surg. 2013;5(4):292–7.
71. Li C, Wang HR, Li XL, et al. The relation between zolendronic acid infusion and interbody fusion in patients undergoing transforaminal lumbar interbody fusion surgery. Acta Neurochir (Wein). 2012;154(4):731–8.
72. Nagahama K, Kanayama M, Togawa D, et al. Does alendronate disturb the healing process of posterior lumbar interbody fusion? A prospective randomized trial. J Neurosurg Spine. 2011;14(4):500–7.
73. Xue D, Li F, Chen G, et al. DO bisphosphonates affect bone healing? A meta-analysis of randomized controlled trials. J Orthop Surg Res. 2014;9:45.
74. Bassett CA, Becker RO. Generation of electric potentials by bone in response to mechanical stress. Science. 1962;137:1063–4.
75. Park P, Lau D, Brodt ED, Dettori JR. Electrical stimulation to enhance spinal fusion: a systematic review. Evid Based Spine Care J. 2014;5(2):87–94.
76. Abeed RI, Naseer M, Abel EW. Capacitively coupled electrical stimulation treatment: results from patients with failed long bone fracture unions. J Orthop Trauma. 1998;12:510–3.
77. Phieffer LS, Goulet JA. Delayed unions of the tibia. J Bone Joint Surg Am. 2006;88:206–16.
78. Johansson T, Jacobsson SA, Ivarsson I, et al. Internal fixation versus total hip arthroplasty in the treatment of displaced femoral neck fractures: a prospective randomized study of 100 hips. Acta Orthop Scand. 2000;71(6):597–602.
79. Ravikumar KJ, Marsh G. Internal fixation versus hemiarthroplasty versus total hip arthroplasty for displaced subcapital fractures of the femur – 13 year results of a prospective randomised study. Injury. 2000;31:793–7.
80. Miller BJ, Callaghan JJ, Cram P, et al. Changing trends in the treatment of femoral neck fractures: a review of the American Board of Orthopaedic Surgery database. J Bone Joint Surg Am. 2014; 96(17):e149.
81. Utrilla AL, Reig JS, Munoz FM, et al. Trochanteric Gamma nail and compression hip screw for trochanteric fractures: a randomized, prospective, comparative study in 210 elderly patients with a new design of the Gamma nail. J Orthop Trauma. 2005; 19:229–33.
82. Parker MJ, Bowers TR, Pryor GA. Sliding hip screw versus the Targon PF nail in the treatment of trochanteric fractures of the hip: a randomised trial of 600 fractures. J Bone Joint Surg Br. 2012;94(3):391–7.
83. Verettas DA, Ifantidis P, Chatzipapas CN, et al. Systematic effects of surgical treatment of hip fractures: gliding screw-plating vs intramedullary nailing. Injury. 2010;41(3):279–84.
84. Schlaich C, Minne HW, Bruckner T, et al. Reduced pulmonary function in patients with spinal osteoporotic fractures. Osteoporos Int. 1998;8:261–7.
85. Leidig-Bruckner G, Minne HW, Schlaich C, et al. Clinical grading of spinal osteoporosis: quality of life components and spinal deformity in women with chronic low back pain and women with vertebral osteoporosis. J Bone Miner Res. 1997;12:663–75.
86. Nguyen HV, Ludwig S, Gelb D. Osteoporotic vertebral burst fractures with neurologic compromise. J Spinal Disord Tech. 2003;16:10–9.
87. Korovessis P, Maraziotis T, Piperos G, et al. Spontaneous burst fracture of the thoracolumbar spine in osteoporosis is associated with neurological impairment: a report of seven cases and review of the literature. Eur Spine J. 1994;3:286–8.
88. Diamond TH, Champion B, Clark WA. Management of acute osteoporotic vertebral fractures: a nonrandomized trial comparing percutaneous vertebroplasty with conservative therapy. Am J Med. 2003;114(4):257–65.
89. Kasperk C, Hillmeier J, Noldge G, et al. Treatment of painful vertebral fractures by kyphoplasty in patients with primary osteoporosis: a prospective nonrandomized controlled study. J Bone Miner Res. 2005;20:604–12.
90. Buchbinder R, Osborne RH, Ebeling PR, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral compression fractures. N Engl J Med. 2009;361(6):557–68.
91. Kallmes DF, Comstock BA, Heagerty PJ, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. N Engl J Med. 2009;361(6):569–79.
92. Bono CM, Heggenes M, Mick C, et al. North American Spine Society: newly released vertebroplasty randomized controlled trials: a tale of two trials. Spine J. 2010;10(3):238–40.
93. Buchbinder R, Kallmes DF. Vertebroplasty: when randomized placebo-controlled trials clash with common belief. Spine J. 2010;10(3):241–3.
94. Lindsey SS, Kalmes DF, Opatowsky MJ, et al. Impact of sham-comtrolled vertebroplasty trials on referral patterns at two academic medical centers. Proc (Bayl Univ Med Cent). 2013;26(2):103–5.
95. Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. JAMA. 2001;285:320–3.
96. Harrop JS, Prpa B, Reinhardt MK, et al. Primary and secondary osteoporosis' incidence of subsequent vertebral compression fractures after kyphoplasty. Spine. 2004;29:2120–5.
97. Huybregts JGJ, Jacobs WCH, Peul WC, Vleggeert-Lankamp LA. Rationale and design of the

INNOVATE Trial: an international cooperative study on surgical versus conservative treatment of odontoid fractures in the elderly. BMC Musculoskelet Disord. 2014;15:1471–8.
98. Schoenfeld AJ, Bono CM, Reichmann WM, et al. Type II odontoid fractures of the cervical spine: do treatment type and medical comorbidities affect mortality in elderly patients? Spine. 2011;36(11):879–85.
99. Chapman J, Smith JS, Kopjar B, et al. The AOSpine North America geriatric odontoid fracture mortality study. Spine. 2013;38(13):1098–104.
100. Smith JS, Kepler CK, Kopjar B, et al. Effect of type II odontoid fracture nonunion on outcome among elderly patients treated without surgery: based on the AOSpine North America geriatric odontoid fracture study. Spine. 2013;38(26):2240–6.
101. Chen CW, Huang TL, Su LT, et al. Incidence of subsequent hip fractures is significantly increased within the first month after distal radius fracture in patients older than 60 years. J Trauma Acute Care Surg. 2013;74(1):317–21.
102. Kannus P, Parkkari J, Sievanen H, et al. Epidemiology of hip fractures. Bone. 1996;18(Supplement):57S–63.
103. Moroni A, VAnnini F, Faldini C, et al. Cast vs external fixation: a comparative study in elderly osteoporotic distal radial fracture patients. Scand J Surg. 2004;93:64–7.
104. Hegeman JH, Oskam J, Vierhout PA, et al. External fixation for unstable intra-articular distal radial fractures in women older than 55 years. Acceptable functional end results in the majority of patients despite significant secondary displacement. Injury. 2005;36:339–44.
105. Ring D, Jupiter JB. Treatment of osteoporotic distal radius fractures. Osteoporos Int. 2005;16(Suppl): S80–4.
106. Gradl G, Gradl G, Wendt M, et al. Non-bridging external fixation employing multiplanar K-wires versus volar locked plating for dorsally displaced fractures of the distal radius. Arch Orthop Trauma Surg. 2013;133(5):595–602.
107. Sanchez-Sotelo J, Munuera L, Madero R. Treatment of fractures of the distal radius with a remodellable bone cement: a prospective, randomised study using Norian SRS. J Bone Surg Br. 2000;82-B: 856–63.
108. Arora R, Milz S, Sitte I, Blauth M, Lutz M. Behavior of ChronOS Inject in metaphyseal bone defects of the distal radius fractures: tissue reaction after 6-15 months. Injury. 2012;43(10):1683–8.
109. Fitzpatrick SK, Casemyr NE, Zurakowski D, et al. The effect of osteoporosis on outcomes of operatively treated distal radius fractures. J Hand Surg Am. 2012;37(10):2027–34.
110. Cabitza P, Tamin H. Occult fractures of tibial plateau detected employing magnetic resonance imaging. Arch Orthop Trauma Surg. 2000;210:355–7.
111. Luria S, Liebergall M, Elishoov O, et al. Osteoporotic tibial plateau fractures: an underestimated cause of knee pain in the elderly. Am J Orthop. 2005;34: 186–8.
112. Broome B, Mauffrey C, Statton J, et al. Inflation osteoplasty: in vitro evaluation of a new technique for reducing depressed intra-articular fractures of the tibial plateau and distal radius. J Orthop Traumatol. 2012;13:89–95.
113. Veitch SW, Stroud RM, Toms AD. Compaction bone grafting in tibial plateau fracture fixation. J Trauma. 2010;68(4):980–3.
114. Schandelmaier P, Stephan C, Krettek C, et al. Distal fractures of the femur. Unflallchirurg. 2000;103: 428–36.
115. Ali AM, El-Shafie M, Willett KM. Failure of fixation of tibial plateau fractures. J Orthop Trauma. 2002;16:323–9.

The Orthogeriatrics Model of Care

16

Susan M. Friedman

Rationale of Orthogeriatric Collaboration

As discussed in Chap. 7, osteoporosis and resulting fragility fractures can be thought of as a geriatric syndrome. Most osteoporotic individuals who sustain fragility fractures are older adults; more than 90 % of hip fractures occur in individuals who are 65 or older [1]. The risk of hip fracture doubles with every decade after the age of 50 [2], so that a woman who reaches the age of 90 years has a one in three chance of sustaining a hip fracture [3].

The association of osteoporotic fractures with age and frailty means that patients who present with these types of fractures often have significant comorbidities. This is particularly true in recent years; primary prevention efforts have led to a delay in the onset of first fracture [4], and so patients are presenting at older ages [5], and, concomitantly, have more comorbidities. These chronic conditions in turn increase perioperative risk, and the concern for postoperative complications.

The stakes are high, not only in terms of mortality, but also for outcomes that significantly impact the quality of an individual's life. These include mobility, the ability to be independent in activities of daily living, and the ability to stay in one's home. In addition to physical function, patients who sustain fragility fractures – particularly those with hip fractures – are at high risk of developing transient cognitive decline, as a result of delirium, and may even have permanent decrements in cognition [6]. Depression is also seen commonly after a hip fracture [7].

Geriatricians have skills and a clinical emphasis on issues that are central to optimizing outcomes of a fragility fracture. They are trained to understand comorbidity, frailty, and complexity, allowing them to identify and manage patients at high risk for adverse outcomes. They are comfortable with assessing patients' goals, and helping patients and their families make decisions that are consistent with those goals. The synergy of this expertise and the clinical skills of the orthopaedic surgeon can lead to improved outcomes for patients.

The History of Comanagement

The concept of co-management of fracture patients by orthopaedic surgeons and geriatricians is certainly not new. In the 1940s and 1950s, Lionel Cosin, a general surgeon in England, realized that early rehabilitation after a femoral neck fracture could enable patients who were initially thought to require permanent care, to return to their homes. Michael Devas, an orthopaedic

S.M. Friedman, MD, MPH
University of Rochester School of Medicine and Dentistry, Rochester, NY, USA
e-mail: Susan_Friedman@urmc.rochester.edu

G. Duque, D.P. Kiel (eds.), *Osteoporosis in Older Persons: Advances in Pathophysiology and Therapeutic Approaches*, DOI 10.1007/978-3-319-25976-5_16

surgeon in England in the mid-1950s, referred to himself as a "humble carpenter" who needed "physicians to tell him what was wrong with the patients" [8]. Together with geriatrician Bobby Irvine, he developed a physician-surgeon liaison service. Key components of this model were early surgery and early rehabilitation.

Variations on this approach to care of patients with fragility fractures have been developed across the world in the decades following. The first randomized controlled trial evaluating an orthopaedic-geriatric inpatient service and comparing it to traditional care was published over a quarter century ago [9]. Since that time, many other studies have shown improved outcomes with orthogeriatric care. Although the specifics of health care systems in different countries have led to differences in how care is delivered, co-management has become more common worldwide in the past decade.

Outcomes of Orthogeriatric Care

Orthogeriatric care has been shown to favorably impact several important clinical and organizational outcomes. Most of the studies have evaluated outcomes for hip fractures, and these programs are presented below. Because the health care systems, institutions, and the specific components are different for the different programs, it is impossible to identify other elements that optimize outcomes. Additionally, several of the outcomes are measured differently, which also makes it challenging to compare programs. However, the common thread for these programs is the element of co-management. The most consistent benefits include reductions in time to surgery, complications, and mortality. Table 16.1 below identifies several of the benefits of orthogeriatric care [10–19].

Models of Orthogeriatric Care

The focus of orthogeriatric care models has been on treatment of hip fractures, although other fractures have also been managed using this approach to care. The common thread between these models has been care provided by multiple disciplines, identification and management of medical problems in a timely fashion, early mobilization, and thoughtful discharge planning. Giusti and colleagues have described five different models of care for older adults with hip fracture [20] (See Table 16.2), with similar categorization by Kammerlander and colleagues [21].

Details of the different models of care are described in more detail below. Table 16.3 following provides specifics of the contrasts between these different approaches.

Traditional model In the traditional approach to care, patients are admitted to the orthopaedic ward, under the care of the orthopaedic surgeon. Medical physicians are consulted on an as-needed basis, depending on the surgeon's perception of the patient's needs. These consults may be obtained either pre- or post-operatively, and often involve a one-time assessment. Early rehabilitation takes place on the unit, and patients may be discharged to home, a skilled nursing facility, or a rehabilitation facility.

Consultant team This model was the first approach to developing multidisciplinary care for fragility fracture patients. In the consultant model of care, a consultant team participates routinely, and is skilled in the evaluation and care of older adults. Patients are still admitted to an orthopaedic ward, and are under the care of the surgeon. The individual surgeon or physician determines how common problems or complications are prevented and managed, so there is variability within the system. Timing of discharge planning is determined by the orthopaedics team.

Multidisciplinary care/clinical pathway The multidisciplinary care/clinical pathway involves healthcare professionals from different disciplines, but, in this approach to care, there is no true leadership in terms of who is in charge of the care. Rather, the patient is managed via evidence-based guidelines and protocols and care pathways, as they move through the hospital from emergency room to hospital floor, to

Table 16.1 Improved outcomes with orthogeriatric care

Outcome	First author, date	With orthogeriatric care	Without orthogeriatric care
Reduced time to surgery, days	Friedman, 2009 [10]	1.0[a]	1.6
	Gozalez Montalvo, 2010 [11]	5[a]	6
Fewer complications, %	Vidan, 2005 [12]	41.2[a]	61.7
	Fisher, 2006 [13]	49.5[a]	71.0
	Friedman, 2009 [10]	30.6[a]	46.3
Lower length of stay, days	Khan, 2002 [14]	26	27
	Adunsky, 2003 [15]	26.9[a]	31.9
	Vidan, 2005 [12]	16	18
	Barone, 2006 [16]	21	21
	Fisher, 2006 [13]	10.8	11.0
	Friedman, 2009 [10]	4.6[a]	8.3
	Gozalez Montalvo, 2010 [11]	12[a]	18
Reduced readmission rates	Shyu, 2005 [17]	7.9	14.1
	Fisher, 2006 [13] (6 months)	7.6[a]	28
	Friedman, 2009 [10] (30 days)	9.8	13.2
Reduced in-hospital mortality, %	Khan, 2002 [14]	10.4	11.1
	Vidan, 2005 [12]	0.6[a]	5.5
	Barone, 2006 [16]	4.8[a]	9.9
	Fisher, 2006 [13]	4.7[a]	7.7
	Friedman, 2009 [10]	1.6	2.5
Improved function/mobility, %[b]	Adunsky, 2003 [15]	[a]	
	Vidan, 2005 [12]	53	43
	Shyu, 2005 [17]	78.1[a]	50.8
	Prestmo, 2015 [18]	5.12[a]	4.38
Lower cost, $	Kates, 2011 [19]	7,610[a]	11,071
Improved quality of life[c]	Shyu, 2005 [17]	67.5	53.9
	Prestmo, 2015 [18]	0.54[a]	0.46

[a]Statistically significant
[b]Measures of function: Adunsky – Absolute FIM functional gain/(maximal possible FIM – actual admission FIM) ≥ 0.5 – adjusted OR was 1.97; Vidan – recovery of ADLs at 3 months; Shyu – recovery of walking ability by 3 months; Prestmo – Mean score on Short Physical Performance Battery at 4 months
[c]Measures of quality of life: Shyu – Mean SF-36 vitality score; Prestmo – Mean EuroQoL-5 dimension-3 L score at 4 months

Table 16.2 Models of orthogeriatric care

Traditional model
Consultant team
Multidisciplinary care/clinical pathway
Geriatric-led fracture service
Geriatric co-managed care

Adapted from Giusti et al. [20]

surgery, to initial rehabilitation. There are usually regular rounds and team meetings, and continuous communication between members of the team, with resulting coordination of care. This model incorporates a heterogeneous group of programs, with different locations for inpatient care depending on the program.

Geriatric-led fracture service In the geriatric-led fracture service, patients are admitted to a geriatric ward, under the care of a geriatrician, who serves as the primary attending. Unlike the other models of care, the orthopaedic surgeon serves as a consultant. The attending geriatrician coordinates with surgery to determine the timing of surgery, diagnostics, and other treatments, as

Table 16.3 Differences between models of orthogeriatric care

	Traditional model	Consultant team	Interdisciplinary/ clinical pathway	Geriatric led	Comanaged
Where is the patient admitted?	O	O	Variable	GW	O
Who is in charge of care?	O	O	Pathway	G	O/G
What is role of Medicine/Geriatrics?	Consultant	Consultant	Part of team	Attending	Co-manage
Is Medicine/ Geriatrics involved routinely or as-needed?	As needed	Routine	Routine	Routine	Routine
Where are patients discharged?	Home, SNF, inpt rehab	Home, SNF, inpt rehab	Home, SNF, inpt rehab	SNF or geriatric rehab	Home, SNF or geriatric ortho rehab unit

Adapted from Giusti et al. [20]
O Orthopaedics, *GW* Geriatrics ward, *G* Geriatrician, *SNF* Skilled nursing facility

well as discharge planning, but it is the geriatrician who is responsible for all of these elements. Care is supported by a multidisciplinary team. Rehabilitation may occur either on a geriatric rehabilitation unit, or patients may be discharged to a skilled nursing facility, similar to the previous models.

Geriatric co-managed care This approach to care is the most complex and well integrated model of care. A central feature of this care model is true interdisciplinary care. As compared with multi-disciplinary care, in which representatives from different disciplines participate in the care of the patient, but may not work together in an integrated way, care provided in an interdisciplinary fashion is coordinated, with the different disciplines working together in collaboration and cooperation. Each discipline writes notes and orders on the patient, and communication between disciplines is frequent and collegial. Care is integrated around the needs of the patient, with each discipline taking ownership of the care. One well-known example of this is the Geriatric Fracture Center Model (also cited as the Rochester Model), which is described in more detail in the next section.

An Example of Geriatric Co-managed Care: The Geriatric Fracture Center Model

The Geriatric Fracture Center Model was organized with five principles, as summarized in Table 16.4 [22].

Most patients benefit from surgical fracture stabilization Chapter 15 describes the specifics of surgical management of hip fractures. Surgery accomplishes several goals, namely, pain management, restoration of function and mobility, reduced blood loss, promotion of fracture healing, and reduced risk of institutionalization [23, 24]. Ideally, surgery enables the patient to weight-bear

Table 16.4 Principles of the Geriatric Fracture Center

Most patients benefit from surgical fracture stabilization.
The sooner patients have surgery, the less time they have to develop complications and functional decline.
Co-management, with frequent communication between disciplines, avoids iatrogenesis.
Standardized protocols decrease unwarranted variability.
Discharge planning begins when the patient is admitted to the hospital.

Adapted from Friedman et al. [22]. With permission from Wiley

as tolerated, to optimize post-operative mobility and the ability to participate in rehabilitation. Even patients who are non-ambulatory may benefit from the pain relief provided by surgical fixation, as well as the improved ability to tolerate personal care. Non-operative management is indicated for some patients: those who have a very limited life expectancy and where risks outweigh benefits, those who present late and already have signs of healing, those with a stable fracture pattern and minimal pain, and those who refuse after reviewing the risks and benefits of surgery.

The sooner patients have surgery, the less time they have to develop complications and functional decline Conclusions about the impact of delay to surgery are based on observational data, due to the ethical nature of randomized trials to answer this question. Delays to surgery may occur for patient-related or system-related issues. In patients who are otherwise stable, delays to surgery may increase mortality [25], increase severity and duration of pain [26], lead to longer length of stay [26, 27] and result in worse self-care at 6 months [26]. Patients with functional impairment at baseline appear to be particularly impacted by surgical delays [28]. Patients who have concomitant acute medical issues (as contrasted with chronic comorbidities) have higher mortality than those without, but this is not impacted by timing of surgery [25]. Patients therefore need a rapid assessment to identify acute issues that impact ability to tolerate surgery, and distinguish them from chronic comorbidity and frailty. This will avoid the declines in function, nutrition, and cognition that may occur as a result of prolonging immobility and pain when surgery is delayed to evaluate conditions that are longstanding [29].

Co-management, with frequent communication between disciplines, avoids iatrogenesis True co-management implies co-ownership of the patient, in which all disciplines taking care of the patient feel responsible for the outcome. This approach leads to the different disciplines respecting what each member can contribute to positive patient outcomes. Communication is frequent and bi-directional. This approach is based on previous models of geriatric care, specifically, Geriatric Evaluation and Management units, which have shown that outcomes are better when geriatricians are responsible for implementing their recommendations rather than merely offering recommendations and suggestions for care [30].

Standardized protocols decrease unwarranted variability There is significant local, national, and international variability in hip fracture management [23]. By using geriatrics principles and literature-based evidence, the program ensures that "usual" care is optimal care of this patient population. The program has collaboratively developed standardized order sets, nursing care plans, and protocols, starting from when the patient is seen in the emergency room, and continuing through until hospital discharge. Deviations from the protocols are based on patient-specific characteristics and circumstances, rather than on provider preferences or systems issues. Standardized elements are updated as new literature becomes available. Standardization both improves quality of care and reduces cost. Some elements of the program that have been standardized are outlined in Table 16.5.

Discharge planning begins when the patient is admitted to the hospital Most patients require rehabilitation after their acute hospitalization. Since hospital length of stay is short (typically less than 5 days), social work is involved early to assure a smooth transition. The social worker works with the patient and their family to assess prior living situation, current needs, supports, and goals. Timely and consistent communication reduces apprehension and avoids delays in hospital discharge. The social worker interacts frequently with the medical and surgical teams to anticipate timing of discharge. The associations developed over time with area facilities help to reduce delays and facilitate transitions to rehabilitation.

Fostering Success

Experience and literature-based findings over the past couple decades have indicated several elements that are important in ensuring the success

Table 16.5 Standardized elements of the Geriatric Fracture Center

Order sets and protocols
Direct admission protocol
Transfer protocol
Emergency department
Admission/pre-operative
Post-operative
Chart
Geriatric consult form
Operative consent form
Nursing care plan
Discharge instructions
Clinical elements
Pre-operative screening
Assessment of function and comorbidity
Osteoporosis assessment and treatment
Thromboembolism prophylaxis
Pain management
Delirium prevention
Antibiotic prophylaxis
Surgical implant selection algorithm
Urinary catheter management
Weight-bearing status
Other
Data collection

Adapted from Mendelson et al. [23]. With permission from Elsevier

Table 16.6 Elements important to the success of a new orthogeriatric co-management program

Strong surgical and medical leadership
Hospital administration support
Availability of outcomes data
Support from the anesthesia department
Operating room time availability
Appreciation of geriatrics principles
Medical expertise in perioperative physiology/ medicine
Sufficient volume of cases to develop expertise
Developing relationships with partner institutions

of a new orthogeriatric co-management program [31]. Starting a program takes significant "up front" time and effort, and it has been estimated that it takes about 6–12 months to implement a program even when all the essential components are present [32]. Key elements are included in Table 16.6 following, and are further discussed below.

Strong surgical and medical leadership Identifying a strong medical and a strong surgical leader is critical to the success of a new Geriatric Fracture Center program, especially early on. In a recent paper, lack of medical or geriatrics leadership in particular was identified as the biggest barrier to implementing a geriatric fracture program [31]. Effective leaders serve as champions to the program, and embody the principles of true co-management and interdisciplinary care; they are respectful and collaborative, and communicate effectively, working together to resolve conflicts that arise. Essential areas of communication include communication between medicine and surgery (interdisciplinary), communication with medical and surgical colleagues who are participating in the program (intradisciplinary), communication with other disciplines (e.g., anesthesiology, cardiology, nursing), and communication with administration. Program leaders should be accessible, reliable, and clinically credible. They should be good problem solvers, lead by example, and serve as role models to their colleagues [32]. They should also be in a position to build consensus with their colleagues.

Hospital administration support Hospital administration support can be gained by presenting the program as a solution to existing problems. A well run program will improve patient care quality and clinical outcomes while reducing costs [19, 33]. Discussions between clinical and administrative leaders should occur prior to implementation, and on an ongoing basis as the program is implemented and evolves. A well-conceived business plan and a presentation to the medical center's board of directors may be useful adjuncts to these discussions. Both administration and program leaders should understand that implementation of the new program is likely to involve culture change, with resulting stresses and benefits.. Discussions should be honest and respectful, and the relationship should be one of trust. Hospital administration can facilitate access

to both quality and financial data, which is necessary for documentation of outcomes.

Availability of outcomes data The availability of data is essential to making the case for an orthogeriatric program, and to documenting its success. Data on baseline length of stay and readmission rate, with comparison to benchmark data – numbers which have implications for both cost and quality – will help determine if there is room for improvement in these numbers. Other important data to track includes time from admission to surgery, inpatient mortality, complications, and costs of care. Review of these clinical and administrative outcomes becomes a cornerstone of a quality assurance program; regular review and oversight will allow for targeting of areas in need of improvement and will assure that the program is continuing to be effective.

Support from the anesthesia department Anesthesia is a critical piece of the interdisciplinary care provided in an orthogeriatric program. The anesthesiologist(s) involved in the program should understand geriatrics principles, including the importance of expediting time to surgery in stable patients, and optimizing operative management of the older adult. It is important that the anesthesiologists consider themselves an integral part of the team, communicating as needed with their medical and surgical colleagues. Early on, and with particularly complex cases, face to face discussions for approaches and timing of care may be necessary. This can avoid last minute cancellation of cases, which can be dismaying to patients and families, in addition to having potential clinical implications. As the program evolves and trust is built between the disciplines, care is more easily expedited.

Operating room time availability The availability of a designated operating room time for geriatric fractures can help the organization of care by several disciplines. Knowing when cases are likely to be scheduled allows the medical team to evaluate the patient in a timely fashion so that they are ready for surgery when the operating room is available. Since the patient has surgery during the day rather than later as an add-on case, he/she is able to return to the hospital room earlier, when more staff and family are present. Setting aside designated operating room time reinforces the need for an adequate volume to ensure that the space and time are optimally used.

Appreciation of geriatrics principles As a group, older adults have higher rates of perioperative complications than the general population. Understanding the delicate homeostasis of older adults, and the difficulty of preserving it during the multiple stresses that occur during this acute period of time, is key in optimizing outcomes [29]. An appreciation of how normal aging, particularly of the cardiovascular, pulmonary, and renal systems can impact stability during surgery, is also critical. Discussion of goals of care, and identifying a patient's priorities for care, including pain control and preservation of physical and cognitive function, is important to establish up front. Unfortunately, there is an ongoing dearth of geriatricians worldwide, and so programs frequently use hospitalists rather than geriatricians to provide medical care to their fracture patients [31]. However, there is evidence that co-managed programs that utilize care provided by hospitalists result in outcomes that are better than traditional care [34]. The hospitalist's clinical experience and focus on geriatrics principles is central to the program's success.

Medical expertise in perioperative physiology/medicine Expertise in perioperative care goes hand in hand with an understanding of geriatrics principles in ensuring the best possible outcomes. Older adults often have multiple comorbidities; it is important to distinguish chronic stable comorbidities which require careful consideration and may need perioperative adjustment of medication regimen, from acute issues which need to be further evaluated prior to the patient's surgical procedure. For frail older adults, there is often a "less is more" (or a "more is less") phenomenon, in which additional testing merely increases time to surgery without improving outcomes [35, 36]. Assessment of risk goes beyond the traditional

evaluation of cardiovascular risk, and should include an evaluation of cognition, functional status, nutritional status and acute vs. chronic needs of medications [29].

Sufficient volume of cases to develop expertise All members of the interdisciplinary team benefit from taking care of a volume of patients that is sufficient to develop the experience and clinical expertise in managing these patients. Although there are no studies to support a minimum number of patients, it has been suggested that it takes about 100 cases per year to develop an effective program [32].

Developing relationships with partner institutions Introducing the program to partners in the community, such as skilled nursing and assisted living facilities, can educate partners on the goals and approach of the program. This enables the partners to understand the value of the program, as well as what patients, their families, and providers can expect when a patient is admitted. Because many of the skilled nursing facilities also provide rehabilitation care, the communication is fostered in both directions, optimizing transitions from one institution to another. Reducing barriers to communication also fosters collegiality which in turn benefits patient care.

Summary

Older adults with osteoporotic fractures are often frail and complex, with multiple comorbidities. As a result, understanding how physiology changes with aging and with the stress of fracture and surgery, is important in managing geriatric patients who are hospitalized and need surgical intervention. Programs that employ the expertise of multiple disciplines in order to optimize outcomes were first seen many decades ago. More recently, these programs have evolved to incorporate true interdisciplinary care, timely surgery, and evidence-based best practices to optimize care. Although geriatricians are scarce worldwide, programs that utilize geriatrics principles and focus on the needs of frail older adults in the acute perioperative setting have seen improved outcomes and improved likelihood of return to baseline function.

References

1. Morris AH, Zuckerman JD. National consensus conference on improving the continuum of care for patients with hip fracture. J Bone Joint Surg Am. 2002;84-A(4):670–4.
2. Gallagher JC, Melton LJ, Riggs BL, Bergstrath E. Epidemiology of fractures of the proximal femur in Rochester, Minnesota. Clin Orthop Relat Res. 1980; 150:163–71.
3. Cummings SR, Black DM, Rubin SM. Lifetime risks of hip, Colles', or vertebral fracture and coronary heart disease among white postmenopausal women. Arch Intern Med. 1989;149(11):2445–8.
4. Haleem S, Lutchman L, Mayahi R, Grice JE, Parker MJ. Mortality following hip fracture: trends and geographical variations over the last 40 years. Injury. 2008;39(10):1157–63.
5. Leslie WD, O'Donnell S, Jean S, et al. Trends in hip fracture rates in Canada. JAMA. 2009;302(8):883–9.
6. Melton 3rd LJ, Beard CM, Kokmen E, Atkinson EJ, O'Fallon WM. Fracture risk in patients with Alzheimer's disease. J Am Geriatr Soc. 1994;42(6): 614–9.
7. Lenze EJ, Munin MC, Skidmore ER, et al. Onset of depression in elderly persons after hip fracture: implications for prevention and early intervention of late-life depression. J Am Geriatr Soc. 2007;55(1):81–6.
8. Barton A, Mulley G. History of the development of geriatric medicine in the UK. Postgrad Med J. 2003;79(930):229–34. quiz 233–224.
9. Gilchrist WJ, Newman RJ, Hamblen DL, Williams BO. Prospective randomised study of an orthopaedic geriatric inpatient service. BMJ. 1988;297(6656):1116–8.
10. Friedman SM, Mendelson DA, Bingham KW, Kates SL. Impact of a comanaged geriatric fracture center on short-term hip fracture outcomes. Arch Intern Med. 2009;169(18):1712–7.
11. Gonzalez-Montalvo JI, Alarcon T, Mauleon JL, Gil-Garay E, Gotor P, Martin-Vega A. The orthogeriatric unit for acute patients: a new model of care that improves efficiency in the management of patients with hip fracture. Hip Int. 2010;20(2):229–35.
12. Vidan M, Serra JA, Moreno C, Riquelme G, Ortiz J. Efficacy of a comprehensive geriatric intervention in older patients hospitalized for hip fracture: a randomized, controlled trial. J Am Geriatr Soc. 2005;53(9):1476–82.
13. Fisher AA, Davis MW, Rubenach SE, Sivakumaran S, Smith PN, Budge MM. Outcomes for older patients with hip fractures: the impact of orthopedic and geriatric medicine cocare. J Orthop Trauma. 2006; 20(3):172–8. discussion 179–180.

14. Khan R, Fernandez C, Kashifl F, Shedden R, Diggory P. Combined orthogeriatric care in the management of hip fractures: a prospective study. Ann R Coll Surg Engl. 2002;84(2):122–4.
15. Adunsky A, Lusky A, Arad M, Heruti RJ. A comparative study of rehabilitation outcomes of elderly hip fracture patients: the advantage of a comprehensive orthogeriatric approach. J Gerontol A Biol Sci Med Sci. 2003;58(6):542–7.
16. Barone A, Giusti A, Pizzonia M, Razzano M, Palummeri E, Pioli G. A comprehensive geriatric intervention reduces short- and long-term mortality in older people with hip fracture. J Am Geriatr Soc. 2006;54(7):1145–7.
17. Shyu YI, Liang J, Wu CC, et al. A pilot investigation of the short-term effects of an interdisciplinary intervention program on elderly patients with hip fracture in Taiwan. J Am Geriatr Soc. 2005;53(5):811–8.
18. Prestmo A, Hagen G, Sletvold O, et al. Comprehensive geriatric care for patients with hip fractures: a prospective, randomised, controlled trial. Lancet. 2015;385(9978):1623–33.
19. Kates SL, Mendelson DA, Friedman SM. The value of an organized fracture program for the elderly: early results. J Orthop Trauma. 2011;25(4):233–7.
20. Giusti A, Barone A, Razzano M, Pizzonia M, Pioli G. Optimal setting and care organization in the management of older adults with hip fracture. Eur J Phys Rehabil Med. 2011;47(2):281–96.
21. Kammerlander C, Roth T, Friedman SM, et al. Orthogeriatric service--a literature review comparing different models. Osteoporos Int. 2010;21 Suppl 4:S637–46.
22. Friedman SM, Mendelson DA, Kates SL, McCann RM. Geriatric co-management of proximal femur fractures: total quality management and protocol-driven care result in better outcomes for a frail patient population. J Am Geriatr Soc. 2008;56(7):1349–56.
23. Mendelson DA, Friedman SM. Principles of comanagement and the geriatric fracture center. Clin Geriatr Med. 2014;30(2):183–9.
24. Friedman SM, Mendelson DA, Kates SL. Hip fractures. In: Hirth V, Wieland D, Dever-Bumba M, editors. Case-based geriatrics. New York, NY: The McGraw-Hill Companies, Inc.; 2011. p. 529–43.
25. Moran CG, Wenn RT, Sikand M, Taylor AM. Early mortality after hip fracture: is delay before surgery important? J Bone Joint Surg Am. 2005;87(3):483–9.
26. Orosz GM, Magaziner J, Hannan EL, et al. Association of timing of surgery for hip fracture and patient outcomes. JAMA. 2004;291(14):1738–43.
27. Siegmeth AW, Gurusamy K, Parker MJ. Delay to surgery prolongs hospital stay in patients with fractures of the proximal femur. J Bone Joint Surg Br. 2005;87(8):1123–6.
28. Pioli G, Lauretani F, Davoli ML, et al. Older people with hip fracture and IADL disability require earlier surgery. J Gerontol A Biol Sci Med Sci. 2012;67(11):1272–7.
29. Nicholas JA. Preoperative optimization and risk assessment. Clin Geriatr Med. 2014;30(2):207–18.
30. Stuck AE, Siu AL, Wieland GD, Adams J, Rubenstein LZ. Comprehensive geriatric assessment: a meta-analysis of controlled trials. Lancet. 1993;342(8878):1032–6.
31. Kates SL, O'Malley N, Friedman SM, Mendelson DA. Barriers to implementation of an organized geriatric fracture program. Geriatr Orthop Surg Rehabil. 2012;3(1):8–16.
32. Kates SL, Mendelson DA, Friedman SM. Co-managed care for fragility hip fractures (Rochester model). Osteoporos Int. 2010;21 Suppl 4:S621–5.
33. Kates SL. Lean business model and implementation of a geriatric fracture center. Clin Geriatr Med. 2014;30(2):191–205.
34. Batsis JA, Phy MP, Joseph Melton 3rd L, et al. Effects of a hospitalist care model on mortality of elderly patients with hip fractures. J Hosp Med. 2007;2(4):219–25.
35. Jettoo P, Kakwani R, Junejo S, Talkhani I, Dixon P. Pre-operative echocardiogram in hip fracture patients with cardiac murmur--an audit. J Orthop Surg Res. 2011;6:49.
36. Ricci WM, Della Rocca GJ, Combs C, Borrelli J. The medical and economic impact of preoperative cardiac testing in elderly patients with hip fractures. Injury. 2007;38 Suppl 3:S49–52.

Index

G. Duque, D.P. Kiel (eds.), *Osteoporosis in Older Persons: Advances in Pathophysiology and Therapeutic Approaches*, DOI 10.1007/978-3-319-25976-5