A Practical Approach to Adolescent Bone Health

A Guide for the Primary Care Provider

Sarah Pitts
Catherine M. Gordon
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Preface

As vertebrates, we rely upon our bones for structure and support, protection of vital organs, a home for marrow, and a biological bank of minerals essential for muscle and nerve function. However, many adolescents take their bones for granted, not considering the long-term implications of poor bone mass accrual at this critical time of their lives. It is up to clinicians to guide adolescents toward optimal bone health to mitigate the fractures, morbidity, and health-care costs associated with osteoporosis.

In this first edition of *A Practical Approach to Adolescent Bone Health*, we seek to provide a clinically relevant text for all clinicians who care for adolescents. Clinical and research experts in the fields of general pediatrics, adolescent medicine, endocrinology, nutrition, radiology, orthopedics, sports medicine, and physical medicine and rehabilitation have contributed to this important compendium. Throughout the text are clinical case vignettes highlighting key concepts for practitioners. In Chap. 1, the stage is set, reminding readers of the importance of adolescent bone health care, followed by an in-depth review of the pathophysiology of bone in Chap. 2. Subsequently, experts outline how diet and exercise impact the dynamic skeletal system (Chaps. 3–4). In Chaps. 5, 6, and 7, a bone-centric review of the clinical history, physical examination, laboratory assessment, and imaging is presented. The final chapters highlight the clinical thinking and latest research supporting the care of adolescents with multiple fractures, eating disorders, athletic involvement, chronic illness, ambulatory limitations, and bone fragility. By way of conclusion, we present additional case examples to illustrate the art and science of adolescent bone health care.

We hope this text can be used as an accessible reference for day-to-day clinical practice.

Before closing, we wish to acknowledge Drs. Jean Emans and Joseph Majzoub whose support of our clinical and research efforts in the field of adolescent bone health has been invaluable. And last, but not least, we acknowledge our families whose patience and support have made this book and all aspects of our work possible. We gratefully acknowledge our husbands, Edward Pitts and Robert Bagley, and our children, Liam and Jane, and Benny and Jack. We dedicate this book with gratitude to all of you.

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Optimizing Bone Mass Accrual in Healthy Adolescents

1

Keith J. Loud

Introduction

Adolescence is a critical period for lifetime bone health, with at least half of all adult mineralized calcium accrued in the skeleton during the adolescent years [1, 2]. An individual's peak bone mass (PBM), a significant predictor of his or her risk of future osteoporosis, is reached by early adulthood. Processes that optimize attainment of PBM may decrease that risk, while factors that create a deficit in bone mass can do the opposite, as shown in Fig. 1.1. The factors that affect bone mass accrual (see Fig. 1.2) described in this chapter include genetics, puberty and hormonal status, body composition (including body weight), certain medications, and other lifestyle choices, with calcium and vitamin D intake and physical activity receiving detailed attention in later chapters.

Bone Mass Accrual

Bones grow at different rates throughout the skeleton. The extremities (appendicular skeleton) largely complete growth coinciding with the pubertal growth spurt (peak height velocity, PHV). Increases in estrogen and testosterone during puberty result in later growth of the trunk and spine (axial skeleton). These increases in vertebral bone size are accompanied by dramatic increases in areal bone mineral density (aBMD) in both cross-sectional [3, 4] and longitudinal studies [5]. It must be appreciated that BMD is most commonly measured by dual-energy x-ray absorptiometry (DXA), a two-dimensional technique which calculates grams of mineral per bone area (in squared centimeters) through which x-rays are projected, hence the term "areal" BMD (aBMD). Bones are three-dimensional structures for which

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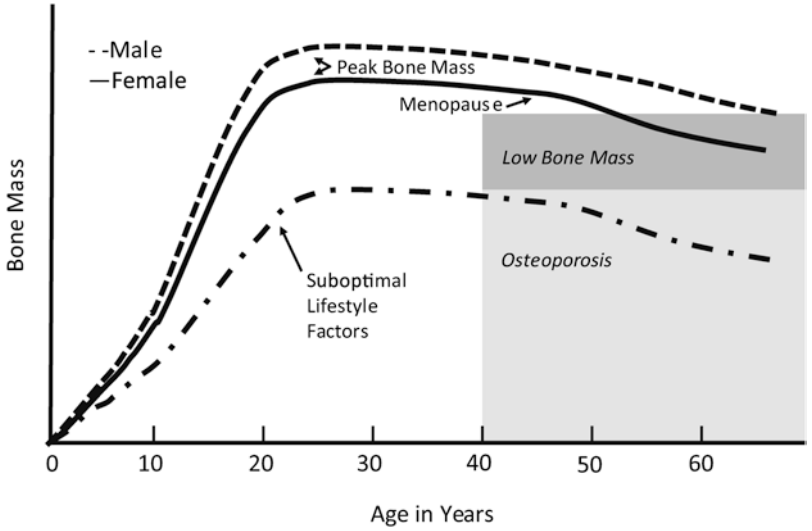

Fig. 1.1 Bone mass across the lifespan with optimal and suboptimal lifestyle choices (Reprinted with permission from Weaver et al. [7])

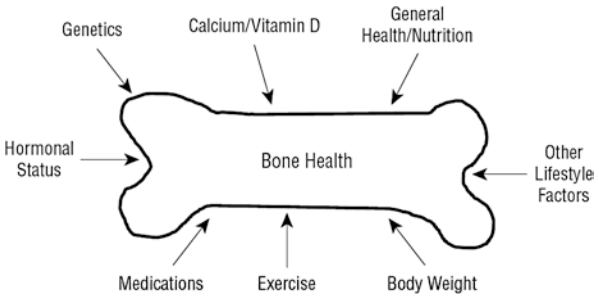

Fig. 1.2 Factors affecting bone health (Courtesy of Keith J. Loud & Catherine M. Gordon)

the true mineral density is based on the volume. Therefore, much of the apparent increase in aBMD in the growing skeleton, as measured by DXA, is due to increases in the size of the bones [6]. Areal BMD at a skeletal site that does not increase over time in a growing adolescent would, therefore, be a source of concern (this and other limitations of DXA is detailed in Chap. 7). Fortunately, the increased size of bones confers increased resistance to fracture, independent of the BMD or other material properties of the bone [7].

Maximal rates of bone mineral accrual follow PHV by approximately 6–12 months [8]. As a consequence, at the time of PHV (Tanner pubertal stage II–III in girls, Tanner III–IV in boys), teenagers have reached approximately 90%

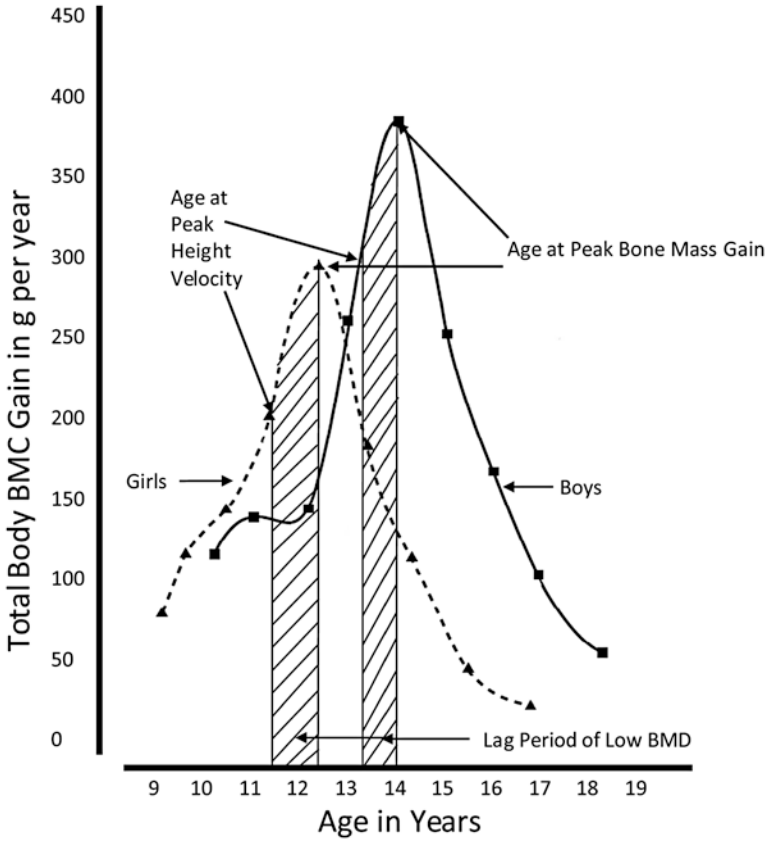

Fig. 1.3 Peak BMC gain and peak height velocity in boys and girls from longitudinal DXA analysis (Reprinted with permission from Weaver et al. [7])

of their adult height, but they have acquired only 60% of their adult total body mineral content, resulting in relatively less mineralized bone (Fig. 1.3) [8]. This vulnerability may account for the increased rate of fractures in early to mid-adolescence, particularly at the distal radius [7]. The seminal Saskatchewan Pediatric Bone Mineral Accrual Study, a 6-year longitudinal investigation of 113 boys and 115 girls in Canada utilizing DXA measurements every 6 months, found a peak calcium accretion of 359 mg/day in boys at age 14.0 years and 284 mg/day in girls at age 12.5 years [9]. Investigators estimated that 26% of all adult calcium is accrued during the 2 years of PHV [9]. This is consistent with classic studies by Thientz et al., showing that girls' BMD may plateau by age 16 (or 2 years post menarche) and boys' by age 20 [2]. In any event, 95% of PBM is likely attained by the end of adolescence [5, 10].

Non-modifiable Factors

Genetics and Ancestry

Unfortunately, 60–80% of the variance in PBM is attributed to heritable factors [7]. Males have a higher bone mass than females at nearly all ages [5, 11]. African-American children demonstrate an approximately 10% higher BMD by DXA than do children of other ancestries [5, 11], even after correcting for bone size [10]. Children of European Caucasian descent generally have higher aBMD than those of Asian and Hispanic ancestry, although that effect is attributable to bone size [7]. An interesting finding among African-American and Caucasian girls was that their spinal BMD was similar until puberty, at which point the African-American girls had an increase of 34% while the Caucasian girls improved only 11% [12]. Family history of osteoporosis in postmenopausal women predicts lower BMD for their daughters [13], and both elderly men and women have an increased risk of osteoporosis when other family members have been affected [14]. Polymorphisms in the genes encoding receptors for vitamin D, estrogen, type I collagen [15], insulin-like growth factor I (IGF-I), transforming growth factor beta (TGF-β), and interleukin 6 (IL-6) are under ongoing study [16], but none have been able, singly or in combination, to account for more than a fraction of this variance in PBM.

Puberty/Hormonal Status

As will be expanded upon in subsequent chapters, a balanced hormonal milieu is essential to attain and maintain normal bone formation. Early menarche and regular menses are strong predictors of increased bone mass in adult women [17], suggesting the importance of estrogen exposure [18]. In the Saskatchewan cohort described previously, PBM content velocity (rate of accrual) was found to coincide with menarche in girls, with earlier age of menarche correlated with greater bone mineral accrual rates [19]. A school-based cohort of adolescents in Kyoto, Japan demonstrated that stage of pubertal development had a significant positive effect on BMD in girls, but not boys, when controlling for height, weight, and grip strength [20]. The Bone Mineral Density in Childhood Study, a large multicenter longitudinal study of youth in the United States, found earlier age of onset of puberty strongly associated with higher peak bone mineral content (BMC) and BMD at all skeletal sites in both girls and boys [21].

Modifiable Factors

Body Composition

At most body weights, there is a direct relationship between body mass index (BMI) and aBMD, with underweight individuals at increased risk for lower BMD [22].

Among otherwise healthy adolescents, greater body weight generally increases the gravitational loading of the skeleton which stimulates bone formation. But most evidence points to lean body mass (LBM), which we do not routinely measure in clinical practice, as the strongest correlate of bone mass and BMD [7]. In addition to being unmeasured, the LBM component of body composition is also highly heritable, making it less amenable to intervention. In the Kyoto cohort, weight and grip strength, a proxy for fitness and lean body mass, were positively and independently associated with aBMD in both girls and boys [20].

Excessive BMI may have a deleterious effect on BMD. Work by Goulding and others has suggested that overweight boys and girls are fracture-prone [23] and have bone mass and bone area that are increased for their age, but not appropriately so relative to their total body weight [24]. An anthropometric study of normal weight, overweight, and obese female adolescents demonstrated no difference in measures of bone mineral content and density when controlling for lean body mass, suggesting a deleterious effect of increased adiposity on the skeletal development of overweight children and adolescents [24, 25]. Clinical investigations linking visceral, rather than subcutaneous, adipose tissue to low bone mass in obese adolescent girls have begun to implicate adipokines (e.g., adiponectin, leptin) and pro-inflammatory cytokines in the pathophysiology [26]. These adipokines also appear to be at play in the mediation of bone loss in female athletes with amenorrhea and adolescent girls with anorexia nervosa [27], the pathophysiology of which is also multifactorial, not due to low BMI alone, as detailed in Chap. 9.

Physical Activity and Exercise

In 2016 the National Osteoporosis Foundation (NOF) issued a comprehensive, rigorous evidence-based review of the literature from the year 2000 forward to identify potentially modifiable factors to improve PBM attainment in early adulthood [7]. Only two lifestyle factors – calcium intake and physical activity – demonstrated consistently strong evidence (Grade A), with both positively associated with improved bone mass and BMD [7]. Another systematic review, performed by MacKelvie et al., suggests that early puberty is a particularly opportune window during which time the bone is especially adaptable to exercise [28]. It is generally believed that in order to enhance bone mineral accrual, exercise, which is defined as planned, purposeful physical activity to achieve improvements in health and performance [29], needs to be high-impact weight-bearing (e.g., jumping) performed several times a week [30]. The effects are site-specific, meaning that different bones benefit from different exercises depending on how they are loaded [6]. However, the authors of the NOF scientific statement lamented the lack of consistency in exercise intervention trials, precluding the evidence to guide clinicians on the optimal frequency, intensity, timing, or type of exercise prescription [7]. Physical activity is explored in more detail in Chaps. 4 and 10, but it is notable that only 48.6% of adolescents meet the US Healthy People 2020 goal of 60 min of moderate-to-vigorous physical activity on 5 or more days of the week, according to the Centers for Disease Control and Prevention's Youth Risk Behavior Survey [31].

Dietary Intake

The only other factor to achieve Grade A evidence for benefit to achievement of peak bone mass in the NOF scientific statement is intake of dietary calcium, with intake of vitamin D and dairy products both having a lower – but still moderate – level of evidence (Grade B), as will be outlined further in Chap. 3. It is notable that physical activity and calcium are synergistic, with a minimum threshold of 1000 mg/day calcium to achieve any benefits from exercise intervention trials, and no benefit from any level of increased calcium consumption without increase in physical activity over baseline exertion [32]. Fewer than 50% of boys aged 9–13 years and girls aged 9–18 years were estimated to achieve the recommended daily allowance of 1300 mg elemental calcium in the most recent National Health and Nutrition Examination Survey (NHANES) [33].

Concern has been expressed about the deleterious effects of other poor dietary choices of adolescents. Cola and other carbonated beverages are associated with increased odds for a history of fracture, particularly in adolescent girls, along with decreased aBMD [34]. It is unclear whether this negative effect is related to impaired metabolism of calcium due to the phosphate load in cola beverages or merely the substitution of carbonated beverages for milk in the diet [35], but evidence is overall considered limited (Grade C) [7]. Recent interest in caffeinated beverages, given a perceived increase in consumption of coffee-containing drinks by adolescents, has similarly generated Grade C evidence of a deleterious effect on the bone [7]. On the positive side, adolescents who meet recommendations for at least five servings of fruits and vegetables daily appear to have an improved bone mineral trajectory (NOF Grade C evidence) [7], although this dietary habit may be a marker for a broader set of healthy behaviors [36].

Contraception

A 2004 US Food and Drug Administration (FDA) "black box" warning on the contraceptive injectable depot medroxyprogesterone acetate (DMPA) because of bone loss attributable to this agent was met with consternation [37], but moderate evidence (Grade B) of the detrimental effect of this injection on bone mass accrual has persisted [7]. Bone loss while using this agent may be partly to fully reversible upon discontinuation [7], although the rebound may be blunted the older the age the DMPA is stopped due to a shrinking window of opportunity. Combined oral contraceptives (OCs), by maintaining some level of circulating estrogen, are considered less deleterious to the bone than DMPA, with inadequate (Grade D) evidence of effect on bone mass accrual, but the experts who authored the NOF scientific statement caution that "low-estrogen" OCs containing 20 ug of ethinyl estradiol or lower may "interfere with the acquisition of peak BMD," particularly within the first 3 years after menarche [7]. Concern over use of either DMPA or low-estrogen OCs must be counterbalanced by the known deleterious effects of pregnancy on the adolescent skeleton, in addition to hindering overall psychosocial development and educational attainment.

Substance Use

History of tobacco use by military recruits is associated with lower aBMD and increased stress fracture rates during basic training [7]. Although the mechanism may be related to nicotine decreasing osteoblast function [38], tobacco use may also be a marker of decreased fitness and physical activity prior to enlistment, causing the evidence to only be considered Grade C. Despite concern for the deleterious effect of excessive alcohol use on BMD in young women, consistent evidence was found lacking (Grade D) in the scientific statement [7]. Nevertheless, there are myriad health-related reasons to counsel adolescents to avoid initiating or decrease use of these substances.

Conclusion

Skeletal development in adolescents occurs in the context of rapid and profound physical, cognitive, emotional, and psychosocial growth. Anticipatory guidance by primary care providers, including promoting healthy physical activity and dietary choices, consequent appropriate weight for height, and avoidance of smoking and alcohol, undoubtedly improves the acquisition of peak bone mass, but this may be the least of the benefits.

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Normal Bone Physiology 101

2

Nora E. Renthal and Nina S. Ma

Introduction

The skeleton gives the human body its physical shape and structure, protects vital internal organs, and provides a home for bone marrow and hematopoiesis. Simultaneously, the bones are mechanically engineered to be flexible and lightweight for movement and locomotion. The skeletal system is also metabolically active, playing a critical role in mineral homeostasis while serving as the body's main repository for calcium, phosphorus, and magnesium ions.

Bone is comprised of three main components: the organic matrix (osteoid and non-collagenous proteins), inorganic matrix or bone mineral (hydroxyapatite), and bone cells (osteoblasts, osteoclasts, osteocytes) (Fig. 2.1). During childhood and adolescence, the bones undergo significant growth and morphological changes in the setting of adequate nutrition and in response to hormonal and mechanical stimulation.

Organic Matrix (Osteoid)

Osteoid, secreted by osteoblasts, forms the foundation of bone and gives the skeleton its flexibility and elastic properties. The makeup of osteoid is 85–90% type 1 collagen (trace amounts of collagen types 3 and 5 are also present in the bone) and 10–15% non-collagenous proteins (e.g., osteocalcin and proteoglycans) [1, 2].

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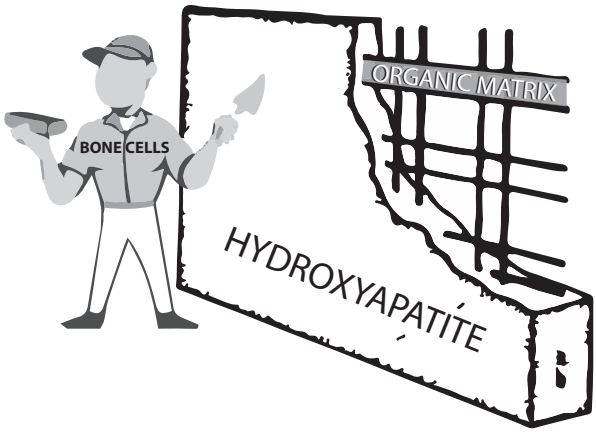

Fig. 2.1 Masonry metaphor of osteogenesis. Skeletal modeling can be conceptualized by comparison to masonry, whereby the bone cells (osteoblasts, osteoclasts, osteocytes) are compared to the mason, the bone mineral to the concrete, and the organic matrix to the framing upon which concrete is applied

Type 1 Collagen

Type 1 collagen is the most abundant collagen in the human body and is the basic building block of the organic matrix. It is a triple-stranded, rope-like molecule formed by two α1 (encoded by *COL1A1*) and one α2 (*COL1A2*) chains. Like other proteins destined for secretion, collagen is synthesized along the rough endoplasmic reticulum (ER)-Golgi secretory pathway, beginning as pre-procollagen at ribosomes along the rough ER. The signal peptides of pre-procollagen are cleaved in the ER lumen to form procollagen. Lysine and proline amino acids are hydroxylated, a process dependent on ascorbic acid (vitamin C) as a cofactor, and procollagen is transported to the Golgi apparatus where it is packaged and secreted by exocytosis. Once outside of the cell, procollagen peptidase cleaves the N- and C-termini of procollagen to form tropocollagen, and tropocollagen gathers to form collagen fibrils via covalent cross-linking of hydroxylysine and lysine residues. Collagen fibrils then assemble to form multiple collagen fibers [3].

Disorders of type 1 collagen are seen in patients with osteogenesis imperfecta (OI), a congenital form of osteoporosis of variable severity. Patients may present with limb deformities, multiple fractures, dentinogenesis imperfecta, and blue sclerae. The majority of OI cases harbor dominant mutations in *COL1A1* and *COL1A2* genes leading to premature termination of the coding sequence or glycine missense mutations that cause haploinsufficiency or structural defects in type 1 collagen, respectively. Mutations in additional genes have also been discovered that affect the posttranslational modification and trafficking of type 1 collagen and cause rarer, autosomal recessive forms of OI [4, 5].

Non-collagenous Proteins

Non-collagenous proteins (NCPs) may be categorized into protein families, including serum-derived proteins, proteoglycans, glycosylated proteins, gamma-carboxyglutamic acid (gla)-containing proteins, small integrin-binding ligand,

N-glycosylated (SIBLING), and other glycoproteins with cell attachment activity [1]. NCPs have a diversity of critical functions that help organize the extracellular matrix, including regulating collagen fiber formation, anchoring bone cells to the matrix, and playing a role in mineral deposition [6].

A familiar and important NCP, alkaline phosphatase, is a glycoprotein enzyme present in multiple tissues. The bone-specific isoform of alkaline phosphatase is tethered to the cell surface of osteoblasts and chondrocytes. It hydrolyzes inorganic pyrophosphate (PPi), an inhibitor of bone mineralization, and increases local phosphate concentrations, facilitating mineral deposition. Alkaline phosphatase is one of the biochemical hallmarks of bone formation and may be increased in adolescents due to rapid bone growth during the pubertal growth spurt. As alkaline phosphatase reflects the biosynthetic activity of osteoblasts, it has been shown to be a sensitive and reliable indicator of bone turnover and is overtly elevated in patients with rickets or fracture [7].

Osteocalcin, a gla-containing protein secreted by osteoblasts, is the most abundant NCP in bone. The precise function of osteocalcin in bone metabolism is still under investigation, but its measurement may be used clinically as a biomarker of bone turnover in patients with osteoporosis [1]. Recent investigations have also implicated osteocalcin as a hormone that stimulates insulin production and increases tissue energy expenditure and insulin sensitivity [8].

Bone Mineral (Hydroxyapatite)

Bone mineral (hydroxyapatite) is the inorganic phase of bone. It accounts for approximately 60% of the weight of bone and gives bone its outer hardness, rigid properties, and mechanical strength [2]. The molecular structure of hydroxyapatite consists primarily of calcium and phosphate, $Ca_{10}(PO_4)_6(OH)_2$, though bone mineral also contains carbonate, magnesium, and other trace elements [9].

Bone mineralization is a regulated process whereby hydroxyapatite is deposited onto the organic matrix (osteoid). The mineralization of bone begins within membrane-bound matrix vesicles that provide microenvironments in which calcium and phosphate form hydroxyapatite crystals. Matrix vesicles then bud from the cell membrane of bone-forming cells (e.g. osteoblasts) and propagate into the extracellular matrix. Here, mineralization promoters (dentin matrix protein 1 and bone sialoprotein), phosphoprotein kinases, and alkaline phosphatase facilitate the deposition of hydroxyapatite in the "hole zones" located at the ends of collagen fibrils [2, 10–12].

Without tight regulation of bone mineralization, there may be hyper- or hypocalcification. In the case of hypophosphatasia (HPP), a genetic deficiency of tissue-nonspecific alkaline phosphatase (*TNSALP*), there is subnormal alkaline phosphatase activity that results in skeletal hypomineralization, rachitic changes, premature loss of deciduous teeth, frequent fractures, and hypotonia. The biochemical hallmark of HPP is a low alkaline phosphatase level in the blood [13].

Rickets (or osteomalacia) is a disorder of bone mineralization, specifically referring to the defective calcification of osteoid in immature bones prior to epiphyseal closure. Children with rickets may present with poor growth, bowed lower extremities, metaphyseal widening, and fractures. Rickets is classified according to the predominant mineral deficiency, specifically calcium (calcipenic rickets) or phosphorus (phosphopenic rickets) [14]. Calcipenic rickets can be secondary to calcium and/or vitamin D deficiency due to insufficient intake, absorption, or metabolism of vitamin D. Phosphopenic rickets occurs due to chronically low intake or absorption of phosphorus, but more commonly results from renal phosphate wasting. X-linked hypophosphatemic rickets associated with *PHEX* gene mutations is the most common hereditary form of rickets with an estimated prevalence of 1:20,000 [14, 15]. In contrast to HPP, rickets typically associates with an elevated alkaline phosphatase [16].

PTH, Vitamin D, and FGF23

Normal serum calcium and phosphorus concentrations are essential for healthy bone mineralization. Calcium and phosphorus homeostasis is regulated by PTH, vitamin D, and FGF23 and the effects they exert on the bone, kidney, and gastrointestinal tract [17–19]. The bones support mineral metabolism as the body's repository of stored minerals and the tissue with the highest FGF23 expression [16, 17].

PTH secretion by the parathyroid cells is continually repressed by the action of the calcium-sensing receptor (CaSR), a G-protein-coupled receptor that acts through a phospholipase C-dependent pathway to inhibit PTH transcription and intracellular calcium-mediated vesicle release [20]. In response to decreased ionized calcium binding to the CaSR, inhibition is decreased and PTH is secreted. PTH then acts at the G-protein-coupled PTH receptor to increase the serum concentration of calcium through its effects on bone and kidney and on the intestine, indirectly, through its role in activating vitamin D. In the kidney, PTH assists with increasing serum calcium levels through reabsorption of calcium in the distal tubule and collecting duct. PTH also decreases the reabsorption of phosphate in the proximal tubule [21]. In bone, PTH drives calcium and phosphorus release from the bone matrix by stimulating PTH receptors on osteoblasts. These cells then increase their expression of RANKL and inhibit their secretion of osteoprotegerin (OPG) [22, 23]. Low OPG and increased RANKL act synergistically to promote osteoclastogenesis.

Vitamin D is synthesized in the skin on exposure to ultraviolet B radiation from the sun or consumed in the diet through vitamin D-enriched foods, beverages, or supplements. Vitamin D is hydroxylated in the liver to form 25-hydroxyvitamin D (the major storage form of vitamin D in the body) and activated to 1,25-dihydroxyvitamin D by renal 1α-hydroxylase in the kidney [18]. 1,25-dihydroxyvitamin D (calcitriol) increases serum calcium and phosphorus concentrations by stimulating intestinal absorption. A direct effect of 1,25-dihydroxyvitamin D in the skeleton may also occur, as vitamin D receptors are found in osteoblasts, osteocytes, and osteoclasts [24, 25].

FGF23 plays a central role in phosphate and vitamin D homeostasis. FGF23 is secreted by osteocytes and signals through an FGF receptor/Klotho co-receptor complex [26, 27]. FGF receptors are tyrosine kinase receptors which activate the mitogen-activated protein (MAP) kinase/extracellular signal-regulated kinase (ERK)1/2 signaling pathway to modulate gene transcription [26].

Elevations in FGF23 decrease 1,25-dihydroxyvitamin D concentrations through reductions in 1α-hydroxylase activity and increased expression of 24-hydroxylase, which degrades calcitriol [17, 28]. Also, FGF23 (similar to PTH) reduces renal phosphate reabsorption through suppression of sodium phosphate co-transporters, NaPi-2a and NaPi-2c, within the proximal tubule [15, 28].

Loss of FGF23 activity results in hyperphosphatemia and inappropriately normal or elevated calcitriol levels, such as in familial tumoral calcinosis, a disorder characterized by dental abnormalities and soft tissue calcifications [16]. Conversely, gain-of-function mutations in FGF23, such as in autosomal dominant hypophosphatemic rickets, result in excessive renal phosphate wasting and skeletal hypomineralization [29].

Bone Cells

Osteoblasts, osteoclasts, and osteocytes are the prototypical bone cells, each with distinct roles in skeletal development and maintenance (Table 2.1 and Fig. 2.2).

Osteoblasts

Pluripotent mesenchymal stem cells differentiate to form bone, cartilage, muscle, and fat tissues. Osteoblasts and chondrocytes arise from a common osteochondrogenic precursor. Commitment toward the osteoblastic lineage requires transcriptional regulators such as Runx2 (Runt-related transcription factor 2) and Osterix which are regulated by various signaling pathways, such as the canonical Wnt (Wingless and INT-1)/β-catenin signaling pathway and the bone morphogenetic protein (BMP) signaling pathway [2, 30].

Canonical Wnt/β-Catenin Signaling Promotes Osteoblastogenesis

Wnt proteins are a family of secreted glycoproteins that bind a dual receptor complex, consisting of frizzled and low-density lipoprotein receptor-related protein (LRP) 5 or 6. In the absence of Wnt, there is constitutive destruction of cytosolic β-catenin. β-catenin is phosphorylated by a β-catenin destruction complex and is targeted for cytoplasmic proteolysis by proteasomes [31, 32]. When Wnt binds to frizzled and LRP5/6 co-receptors, the β-catenin destruction complex dissociates via the action of the cytoplasmic protein, disheveled, and leads to accumulation of cytoplasmic β-catenin (Fig. 2.3). Beta-catenin translocates to the nucleus to initiate

Table 2.1 Comparison of bone cells

	Osteoblasts	Osteoclasts	Osteocytes
Morphology	Uninucleate	Multinucleated	Uninucleate
Lineage	Mesenchymal stem cell	Hematopoietic stem cell	Mesenchymal stem cell, osteoblast
Function	Organic matrix/bone formation	Bone resorption	Mechanosensor
Receptors	PTHRFrizzled LRP5/6	RANK	
Produce	RANKL OPG Alkaline phosphatase Osteocalcin	Cathepsin K Hydrochloric acid	RANKL OPG SOST FGF23 DKK1

RANK receptor activator of nuclear factor kappa B, *RANKL* receptor activator of nuclear factor kappa B ligand, *OPG* osteoprotegerin, *LRP5/6* low-density lipoprotein receptor-related protein 5/6, *SOST* sclerostin, *DKK1* Dickkopf 1

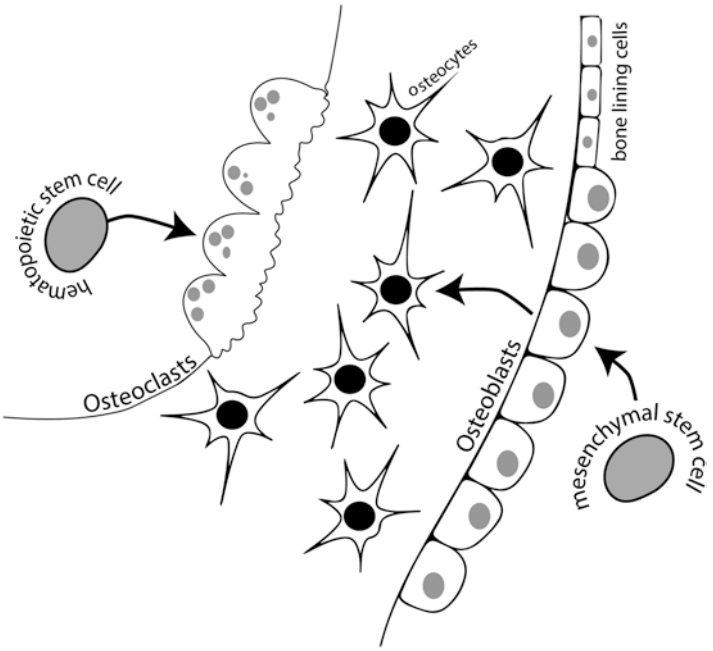

Fig. 2.2 Localization of cells in bone. Found on the surface of bone, osteoblasts are uninucleate cells derived from mesenchymal stem cells. Osteoclasts are multinucleated cells derived from the hematopoietic lineage. Osteocytes are derived from osteoblasts as they become embedded in osteoid. Bone modeling and remodeling processes require bone resorption by osteoclasts and new bone deposition by osteoblasts

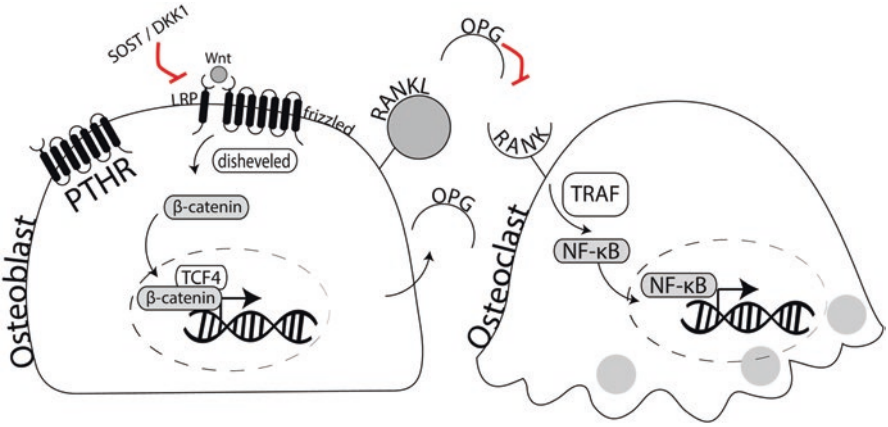

Fig. 2.3 Intracellular signaling and cellular communication. Osteoblastogenesis is driven by canonical Wnt/β-catenin signaling. Mature osteoblasts express cell surface RANKL, which interacts with RANK on preosteoclast cells to drive osteoclastogenesis. Wnt/β-catenin signaling is inhibited by SOST/DKK1. RANK/RANKL signaling is inhibited by osteoprotegerin. *RANK, receptor activator of nuclear factor kappa B; RANKL, receptor activator of nuclear factor kappa B ligand; OPG, osteoprotegerin; LRP5/6, low-density lipoprotein receptor-related protein 5/6; SOST, sclerostin; DKK1, Dickkopf 1*

transcription of target genes [31, 33, 34]. The primary function of osteoblasts is to synthesize new bone (osteoid), but they also communicate with other bone cells that are involved in skeletal development and maintenance. To that end, mature osteoblasts express type 1 collagen, as well as OPG, alkaline phosphatase, and osteocalcin [30]. Their ability to communicate with other bone cells is mediated by their expression of the PTH receptor and RANKL [30].

Ultimately, the majority of osteoblasts undergo apoptosis, but select cells become encased in osteoid as osteocytes or become dormant bone-lining cells [2, 35]. The process by which individual osteoblasts are selected for a particular cell fate is an area of active research [2, 35].

The important role of the canonical Wnt-frizzled-LRP5/6 pathway in human bone biology is illustrated by rare patients with loss- or gain-of-function mutations in *LRP5*. Individuals with loss-of-function mutations develop osteoporosis-pseudoglioma syndrome, characterized by low bone mass and increased fracture risk [36], and gain-of-function mutations in *LRP5* associate with enhanced canonical Wnt signaling and a high bone mass phenotype [37].

Sclerostin and Dickkopf 1 Antagonize the Canonical Wnt/β--Catenin Pathway

Sclerostin (*SOST*) is a secreted glycoprotein produced by osteocytes that acts as an inhibitor of the canonical Wnt signaling pathway by binding to LRP5/6 and preventing the formation of the Wnt-frizzled-LRP5/6 complex (Fig. 2.3) [31, 38, 39].

Sclerostin promotes osteoblast apoptosis and is critical for the maintenance of normal bone mass and prevention of bone overgrowth.

Thus, patients with inactivating mutations in *SOST* (sclerosteosis), or a regulatory element of *SOST* (van Buchem disease), may be predicted to develop skeletal overgrowth characterized by increased osteoblast activity, dense bones, facial disfigurement, deafness, and facial nerve palsy [40]. Patients with sclerosteosis are also tall and have syndactyly [40]. Currently, the canonical Wnt signaling pathway is the focus of much research on potential osteoanabolic treatments for osteoporosis conditions.

Dickkopf 1 (*DKK1*) is expressed in many cell types, but is highly expressed in osteocytes [41]. DKK1 also targets the interaction of LRP5/6 and Wnt-frizzled. DKK1 acts with Kremen (a receptor for DKK) to remove LRP5/6 from the plasma membrane, preventing interactions with frizzled during activation by Wnt [42]. Binding of DKK1/Kremen to LRP5/6 promotes rapid clathrin-mediated internalization of the complex [37, 42].

Osteocytes

Osteocytes are terminally differentiated osteoblasts that may survive for decades and represent the most abundant bone cell type [30, 35, 43]. The osteocyte cell body resides within the bone matrix, and its dendritic processes extend through tiny canals called canaliculi to communicate with neighboring osteocytes and bone surface cells. Thus, despite being surrounded by bone mineral matrix, osteocytes are far from isolated, forming an extensive intercellular network to sense and respond to environmental stimuli [30, 35]. (See “Mechanical Loading” section.) Osteocytes are well positioned to perform their unique sensory role in bone via their ability to modulate both osteoclastogenesis via production of RANKL and osteoblastogenesis via production of SOST and DKK1 [44].

Osteoclasts

Osteoclasts are derived from the bone marrow monocyte-macrophage lineage, and RANKL and macrophage colony-stimulating factor (M-CSF) are essential cytokines for osteoclastogenesis [2]. Osteoclasts are large, multinucleated cells that are responsible for bone resorption. As they mature, osteoclasts become polarized at the surface of bone. The mature osteoclast is characterized by a ruffled apical membrane facing bone and an ion-channel-enriched basolateral membrane facing the marrow space [45]. Osteoclasts act to mobilize stored bone mineral through the production of hydrochloric acid and secreted lysosomal enzymes, such as cathepsin K [45]. The cellular architecture of the osteoclast supports this purpose, with the ability to conduct ions into the cell, concentrate these into acidified vesicles, and deliver these into the resorptive microenvironment at the bone surface [23, 45].

RANK/RANKL Promote Osteoclastogenesis

RANKL is a member of the tumor necrosis factor (TNF) superfamily that is produced by marrow stromal cells and osteoblasts. RANK/RANKL signaling is essential for osteoclastogenesis (Fig. 2.3) [22, 44, 45]. RANKL is expressed on the cell surface of osteoblasts and interacts with RANK on preosteoclast cells. This activates a protein kinase signaling pathway, and classical RANK/RANKL signaling is mediated by TNF receptor-associated factor (TRAF) proteins [45]. The binding of RANK to its ligand recruits TRAFs, activates NF-κB, and induces translocation of NF-κB to the nucleus to induce the transcription of osteoclastogenic genes [22, 44].

Osteoprotegerin Antagonizes RANK/RANKL Signaling

Mainly produced by osteoblasts, OPG binds RANKL with high affinity and acts as a decoy receptor. By neutralizing RANKL and inhibiting RANKL from binding RANK, OPG reduces osteoclastogenesis and bone resorption. Ultimately, the ratio between RANKL and OPG determines the net effect on RANKL-mediated osteoclastogenesis [2].

In OPG deficiency, due to homozygous deletion of *TNFRFSF11B* (juvenile Paget's disease) and unopposed RANKL [46], patients develop profound osteoporosis, bone pain, fractures, and skeletal deformities from excessive bone breakdown, followed by disorganized bone remodeling [47]. Conversely, overexpression of OPG has been associated with an osteopetrosis phenotype in animals [48, 49].

Bone Formation (Osteogenesis)

Bone formation (osteogenesis) occurs through two distinct mechanisms termed intramembranous and endochondral. The flat bones (e.g., skull, mandible, scapulae, sternum, ribs) undergo intramembranous ossification. Intramembranous ossification begins during fetal development and continues through adolescence. The final bones to ossify via intramembranous ossification are the flat bones of the face, which reach their adult size at the end of the adolescent growth spurt [50]. During intramembranous ossification, mesenchymal progenitor cells migrate to specific areas called ossification centers, where they differentiate into osteoblasts. Osteoblasts produce bone matrix from the ossification center, generating extensions called spicules. Newly formed bone is supported by the blood vessels that form and branch around the spicules. The spicules of multiple centers of ossification fuse to form trabeculae, the interconnecting plates and rods of trabecular ("cancellous" or "spongy") bone. Bone remodeling produces the characteristic mature bone, comprised of a marrow cavity and trabecular bone with a cortical shell ("compact" bone) [2].

The long bones (e.g., humerus, radius, ulna, femur, tibia, fibula) undergo endochondral bone formation. The mesenchymal progenitor cells differentiate into

chondrocytes and construct a cartilage template for long bone formation. At the growth plate, chondrocytes proliferate and hypertrophy, which is tightly regulated by major signaling pathways (e.g., Indian hedgehog [Ihh], PTH-related protein, Wnt, FGF, and BMPs). Transcription factors (e.g., Sox9, Runx2) and Ihh synchronize cartilage development with bone formation by inducing osteoblast differentiation [50]. The failure of normal endochondral bone formation can lead to short stature and skeletal dysplasias, such as brachydactyly, achondroplasia, and hypochondroplasia [51].

Key Influences During Adolescent Bone Development

In the growing skeleton, the bones model and remodel as they undergo longitudinal (linear) and radial (cross-sectional) growth [2]. Bone modeling is the adaptation of bone shape and geometry in response to hormonal and mechanical forces [52]. Modeling is achieved through the uncoupled, independent actions of osteoblasts and osteoclasts on separate bone surfaces, and this process is unique to the pediatric and adolescent skeleton [53]. Bone remodeling is the process by which bones preserve their mechanical strength, integrity, and their role in mineral homeostasis throughout life. In bone remodeling, the activity of osteoblasts and osteoclasts is coupled, and the cells work in synchrony alongside one another on the same bone surface to replace old, damaged bone with new, healthy bone [2, 54]. During adolescence, development of secondary sexual characteristics (puberty) and significant skeletal growth occur through the activation of the hypothalamic-pituitary-gonadal (HPG) axis and increased growth hormone (GH) production [55–57].

Sex Steroids

Estrogen receptors (ERs) have been detected in all skeletal cell types, including osteoblasts, osteocytes, and osteoclasts and their progenitors [57]. The binding of estrogen to its nuclear ER in osteoclasts has a pro-apoptotic effect on these cells, whereas estrogen signaling in mesenchymal progenitors promotes the differentiation and survival of osteoblasts in both males and females [57, 58]. Estrogens also act on ERs in the osteocyte to promote osteocyte survival, mediated by activation of the steroid-receptor coactivator (Src)/Src-homology/collagen protein/ERK signaling pathway [59]. In contrast, withdrawal of estrogen correlates with increased osteocyte apoptosis [59].

There are gender differences in bone size and microarchitecture, and these disparities become apparent during puberty [55, 56]. For both sexes, during early puberty, low levels of estrogens stimulate endochondral bone formation to promote linear bone growth. Toward the end of puberty, high concentrations of estrogen are necessary for epiphyseal closure and the eventual cessation of linear growth. There are gender differences in the timing of pubertal onset and duration of puberty, as well as in the progression from a low to high estrogen state. These hormonal

differences may explain the observed gender differences in bone size during adolescence [55–57]. In addition, in boys, androgens preferentially stimulate apposition of bone on the outer (periosteal) surface where the effect on bone strength is the greatest, whereas in girls, estrogen inhibits periosteal apposition and stimulates accretion of bone along the inner (endocortical) surface. Consequently, adult males have bigger (stronger) bones than adult females, which has implications for lifelong osteoporosis risk [60, 61].

Growth Hormone/IGF-1 Axis

An intact GH/insulin-like growth factor (IGF)-1 axis is essential for normal skeletal growth. GH has the ability to signal directly within bone through its G-protein-coupled receptor, but its primary action requires IGF-1. IGF-1 is predominantly produced in the liver, but is also produced in a wide variety of other tissues including bone, and IGF-1 functions in an endocrine, paracrine, and autocrine fashion [62]. IGF-1 receptors are found on all skeletal cell lineages (e.g., chondrocytes, osteoblasts, osteoclasts, osteocytes), and are tyrosine kinase receptors, in the same receptor class as insulin. Binding of IGF-1 induces structural changes within the IGF-1 receptor and activates downstream cell signaling via phosphatidylinositol 3-kinase (PI3K)-Akt and Ras-ERK MAP kinase pathways [63]. The effect of IGF-1 signaling has been shown to promote both RANK-induced osteoclastogenesis and Wnt-induced osteoblastogenesis, consistent with the role of IGF-1 to promote skeletal growth and remodeling [62, 63].

Mechanical Loading

The skeleton adapts to mechanical strains by forming new bone to withstand areas of loading and removing bone in areas of unloading or disuse. The frequency, intensity, and timing of mechanical loading are important factors, as illustrated in the seminal papers describing increased bone mineral density in the playing arm of pro-tennis athletes. The repeated mechanical loading (of the playing arm vs. non-playing arm) increased bone density [64, 65]. In addition, it was observed that the augmentation in bone density in an athlete's playing arm was greater the younger the athlete, and also associated with bone geometric differences, suggesting that the timing of mechanical loading in pre- vs. postpubertal youth is important and influences skeletal development [64, 65]. Conversely, without weight-bearing, as is the case for astronauts in space, the human skeleton undergoes adaptive bone loss in response to the body's low-gravity environment [66]. Chronically ill youth who are non-weight-bearing are at a significant disadvantage due to dysfunction of the HPG axis during illness, as well as to decreased mechanical loading. Such patients experience bone loss and are unable to accrue healthy bone during adolescence, predisposing them to osteoporosis and multiple fractures [53].

Investigations into the cellular mechanisms underpinning the bone's response to mechanical forces have focused on the osteocyte as the critical sensory integration cell in bone [67]. Specifically, osteocytes are thought to sense bone fluid flow that is driven by mechanical strain and loading and transduce these signals via the lacunar-canalicular system and gap junctions into biologic responses [30, 35]. The osteocytes are capable of sending signals of bone resorption and formation [27, 30]. Mechanical loading improves bone mass via the addition of new bone specifically onto bone surfaces experiencing the highest strains, with other surfaces remaining unaffected [68]. Osteocytes promote local osteogenesis in response to increased mechanical stimulation via decreased expression of sclerostin. This results in increased Wnt/LRP5 signaling, promoting osteoblastogenesis [67, 69].

Conclusion

The bones have structural and metabolic importance. The adolescent skeleton undergoes significant growth and maturation through the intricately coordinated actions of bone cells and molecular pathways that are influenced by growth and pubertal hormones and mechanical loading. Understanding bone physiology at a cellular level allows for a deeper understanding and appreciation for the phenotype of certain skeletal disorders and opens opportunities for further investigation into targeted therapeutics in the future.

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Optimizing Nutrition to Promote Adolescent Bone Health

3

Deena Altschwager and Kendrin R. Sonneville

Introduction

To optimize their bone health, adolescent patients should consume an overall healthy diet that includes adequate amounts of protein, at least five daily servings of fruits and vegetables, and adequate amounts of calcium and vitamin D. Many adolescents are below recommended intakes when it comes to calcium, vitamin D, magnesium, and iron. If these patients are unable to obtain adequate amounts of these nutrients from their diet alone, they may require supplementation.

Nutrient Recommendations

Dietary Reference Intakes

An essential component of optimizing adolescent bone health is ensuring that key nutrient needs are being met. The Dietary Reference Intakes, or DRIs, include reference values for nutrient intakes of healthy people that vary by age and sex. The DRIs include several reference values: the Recommended Dietary Allowance (RDA), the Adequate Intake (AI), and the Tolerable Upper Intake Level (UL). The RDA is the average daily nutrient intake that meets the requirements for 97–98% of healthy individuals in a group [1]. If the RDA cannot be calculated due to insufficient data on a particular nutrient, the AI is created. The AI is thought to

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cover the needs of all healthy people in the groups, but the exact percentage of individuals covered by this recommendation cannot be specified [1]. Table 3.1 shows the RDAs and AIs for nutrients important for your adolescent patients' bone health. The last DRI, the UL, is the maximum level of a nutrient that will not pose adverse health risks to most individuals in the healthy population [1]. Understanding these different nutrient values is important to ensure your patients are getting enough, but not too much, of the various nutrients they need to stay healthy.

Protein

Jason is a 15-year-old patient who wants to gain more muscle mass. He drinks two protein shakes per day in addition to consuming a source of protein at each meal. As his healthcare provider, should you be concerned?

Protein, found in both animal-based and plant-based foods including chicken, turkey, beef, pork, fish, eggs, nuts, nut butters, and dairy products, is part of a healthy diet. Children aged 9–13 years should consume 0.95 grams (g) of protein per day for every kilogram (kg) of their weight [2]. For adolescents aged 14–18 years, 0.85 g/kg per day is recommended [2]. Most adolescents in the United States far exceed the RDA for protein [3].

Protein is involved in both the absorption and excretion of calcium, in addition to contributing to bone mineral density and the synthesis of the bone matrix. Protein in the stomach causes the release of gastric acid which enhances the absorption of calcium into the body [4]. However, the increase in total acidic load that results from protein metabolism also increases urinary calcium excretion [4–6]. The acid-base balance of the body and its contribution to bone health will be discussed later in this chapter. The National Academy of Medicine has concluded that the implications of high intakes of protein are not clear enough to advise the general population to restrict their protein intake [2]. However, encouraging your patients to meet the RDA for protein without greatly exceeding the recommendations will allow them to optimize their bone health.

Minerals

Calcium

Suzanne is a 16-year-old female patient who does not consume milk, yogurt, or cheese on a regular basis, but is not opposed to consuming these products. What would you discuss with her at her next visit?

Calcium is the dietary component most often associated with bone health. The human body contains about 1200 g of calcium, which is approximately 1–2% of body weight [7, 8]. Ninety-nine percent of total body calcium is found in the bones with the remaining calcium present in the plasma, extracellular fluid, and soft tissue [5, 8].

Table 3.1 Dietary reference intakes for vitamins and minerals pertinent to bone development

	Years	Vitamin A (μg/d), RDA	Vitamin D (IU/d), RDA	Vitamin K (μg/d), AI	Calcium (mg/d), RDA	Copper (μg/d), RDA	Fluoride (mg/d), AI	Iron (mg/d), RDA	Magnesium (mg/d), RDA	Manganese (mg/d), AI	Phosphorus (mg/d), RDA	Zinc (mg/d), RDA
Males	9–13	600	600	60	1300	700	2	8	240	1.9	1250	8
	14–18	900	600	75	1300	890	3	11	410	2.2	1250	11
	19–30	900	600	120	1000	900	4	8	400	2.3	700	11
Females	9–13	600	600	60	1300	700	2	8	240	1.6	1250	8
	14–18	700	600	75	1300	890	3	15	360	1.6	1250	9
	19–30	700	600	90	1000	900	3	18	310	1.8	700	8

Based on data from Refs. [4, 26]

To support bone growth, the RDA for male and female adolescents aged 9–18 years is 1300 mg of calcium per day. This is an increase from childhood, when the recommendation is 1000 mg of calcium per day. When an adolescent turns 19 years old, the recommendation decreases back to 1000 mg of calcium per day [4]. Unfortunately, few adolescents meet their calcium needs. In fact, the 2015–2020 Dietary Guidelines for Americans stated that calcium is a nutrient of public health concern because low intakes can have adverse health consequences including increased risk of osteoporosis [9].

The RDA for calcium takes into account its low absorption. Specifically, it is estimated that only 30% of calcium that is ingested in the diet is able to be absorbed [4]. In general, the efficiency of calcium absorption is indirectly proportional to the amount of calcium consumed at that time [4]. It is generally recommended that calcium intake be split up throughout the day to compensate for lower absorption at higher calcium intakes. Intakes above 1300 mg of calcium per day do not provide any additional benefit to bone health, and most of the additional calcium will be excreted [5]. Individual factors may also alter calcium retention. For example, retention of calcium appears to differ according to race. Black adolescent females retain more calcium than white adolescents due to higher net absorption and lower levels of calcium excretion [10, 11].

Various components of food may interfere with calcium absorption such as oxalic acid or phytic acid that can form insoluble complexes with calcium [4, 5, 12]. Foods with high oxalic acid levels, such as spinach, collard greens, sweet potatoes, and beans, and foods that contain phytic acid, such as whole-grain products, wheat bran, seeds, nuts, beans, and soy isolates, are considered poor sources of calcium due to the absorption interference [4]. These foods can have as little as 5% absorption of the calcium they provide [13]. One exception to this rule is soybeans. Despite high levels of oxalate and phytate, the calcium present in soybeans is highly bioavailable [13].

Americans obtain approximately 75% of their dietary calcium from dairy products including fluid milk (51% of calcium consumption), cheese (45% of consumption), yogurt (2.6%), and fortified soy milk (1.5%) [9, 13]. Milk is primarily consumed as a beverage or with cereal. Cheese is commonly part of a mixed dish, such as on pizza or in a sandwich; however, the sodium and saturated fat present in cheese make it a less desirable choice than fat-free or low-fat milk and yogurt [9]. Breakfast cereals are another source of calcium. A high calcium-containing cereal can provide an additional 213 mg of calcium per day when consumed for breakfast or as a snack [14]. There are some breakfast cereals that contain over 500 mg of calcium per serving. Because calcium absorption is greater when lower amounts of calcium are consumed at one time, calcium added to a product in excess of 500 mg is likely to have poor absorption, thus would not offer additional benefits [4].

The 2015–2020 Dietary Guidelines for Americans recommends increasing intakes of fat-free or low-fat milk and yogurt to increase calcium intake. To obtain the recommended amount of calcium (1300 mg) through milk alone, an adolescent would need to consume four 1 cup glasses of milk per day. More likely, an adolescent will meet their needs using mixed dietary sources. For example, an adolescent

could have a glass of calcium-fortified orange juice with breakfast, yogurt for a morning snack, a glass of milk with lunch and dinner, and a serving of cheese after dinner to meet their needs. A more extensive list of calcium-containing foods can be found in Table 3.2.

As a child becomes an adolescent, intakes of fluid milk decline [15, 16]. Among 11- and 12-year-olds, fluid milk contributes 44% of needed calcium and declines to 34% for 15–18-year-olds [17]. Sugar-sweetened beverages replacing milk consumption is one explanation for the decline in calcium intake. The highest consumers of sugar-sweetened beverages have the fewest servings of dairy and other calcium-containing beverages [15, 18, 19]. While juice is generally fortified with calcium in similar amounts to what is found in milk, juice contains large amounts of sugar and lacks other nutrients that are present in milk making milk the more nutritious choice [20].

Cow's milk contains several components in addition to calcium that assist with bone health including phosphorus, lactose, and casein phosphopeptides that increase calcium absorption and mineral retention [21]. Today, there are many different milk choices, as seen in Table 3.3, that are used as an alternative to cow's milk. Unlike cow's milk, most of these alternatives are not naturally high in calcium. While almond milk is a popular choice among adolescents, it is not nutritionally comparable to cow's milk because it is low in protein and does not provide calcium naturally (it must be fortified). Thus, if teenagers are looking for alternatives to cow's milk, it is best to direct them to lactose-free or soy milk which provides protein in similar amounts to cow's milk. Refer to the "Special Populations" section of this chapter for more information on this topic.

Calcium is listed on the food label of most packaged foods and is reported as a percent of the daily value for adults (1000 mg). To calculate how much calcium is in a food based on the current nutrition label, a "0" should be added to the percent daily value found near the bottom of the nutrition facts label. For example, if a food is labeled with 20% daily value for calcium, it contains approximately 200 mg of calcium. A new nutrition label will be in effect by July 2018. This new label will require manufacturers to print the actual amount of calcium, in milligrams rather than percent, on the nutrition facts label [22]. The new label will also increase the daily value to 1300 mg, the highest RDA, and the amount adolescents require.

Many adolescents are unable to meet their calcium needs from food alone. Only 22% of males aged 9–13 years consume the RDA for calcium from food alone compared to 42% of 14–18-year-olds and 63% of 19–30-year-olds [23]. Fifteen percent of females aged 9–13 years consume the RDA for calcium, as do 10% of 14–18-year-olds and 26% of 19–30-year-olds [23]. These numbers help to illustrate that most adolescents consume less than the RDA for calcium and would benefit from dietary counseling and/or calcium supplementation. Approximately 20% of males and 24% of females aged 9–18 years take calcium supplements [23]. While dietary supplements allow for an increase in calcium intake, one study found that 46% of children aged 9–13 years had inadequate intakes of calcium, even with supplements, in addition to 36% of adolescents 14–18 years old [24]. With proper counseling on food sources and calcium supplementation dosing, adolescents can obtain enough

Table 3.2 Calcium content of foods

Food	Serving size	Calcium (mg)
Milk		
Unsweetened almond milk	1 cup	450[a]
Cow's milk (1%)	1 cup	305
Fortified soy milk	1 cup	301[a]
Cow's milk (fat-free)	1 cup	299
Other dairy		
Ricotta cheese (part skim)	1/2 cup	337
Yogurt (plain, low fat)	6 ounces	311
American cheese	1 ounce	296
Swiss cheese	1 ounce	252
Yogurt (fruit, low fat)	6 ounces	235
Greek yogurt (plain, low fat)	7 ounces	230
Cheddar cheese	1 ounce	201
Frozen yogurt	1/2 cup	103
Ice cream	1/2 cup	84
Cottage cheese (low fat)	4 ounces	69
Protein		
Canned sardines (with bones)	3 ounces	325
Soybeans, cooked	1 cup	261
Tofu (firm, nigari)	1/2 cup	253[a]
Sesame seeds	1 Tbsp	88
White beans	1/2 cup	81
Almonds	1 ounce (23 nuts)	76
Kidney beans	1/2 cup	44
Fruits, vegetables, and juice		
Calcium-fortified orange juice	1 cup	349[a]
Collard greens, cooked	1/2 cup	134
Spinach, cooked	1/2 cup	122
Orange	1	52
Broccoli, raw	1 cup	43
Cereals and bars		
Total® raisin bran cereal	1/2 cup	500[a]
Luna® bar	1 bar	300–350[a]
Cream of Wheat® cereal	1 cup	303[a]
Clif® bar	1 bar	200[a]
Kix® cereal	1 1/4 cup	171[a]
Honey nut cheerios®	3/4 cup	100[a]
Lärabar®	1 bar	0–60[a]
Frosted flakes®	3/4 cup	0

Based on data from the USDA National Nutrient Database for Standard Reference [44]
[a]Indicates calcium was added to the product (fortified)

Table 3.3 Nutrient content of milk and milk substitutes (per 1 cup serving)

Milk	Calories	Protein (grams)	Fat (grams)	Calcium (mg)	Vitamin D (IU)
Cow's milk, 1%	102	8	2	305	117[a]
Cow's milk, 2%	122	8	5	293	120[a]
Cow's milk, skim	83	8	0	299	115[a]
Cow's milk, whole	149	8	8	276	124[a]
Lactaid milk (cow's milk), 1%	110	8	3	300	110[a]
Almond milk	60	1	2.5	450[a]	250[a]
Cashew milk	25	<1	2	450[a]	250[a]
Coconut milk	80	0	5	450[a]	250[a]
Goat's milk	168	9	10	327	124[a]
Hemp milk	70	3	5	300[a]	300[a]
Rice milk	110	< 1	2	283[a]	101[a]
Soy milk	110	7	5	299[a]	104[a]

Based on data from the USDA National Nutrient Database for Standard Reference [44]
Note: The addition of calcium and vitamin D does not occur across all brands of plant-based milk. Additionally, there may be differing amounts of these nutrients between brands; the standard reference is listed above
[a]Indicates nutrient was added to the product (fortified)

calcium; however, these numbers help to show that there is much work to be done in this area. Calcium intake from supplements should be carefully monitored so patients do not exceed the 2500 mg UL. Intakes above this limit have adverse side effects such as kidney stones and renal insufficiency, in addition to interfering with intakes of other minerals such as zinc, magnesium, and phosphorus [25].

When taking a calcium supplement, vitamin D supplementation should be taken, as well, to allow for maximum absorption [25]. There are many different forms of calcium that can be present in supplements, but calcium carbonate and calcium citrate are the most commonly used. Calcium carbonate supplements contain 40% calcium and calcium citrate supplements contain only 21% calcium, suggesting that calcium citrate may require additional tablets to obtain the same amount of calcium found in calcium carbonate [25]. Calcium carbonate requires an acidic environment for absorption. Calcium citrate should be used by patients with inflammatory bowel disease, an absorption disorder, or those who have had bariatric surgery. Additionally, patients taking proton pump inhibitors or H2 blockers should use this form of calcium because an acidic environment is not necessary for absorption [25].

Because there are so many supplements on the market, it can be hard for patients to choose one. As a clinician, one should evaluate how much calcium the adolescent is lacking in their diet to know how much calcium they should supplement. As long as it is not contraindicated, adolescents should consume calcium carbonate. If a multivitamin is recommended for your patient, keep in mind that the calcium dosage will often be less than 200 mg due to all other components in the supplement.

Additionally, gummy vitamins generally do not have calcium. Therefore, if an adolescent needs more than 200 mg, they should take a separate calcium and vitamin D supplement to increase their absorption. Because calcium absorption is greater when lower amounts of calcium are consumed at one time, most supplements contain no more than 500 or 600 mg calcium [4]. Having smaller doses of calcium four times per day can lower PTH levels and decrease bone resorption [25]. For an adolescent who consumes very little calcium, supplements should be recommended twice daily to maximize intake and absorption.

Phosphorus

Phosphorus is the second most abundant mineral in the human body. Eighty-five percent of phosphorus is present in bone and the remaining in the soft tissues [26]. Phosphorus helps to maintain normal pH by buffering acid or alkali balances in the body and contributes to bone mineralization along with calcium [26]. As noted in Chap. 2, there is a significant relationship between phosphorus, calcium, and vitamin D. While phosphorus is a necessary mineral for bone health, consuming too much may negatively impact bone health. One study of adults aged 18–25 years found that increased phosphorus, combined with low calcium intake, can elevate PTH action [27]. This increase in PTH can inhibit bone resorption leading to bone loss.

The RDA for males and females aged 9–18 years is 1250 mg per day [26]. Requirements are higher during this time to compensate for the rapid period of growth that adolescents endure. Following this time, the RDA for men and women aged 19–30 years decreases to 700 mg per day. Phosphorus can be found in meat, poultry, fish, eggs, dairy products, nuts, legumes, cereals, grains, cola beverages, and as part of a salt used in processing. A national study found that average intakes of phosphorus among adolescents under age 18 are around 1300 mg per day, with only 5% of children this age being unable to meet their needs [28]. In this study, children were not above the UL for this mineral, indicating that consumption is not likely high enough to be harmful to bone health. The use of phosphorus as a food additive and in cola beverages has led to a recent increase in intake [26], although the phosphorus content of cow's milk is five times the phosphorus found in cola. The effects of carbonated cola beverages are discussed later in this chapter; the primary issue with cola beverages is not the content of phosphorus, but rather its displacement of calcium-rich milk.

Phosphorus absorption can be reduced by ingestion of antacids that contain aluminum and large doses of calcium carbonate [26]. However, considering that typical calcium consumption is below recommendations, it is likely that there is no significant interference of absorption due to calcium levels [26]. The majority of your adolescent patients will be able to meet their phosphorus needs from foods. However, if your patients consume too much phosphorus and not enough calcium, that may negatively impact their bone health.

Magnesium

Magnesium is another mineral that is important for bone health. Approximately half of the magnesium in the body is stored in the bones [26]. Magnesium is an alkaline-producing mineral that contributes to the maintenance of bone mineral density (BMD) [29]. Magnesium intake is significantly associated with greater BMD in adult men and women, and low intake has been associated with increased bone resorption [29, 30].

Magnesium is an under-consumed nutrient relative to the RDA [9]. The RDA for males and females aged 9–13 years is 240 mg per day [26]. The RDA increases from age 14 to 18 years to 410 mg per day for males and 360 mg per day for females [26]. The RDA for males 19–30 years is 400 mg per day and for females, in the same age group, 310 mg per day [26]. Green leafy vegetables, whole grains, and nuts have high magnesium content in addition to milk, meats, and starches, such as breakfast cereal. Foods that contain dietary fiber will often also contain magnesium.

While there are many sources of magnesium, foods that contain this nutrient often do not contain this mineral in significant amounts. Because the magnesium content of a food is typically less than 20% of the daily value, an adolescent will need to eat many magnesium-containing foods to meet their needs. For example, an 18-year-old boy could have 2 slices of wheat toast with 2 tbsp of peanut butter and 1 ounce of almonds for a snack, ½ cup of cooked spinach with their lunch, and dinner that includes 1 cup of cooked broccoli, ½ cup of brown rice, and 3 ounces of chicken, in addition to 3 glasses of cow's milk during the day to meet their magnesium needs.

The dietary guidelines list magnesium as an under-consumed nutrient [9]. If you believe an adolescent is deficient in magnesium after assessing their diet, recommend that they increase their intake of green leafy vegetables, whole grains, and nuts throughout the day. If this is not a feasible goal for them, they may need to add a magnesium supplement.

Trace Minerals

Boron

Research has indicated that boron may be important for bone health. In one study conducted in rats, boron was shown to increase bone strength [31]. A separate study of postmenopausal women showed that supplementation of 3 mg of boron reduced urinary excretion of calcium, phosphorus, and magnesium, which are all minerals important for bone health [32]. This finding was contradicted in the rat study where phosphorus, magnesium, and chloride were seen to decrease [31]. One theory on the varying effects of boron is that a diminished intake of fruits and vegetables increased acidic load and removed dietary calcium absorption inhibitors, such as phytates and oxalates, leading to an increased loss of calcium in the urine [33]. Unfortunately, there has not been enough research in this area to establish an RDA or AI for boron; however, ULs of 11 mg of boron per day have been established for ages 9–13 years

and 17 mg/day for 14–18-year-olds [34]. Adolescents obtain the majority of their boron from milk (despite low levels), milk products, fruits, and vegetables [35]. The foods that contain the most boron include avocados, peanut butter, dry peanuts, prune juice, chocolate powder, wine, raisin-containing granola, grape juice, pecans, and raisin bran cereal [35]. As a provider, it is important to be aware that adolescent females consume the lowest amount of boron across all age groups [35]. While an RDA has not been set for boron, recommending a diet that includes five servings of fruits and vegetables is one way to ensure adequacy of boron intake [35].

Copper

Copper is essential for collagen formation within bones. It is the cofactor for lysyl oxidase, a protein needed for collagen and elastin cross-linking within bones. The rate of bone remodeling is high in children and adolescents leading to a high dependence on collagen cross-linking [36]. Copper deficiency may weaken the 3D collagen lattice, which could alter bone composition and structure in a negative way [36, 37]. While the liver regulates the plasma copper concentration, the majority of copper is stored in the skeleton and muscle [34]. Studies have shown rats fed copper-deficient diets had decreased bone strength compared to controls [36, 37]. The RDA for males and females aged 9–13 years is 700 mcg, increases to 890 mcg for 14–18-year-olds, and increases again at age 19 to 900 mcg/day [34]. Due to the risk of liver damage, an UL was set for copper at 10 mg/day [34]. Average consumption of copper among all Americans is 1–1.6 mg/day, meeting the RDA, while staying below the upper limit [34]. Copper absorption is higher when copper intakes are low; about 50% of copper is absorbed when intake is low and approximately 20% is absorbed when intakes are high (above 5 mg per day) [34]. Copper is present in many foods, but richest in legumes, nuts, whole grains, beef liver, and shellfish. In the United States, organ meats, grains, and cocoa products contribute high amounts of copper. Tea, potatoes, milk, and chicken are low in copper, but are consumed in substantial amounts in the American diet and thus significantly contribute to copper intakes [34]. Because copper is abundant in the food supply and the majority of Americans are able to meet their copper needs, it is unlikely that your healthy adolescent patients, consuming a diet with a wide variety, will have an insufficient intake of copper.

Iron

Abigail is a 14-year-old runner with heavy periods. She has decided to become a vegetarian, and her mother asks you if her daughter should take an iron supplement.

Iron, along with copper, is a trace element known to influence collagen maturation and can alter the composition and structure of bones [36, 38]. When rats are fed an iron-deficient diet, they develop decreased bone mass and increased fragility [38]. Additionally, iron deficiency's negative impact on bone health is exacerbated

by a calcium-restricted diet [38]. Because iron deficiency can lead to poor growth and development in addition to cognitive deficits in children, the Dietary Guidelines list iron as an under-consumed nutrient of public health concern [9]. Adolescent girls are the most likely to be afflicted with iron deficiency due to increase in needs and food preferences. Unfortunately, this deficiency occurs when peak bone mass and bone formation are critical [9, 38]. Screening for anemia is recommended for adolescent patients following a vegetarian or vegan diet or a diet of poor overall quality by the American Academy of Pediatrics [39].

The RDA for children aged 9–13 years is 8 mg per day [34]. For males, the RDA increases to 11 mg per day at age 14–18 years but returns to 8 mg per day at age 19 [34]. For females, iron needs increase to 15 mg per day from age 14 to 18 years and increase again at age 19 to 18 mg per day [34]. The increase in recommendations compensates for growth and menses.

Heme iron, from lean meats, is a highly bioavailable source of iron. Non-heme iron, found in lentils, beans, spinach, and enriched and fortified breads and cereals, is not as bioavailable. Unfortunately, the absorption of iron is low, with only 5–20% of iron that is consumed being absorbed. However, non-heme iron absorption can be enhanced with ascorbic acid, or vitamin C, because this vitamin assists with the reduction into the ferrous form of iron [34]. Phytates, polyphenols (found in tea and coffee), and calcium are components that are known to inhibit iron absorption and should be consumed separately from iron when possible [34, 40]. Unfortunately, many teenagers skip breakfast, and this could cause them to miss out on iron-fortified breakfast cereals and vitamin C-containing fruit or juice to help absorption [39].

If an adolescent is unable to meet their iron needs, prophylactic iron supplementation of 60–100 mg/day is recommended in one to two divided doses [39]. The form of iron is not specified among these recommendations. Iron supplementation is often linked to gastrointestinal symptoms that include nausea, vomiting, abdominal pain, and constipation [39]. These symptoms should be monitored in your patients. Adolescents should consume a source of heme-containing iron at every meal and should combine non-heme sources of iron with a source of vitamin C, such as a fruit. Additionally, they should avoid drinking tea and coffee with their meals. If they are unable to meet their needs, as is true in most adolescent females, an iron supplement may be indicated.

Manganese

Manganese is involved in the formation of bone and connective tissue [34]. The AI for males aged 9–13 years is 1.9 mg, increases to 2.2 mg from age 14 to 18 years, and increases again to 2.3 mg at 19 years [34]. For females aged 9–18 years, the AI is 1.6 mg per day and increases to 1.8 mg at age 19 [34]. Rich sources of manganese include whole grains, nuts, leafy vegetables, and teas. Only a small percentage of dietary manganese that is consumed is absorbed [34]. Men absorb less manganese than women, potentially due to iron status, causing men to have higher manganese needs than women [41]. Foods that are high in phytic acid and oxalic acid may

inhibit manganese absorption [34]. Additionally, tannins, present in tea, a rich source of manganese, may reduce the absorption of manganese. However, most healthy adolescents, with varied diets, are able to meet their manganese needs [42].

Zinc

Zinc has a role in bone formation, mineralization, and inhibition of bone resorption [43]. Consuming dietary zinc causes an increase in bone mass [43]. The RDA for males and females aged 9–13 years is 8 mg per day [34]. For males, the RDA increases to 11 mg from age 14 and on [34]. For females, the RDA increases to 9 mg from age 14 to 18 years and decreases to 8 mg from ages 19 to 30 years [34]. Approximately 8% of children under 18 are unable to meet their needs for zinc [28]. Zinc is found in red meats, seafood, and whole grains [34]. One serving of oysters greatly exceeds zinc needs, one serving of beef provides 5–7 mg of zinc, and breakfast cereals provide approximately 4 mg [44]. Unfortunately, phytates limit the absorption of zinc, and adolescents should be counseled on this if they do not consume meat [34]. Individuals who are unable to meet their zinc needs should be counseled to increase their intake through food sources. Caution should be given when using zinc supplements as interference with copper absorption is possible [34].

Vitamins

Vitamin A

Vitamin A is important for bone health due to its role in bone growth [45]. However, dietary intake of retinol greater than 1.5 mg/day is associated with reduced bone mineral density and increased risk (approximately 40%) for hip fracture among women aged 28–74 years [46, 47]. Retinol, preformed vitamin A, is found in some animal products; provitamin A, or carotenoids, such as beta-carotene, is found in darkly colored fruits and vegetables [34]. The body converts provitamin A found in plants into vitamin A. This needed conversion requires a larger amount of provitamin A to meet the vitamin A requirements [34]. It takes approximately 12 mcg of dietary beta-carotene to provide one retinol activity equivalent (RAE) [34]. The RDA for boys aged 9–13 years is 600 mcg RAE per day [34]. At age 14, the RDA increases to 900 mcg RAE per day [34]. For females aged 9–13 years, the RDA is 600 mcg RAE per day and increases to 700 mcg RAE/day at age 14 [34]. Approximately one third of children under 18 are unable to meet their needs for vitamin A [28]. A greater amount of fruits and vegetables may be required for vegetarians to ensure they meet their needs due to the conversion for provitamin A. Preformed vitamin A comes from liver, dairy products, and fish, and beta-carotene can be found in carrots, cantaloupe, broccoli, squash, peas, and spinach [34]. These fruits and vegetables are more efficiently converted to vitamin A than equal amounts

of dark green leafy veggies [34]. Additionally, vitamin A is fortified in milk and cereal to provide additional sources of this nutrient. As a fat-soluble vitamin, vitamin A is best absorbed when consumed with fat. While some individuals are unable to meet their vitamin A needs, others greatly exceed their needs, primarily with supplementation. On average, multivitamin supplements provide 2500 IU or 750 mcg of vitamin A [48]. It is possible for adolescents to consume too little vitamin A; in this case, these patients should be counseled to increase their dietary consumption of foods that contain vitamin A. Caution should be exercised when recommending supplementation as adolescents can greatly exceed their needs which can be harmful to their bone health.

Vitamin D

Tom is a 16yo who presents for his yearly physical. He says his siblings have been told they have vitamin D deficiency. He started taking 2000 IU vitamin D3 daily to support his bone health. Should he?

Vitamin D is often the other nutrient that is commonly thought of when it comes to bone health. The key role of vitamin D is to enhance calcium absorption. Vitamin D is responsible for increasing the plasma levels of calcium and phosphate to allow for bone mineralization [4]. This vitamin is also needed for bone growth and remodeling. In severe cases of vitamin D deficiency among young children, rickets can develop. Due to high rates of osteoporosis and low bone density, vitamin D was named as an under-consumed nutrient of public health concern in the most recent Dietary Guidelines for Americans [9]. The recommended amount of vitamin D for male and female adolescents of all ages is 600 international units (IUs) per day [4].

There are two different forms of vitamin D: vitamin D2, or ergocalciferol, the form that is human made and can be added to foods, and vitamin D3, or cholecalciferol, the form that can be synthesized in the skin of humans and consumed from animal-based foods [4]. Vitamin D3 can be synthesized in the skin of humans from the UVB rays of the sun [49]. The availability of UVB rays is affected by many factors including latitude, season, time of day, time spent outside, cloud cover, pollution, skin pigmentation, skin coverage, use of sunscreen, age, and body composition [4, 49]. There is no established safe threshold of UV exposure for sufficient vitamin D synthesis as the exposure would come with an increased risk of skin cancer [49].

Vitamin D is best absorbed when consumed with a source of fat, although the optimal amount of fat that should be consumed is unknown [4]. Individuals who are obese, with greater amounts of body fat stores than their normal weighted counterparts, have lower levels of 25-hydroxy vitamin D (25(OH)D) [50]. This larger pool of fat does not affect the ability of the skin to produce vitamin D, but alters the release of vitamin D3 from the skin into the circulation [50]. Researchers have concluded that morbidly obese individuals may require increased amounts of vitamin D due to the storage that occurs in adipose tissue.

Table 3.4 Vitamin D content of foods

Food	Serving size	Vitamin D (international units)
Salmon (cooked)	3.5 ounces	518
Fish oil, cod liver	1 tsp	450
Shrimp (canned)	3 ounces	152
Total® cereal	1 cup	133[a]
Fortified cow's milk	1 cup	116[a]
Fortified soy milk	1 cup	104[a]
Fortified orange juice	1 cup	100[a]
Fortified, unsweetened almond milk	1 cup	100[a]
Raisin bran cereal	1 cup	91[a]
Yogurt	6 ounces	86[a]
Tuna (canned)	3 ounces	68
Margarine	1 tsp	60[a]
Frosted flakes®	3/4 cup	56[a]
Honey nut cheerios®	3/4 cup	52[a]
Egg (whole)	1 large	41

Based on data from the USDA National Nutrient Database for Standard Reference [44]
[a]Indicates vitamin D was added to the product (fortified)

The best indicator of vitamin D status is 25(OH)D. This is the main form of vitamin D in circulation, but this measurement does not specify the amount of vitamin D in the body's tissues [4]. When a healthy adolescent population at Boston Children's Hospital was surveyed, it was found that 24% of the patients were vitamin D deficient (with 25(OH)D levels <15 ng/L) and 42% had blood levels below 20 ng/mL, classified as vitamin D insufficiency at that time [51]. These researchers noticed a correlation between the deficiency and the consumption of sodas, fruit juice, and iced tea. There was an inverse relationship between vitamin D deficiency and the consumption of milk and cold cereal, foods that are fortified with this vitamin [51]. In the summer, 25(OH)D was higher than in winter. Because the body is able to synthesize vitamin D from the sun in the summer months, this result is not surprising. Additionally, the researchers noted that adolescents of African American descent had increased risk of deficiency [51].

To increase the intake of vitamin D, the Dietary Guidelines recommends consuming seafood such as salmon, herring, mackerel, and tuna and vitamin D-fortified foods such as milk, soy milk, yogurt, orange juice, and breakfast cereals [9]. Table 3.4 provides a more complete list of foods that contain vitamin D. As noted in the "Calcium" section, cow's milk substitutes, found in Table 3.3, may not be fortified with vitamin D.

In the United States, fluid cow's milk is voluntarily fortified with 400 IU of vitamin D per quart, or approximately 100 IU per 1 cup serving. This voluntary fortification began in the 1930s. It is up to the manufacturer to decide which form of vitamin D they will use and what amount they would like to add to the food [4]. Other foods that can be fortified with vitamin D include margarine, cereal, yogurt, and juice.

Nutrition facts labeling of vitamin D is currently voluntary, meaning that manufacturers do not need to list this vitamin on the label, but they can if they want to. The current daily value for vitamin D if it is added to the nutrition facts label is 400 IU or 10 mcg [22] as 1 IU of vitamin D is equal to 0.025 mcg. When the new nutrition label debuts in July 2018, the label will require that vitamin D is listed on the label in micrograms. Manufacturers may voluntarily also list the amount of vitamin D in international units, as well as daily value percentage (based on 20 mcg or 800 IU, the amount needed for adults over the age of 70) [22].

From food alone, only 39–53% of male adolescents and 21–47% of female adolescents are able to meet their vitamin D needs depending on age group [23]. This is likely due to declining milk intakes that were discussed in the calcium section. If an adolescent consumes fatty fish, such as salmon, three times per week along with an average of 1.5 glasses of fortified milk daily, they will meet their vitamin D needs. Alternatively, if an adolescent does not eat fish, they can meet their vitamin D needs by consuming three glasses of fortified cow's milk, along with a serving of fortified breakfast cereal daily.

Because many adolescents have insufficient 25(OH)D levels, they should be counseled to increase their intake of vitamin D-rich foods such as fatty fish and cow's milk. If they are unable or unwilling to do this, a vitamin D supplement should be recommended. This is especially true for adolescents with limited sun exposure, those who regularly use sunscreen, and obese adolescents. Vitamin D supplements are able to increase intakes among those who take them. For example, 16–27% of male adolescents used vitamin D supplements giving them an extra 5.7–8.4 mcg/day of vitamin D [23]. Even with supplements, there are a variety of reasons adolescents may be unable to meet their needs, including inconsistent intake, poor absorption (not taken with fat), and too low dosing. Overall this leaves 32% of children aged 9–13 years with inadequate intakes of vitamin D, in addition to 36% of adolescents 14–18 years old [9, 24].

There is presently no research consensus on the amount of vitamin D that should be supplemented. In one study among children, it was noted that 400 IU of vitamin D was sufficient to maintain winter 25(OH)D levels in healthy black, but not white children [52]. According to the Endocrine Society, adolescents under 18 may require 1000 IU per day to maintain their vitamin D levels above the deficient range [53]. Adolescents over age 18 may require 1500 to 2000 IU per day of vitamin D. Of note, the most common amount of vitamin D in a multivitamin and mineral supplement is 400 IU [48], but supplements that only contain vitamin D, or a combination of vitamin D and calcium, will have higher amounts. Vitamin D2 and vitamin D3 appear to be equally effective for daily treatment [4, 49, 53]. At this time, more concrete conclusions about these two vitamin forms cannot be determined [4]. However, for large, single doses, vitamin D3 is preferred due to a longer half-life [49].

If treating a vitamin D deficiency, supplementation is recommended for a minimum of 12 weeks, but some adolescents may require longer amounts of time [49]. The Endocrine Society recommends that adolescents under age 18 take 2000 IU of vitamin D2 or D3 once per day for 6 weeks, followed with maintenance therapy of

600–1000 IU per day [53]. For adults, 50,000 IU is recommended once weekly for 8 weeks or 6000 IU daily followed by maintenance of 1500 to 2000 IU day [53]. In obese patients, 6000 to 10,000 IU per day is recommended to maintain level above deficient followed by maintenance of 3000 to 6000 IU [53].

Vitamin K

Vitamin K acts as a coenzyme for bone metabolism [34]. Osteocalcin, an abundant non-collagenous protein in bone, is a vitamin K-dependent protein [54]. In one study among healthy adolescent females, those with better vitamin K status had a decreased rate of bone turnover [55]. Other studies in older adults have shown that increased intakes of vitamin K are associated with decreased risks of hip fracture [54, 56]. The AI for children aged 9–13 years is 60 mcg/day and increases to 75 mcg/day for 14–18-year-olds [34]. For men aged 19 and older, the AI is 120 mcg per day, and for women over 19 years, the AI is 90 mcg per day [34]. Vitamin K is an under-consumed nutrient in children, with only 35% meeting the adequate intake [28]. This nutrient is found primarily in green leafy vegetables such as kale, collard greens, and spinach, in addition to plant oils, such as canola and olive oil. Americans commonly obtain their vitamin K from spinach, broccoli, iceberg lettuce, fats, and oils. Because vitamin K is a fat-soluble vitamin, consuming vegetables rich in vitamin K with fat can help with absorption. Additionally, the vitamin K found in fats is better absorbed than that found in vegetables. Vitamin K is not generally fortified in foods. However, consuming 1 cup of raw spinach, 1 cup of kale, or ½ cup of cooked broccoli will allow an adolescent to exceed their AI for the day. Thus, nutritional counseling should be provided on increasing the intake of green leafy vegetables to help adolescents meet their vitamin K needs if an adolescent is not currently meeting their needs.

Other Dietary Components

Alcohol

Research regarding bone health and alcohol consumption has shown inconsistent results, and, unfortunately, there is a lack of research among adolescents. Although it is illegal for adolescents under 21 to consume alcohol, some adolescents do consume alcohol, and these adolescents are more likely than adults to engage in binge drinking [57]. Binge drinking can have negative consequences when it comes to bone health. One study among rats has shown that binge drinking can negatively impact bone resorption and formation after just 3 weeks [58]. Drinking a moderate amount of alcohol (up to two drinks per day) has been noted to be beneficial to the bone density and risk of hip fractures among adult men and is unlikely to be harmful to bone health of adult women [59]. However, consuming alcohol can also be associated with a lower consumption of micronutrients and increased risk of

experiencing a fall. Both events are harmful to bone health. At this time, it is unclear whether moderate amounts of alcohol have an impact on adolescent bone health, although such intake is certainly harmful in other ways. Binge drinking is harmful to bone health among adult rats and could impact adolescent bone health in a negative way.

Caffeine and Carbonated Beverages

Consumption of caffeine and carbonated beverages is not beneficial to adolescent bone health as they have been shown to increase the amount of calcium excreted in the urine and increase the risk of bone fractures. Additionally, as described earlier, the consumption of sugar-sweetened beverages, including some carbonated sodas, is associated with a decline in milk consumption. This leads to a decline in vitamins and minerals that are beneficial to bone health, most notably calcium. Compared to individuals who do not drink cola beverages, those who drink cola beverages are three times more likely to experience bone fractures [60–62]. In addition to the displacement of milk consumption, another possible explanation could be the acidic load that results from consumption of carbonated beverages.

Caffeine increases urine calcium excretion, although one cup of coffee will decrease calcium retention by only 2–3 mg. This indicates that even heavy caffeine consumers will likely only experience a small decrease in calcium retention [13, 63]. One way to compensate for this decreased retention is to add a small amount of additional calcium to the diet, such as adding milk to coffee.

Dietary Fiber

Fiber, as a prebiotic, may enhance calcium absorption, but may also reduce the bioavailabilty of minerals important to bone health. Dietary fiber is present in many fruits, vegetables, whole grains, nuts, and legumes. Young men aged 9–13 years are recommended to have 31 g per day of fiber; when they are 14–50 years old, the recommendation increases to 38 g per day [2]. Young women aged 9–18 years are recommended to consume 26 g per day and 25 g/day from age 19 to 50 [2]. Adolescents can meet their fiber needs with five daily servings of fruits and vegetables, in addition to a serving of whole grains at every meal. Fiber in general may reduce the bioavailability of minerals including iron, calcium, copper, magnesium, phosphorus, and zinc as they may form insoluble complexes with phytate [64]. However, this can be offset by adequate mineral intake.

Inulin is a type of dietary fiber classified as a fructan and is recognized as a prebiotic. Inulin is found in wheat, onion, bananas, leeks, artichokes, and asparagus and is also added (often as “chicory root”) to high-fiber energy bars and breads. The consumption of inulin is a potential way to increase adolescent’s calcium absorption and enhance bone mineralization [12].

However, it is not known if a prebiotic would be beneficial in individuals consuming less than 450 mg of calcium per day [12]. The net benefit of prebiotics could be up to 30 mg of additional calcium daily or the equivalent of 11 g of increased calcium added to the skeleton per year [12, 65]. Unfortunately, not all adolescents responded to the prebiotic treatment. This may be due to genetics, usual inulin intake, or other dietary aspects [65]. Although further research is needed in this area, prebiotics may be one way to increase calcium retention.

Sodium

Dietary sodium is often a harmful nutrient for bone health because sodium and calcium share the same proximal tubule transport system. This can lead to a reduction in calcium retention in the body as dietary sodium can lead to calcium loss in the urine [13, 66]. This was observed in a study of postmenopausal women where higher urinary sodium excretion led to greater bone loss [67]. The authors concluded that increasing calcium intake and decreasing sodium intake to recommended levels may lead to a reduction in bone loss [67]. The AI for sodium is 1500 mg for male and female adolescents [68], but most adolescents consume more sodium than what is recommended. The majority of ingested sodium comes from processed foods and the use of a salt shaker; however, intake estimates often do not include the amount of sodium from a salt shaker [68]. Most of the sodium that is ingested is excreted in the urine [68]. Counseling your patients to stay within recommended sodium guidelines while consuming enough calcium will benefit their bone health.

Acid-Base Balance

The acid-base balance of the body is another important factor for bone health. Protein foods create a more acidic environment, while fruits, vegetables, and vegetable proteins contribute to a more basic environment [69, 70]. When the body is facing an acidic level, it needs to compensate with cations. Magnesium, potassium, calcium, and sodium can be pulled from the skeleton to buffer excess acid [70]. This process is thought to lead to the demineralization of bone and, over time, can lead to osteoporosis due to the reduced mineral content and bone mass [69–71]. One way to combat this imbalance is to ensure that your patients are not consuming too much protein in their diets and that they consume fruits and vegetables in adequate amounts. This will allow their acid-base balance to support bone health.

Potassium Bicarbonate

The consumption of potassium bicarbonate is an area of research that has not yet reached consensus. In postmenopausal women, a potassium bicarbonate supplement was seen to neutralize the body's acid balance, reduce calcium and

phosphorus excretion, reduce bone resorption, and increase the rate of bone formation [72]. One study has suggested that the bicarbonate, not potassium, may be responsible for the positive effect on bone resorption and diminished calcium excretion due to its ability to reduce the acidity caused by the diet [73]. Until a consensus is able to be determined, adolescents should continue to aim for five servings of fruits and vegetables daily, as they are sources of both potassium and bicarbonate.

Special Populations

Lactose Intolerance

Paige is an 18-year-old who believes that she is lactose intolerant but is otherwise healthy. She avoids all dairy products, but consumes a wide variety of nondairy foods. She does not take any supplements and is not concerned about her intake. Should she be?

Lactose intolerance can cause a range of symptoms including abdominal pain, diarrhea, nausea, flatulence, and/or bloating after the ingestion of lactose or lactose-containing foods and often develops in the teenage or young adult years [74]. While consuming lactose will cause gastrointestinal (GI) upset, no harm will occur to the GI tract [74]. Many factors including activity of lactase, rate of gastric emptying, fecal bacterial metabolites, colonic absorption, and intestinal transit time can influence the susceptibility of a patient to intolerance symptoms [75]. Additionally, the amount of lactose that will cause symptoms varies from person to person. This depends on the amount of lactose consumed, the composition of the lactose-containing food, and the extent of lactose deficiency [74]. Small amounts of lactose from milk, yogurt, hard cheese, and reduced lactose foods equivalent to 12 grams of lactose, or 1 cup of milk, appear to be tolerated in most lactose-intolerant individuals [75]. Milk and yogurt have similar amounts of lactose, but the bacteria in yogurt can partially digest lactose before consumption making this easier for lactose-intolerant patients to tolerate. Additionally, the consistency of yogurts slows gastric emptying resulting in fewer symptoms [74]. Cheese has lower lactose composition than yogurt and milk; 1.5 ounces of cheese has approximately 1 gram of lactose. This information helps to illustrate that adolescents with lactose intolerance do not need to eliminate dairy consumption completely. In fact, adolescents who avoid dairy are at risk of ingesting too little calcium and vitamin D and may require supplementation [74]. Lactase-containing enzyme supplements are available over the counter and can help with digestion of lactose. Adolescents can also find other calcium sources, like products that contain lactase or products that are made from soy. It is important to keep in mind that milk that comes from other mammals, such as goat's milk, also contains lactose [74]. While there are cow's milk substitutes, as seen in Table 3.3, they are not all nutritionally equivalent to cow's milk.

Milk/Dairy Allergy

Contrary to lactose intolerance, individuals with a milk allergy cannot consume any milk or milk products without the possibility of serious and potentially life-threatening reactions such as anaphylaxis. A milk allergy generally develops in infancy or early childhood, but many individuals will grow out of the allergy. The percentage of children who outgrow the allergy and the age at which this occurs is not consistent in the literature [76–78]. Adolescents with a milk allergy need to avoid all mammalian milk including cow's milk, goat's milk, and sheep's milk as there is a possibility that an individual could react to any of these milks. Additionally, they need to avoid all products that contain milk. This can be confusing as foods labeled as nondairy may contain other milk-containing ingredients [74]. The Food and Drug Administration requires that all allergens, including milk, be specified in bold on the nutrition facts label after the ingredient list. This is one way to check if products contain milk.

Adolescents with milk allergies consume less calcium than their peers and may have reduced bone mineral density and reduced peak bone mass [79]. Thus, adequate intake of calcium is one of the biggest concerns for adolescents with a milk allergy. Alternative dairy products that can be consumed by individuals with a milk allergy include soy, almond, rice, oat, flax, cashew, and coconut products, but it is important to ensure that these alternative products are fortified with calcium if it is not present naturally. In addition to alternative dairy products, adolescents should consume plant-based sources of calcium, which will be discussed further in the next section. It is important to ensure these patients are obtaining enough calcium, and if not, they may require supplementation.

Vegans

To ensure adequate bone health for your vegan patients, it is important to ensure that they consume adequate amounts of all nutrients, especially calcium, vitamin D, and vitamin B12 as they all play a vital role in bone health [80]. The importance of calcium and vitamin D has been discussed earlier; inadequate vitamin B12 levels have also been linked with low bone mineral density. The general composition of a vegan diet often has increased fruits and vegetables and is occasionally lower in protein when compared to omnivores. Vegans may also consume larger amounts of phytates that can interfere with the absorption of nutrients. Generally speaking, however, vegan diets do not come with an increased risk of fractures as long as calcium intake is adequate [80]. Vitamin B12 is found in some fortified products such as soy, dairy substitutes, and breakfast cereals. If an adolescent is not consuming these products, they will need a supplement. Sources of calcium in line with a vegan diet include tofu, green leafy vegetables, and calcium-fortified orange juice, dairy substitutes, and protein bars. The absorption of these foods is variable, anywhere from less than 5% to greater than 50%, depending on other components in the foods, such as oxalate [13]. Vegans consume 30% less protein than omnivores, and they do not excrete as much calcium, likely due to the role protein plays in calcium excretion [81].

Vitamin D, commonly found in fortified dairy and fish, may require supplementation if other dietary sources, such as mushrooms exposed to ultraviolet light, fortified dairy substitutes, or fortified orange juice, are not consumed in adequate amounts by an adolescent patient. Vitamin D3, or cholecalciferol, is created from sheep's wool, which vegan patients may prefer to avoid. Vitamin D2, on the other hand, can be a more appealing nutrient source for a vegan patient [80]. Finally, the acid-base body composition that results from a vegan diet may be protective for bone health. The structure of a vegan diet, that is, the consumption of more fruits and vegetables than omnivores, allows vegans to have a more alkaline balance as noted in urinary pH [71, 81].

Dietary Supplements

Adolescents can obtain all of the nutrients they need through food. However, adolescents who avoid a food or food group may require a dietary supplement. If you believe one of your patients requires supplementation, it is important to counsel them on the specific vitamin or mineral you would like them to take and the dosage you recommend. This will help to minimize the risk of your patients exceeding the UL for micronutrients. Additionally, counsel your patients about the lack of regulations on supplementation and the unsupported health claims that may appear on the bottles. Because supplement manufactures may pay to get their supplements tested and certified, you may also instruct your patients to look for supplements that have been certified by organizations such as the US Pharmacopeia or NSF International. Finally, consider asking your adolescent patients to bring in the bottles of any supplements they are taking so you can ensure they are only taking the nutrients they are lacking in appropriate doses.

Conclusions

There are many important factors to consider when thinking about the bone health of a practice of adolescent patients. It is important to assess their diets for macronutrient and micronutrient adequacy. A general, healthy diet that includes adequate protein, five daily servings of fruits and vegetables, and adequate calcium and vitamin D intake is supportive of adolescent bone health. Unfortunately, many adolescents are unable to meet their nutrition needs for calcium, vitamin D, magnesium, and, for adolescent females, iron. Counseling to increase intakes of these nutrients, through diet or supplementation, is vital to bone health.

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Physical Activity to Promote Bone Health in Adolescents

4

Stuart J. Warden and Robyn K. Fuchs

Introduction

Physical activity (PA) refers to any task requiring energy expenditure beyond resting levels, with the latter quantified as a caloric consumption of 1 kcal/kg/h and expressed as 1 metabolic equivalent (MET). PA includes exercise as a subcategory, which is structured activity that has improvement or maintenance of physical fitness as an objective. PA has multi-system benefits which contribute to improved function and reduced disease risk [1]. Ultimately, regular participation in moderate-to-vigorous PA (≥3 METs) reduces all-cause mortality [2–4].

Despite the well-known health benefits of PA, a large proportion of the population does not meet recommended PA levels. For instance, less than a third of adolescents meet the Centers for Disease Control and Prevention guidelines of completing 1 h of moderate-to-vigorous PA each day, with 36% of males and only 18% of females meeting the recommended levels [5]. In addition, PA levels gradually decline with increasing age across adolescence [6]. These data are of concern as the formative adolescent years represent a time to instill lifelong health behaviors, with physical inactivity in adolescence negatively impacting cardio-metabolic risk factors and most likely contributing to recent increases in the rates of adolescent-onset obesity and type 2 diabetes [7–9].

PA and inactivity during adolescence have particular implications for skeletal health. The skeleton has a number of functions ranging from calcium metabolism to a more recently identified role as an endocrine organ influencing energy metabolism; however, its most classical function is mechanical. The skeleton provides an internal framework enabling gravity to be countered and presents attachment sites allowing muscles to generate motion at specialized bone-to-bone linkages (i.e., joints).

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Given the mechanical role of the skeleton, it follows that skeletal tissue is capable of responding and adapting to its mechanical environment.

The ability of the skeleton to adapt to mechanical loads has been known for centuries and is loosely referred to as "Wolff's law," named after the German anatomist/surgeon Julius Wolff who suggested that the form of the bone is related to mechanical stress by a mathematical law [10]. Although basic tenets of Wolff's law contain inaccuracies [11], the general concept that bone adapts to mechanical loading is indisputable. In particular, studies investigating bone health within individuals participating in PA that unilaterally overload one extremity have confirmed the extreme osteogenic potential of mechanical loading, with professional baseball players exhibiting a near doubling of the strength of the humeral diaphysis in their throwing arm compared to their contralateral non-throwing arm [12].

Skeleton mechanoadaptation begins in utero, where muscle-generated forces impact bone shape and strength development [13], and continues postnatally. However, the years up to and including the pubertal growth period during adolescence appear the most opportune time to take advantage of skeletal mechanoadaptability. Muscle-generated mechanical stimuli associated with PA during this period is anabolic (i.e., stimulates bone formation and mass accrual). This has the potential of "putting more in the bank" during adolescence to offset the progressive bone loss and subsequent increased risk for osteoporotic fracture later in life. In contrast, skeletal mechanosensitivity appears to decline with advancing age making it more difficult to induce adaptation following adolescence, with PA during aging having more of an anti-catabolic influence on the skeleton (i.e., decreases bone resorption to maintain mass).

This chapter discusses (1) adolescence as the optimal time to promote the lifelong skeletal benefits of PA, (2) the design of PA to enhance bone adaptation, and (3) how to encourage adolescents to get sufficient PA for lifelong bone health.

Lifelong Skeletal Benefits of Physical Activity During Adolescence

Adolescence Presents a "Window of Opportunity"

Adolescence presents a highly permissive skeletal state. There is great bone activity which leads to increases in bone length and gains in stature but also increases in bone mass, cross-sectional bone size, and bone strength. Approximately 25–30% of adult bone mineral is accrued within the 2–3 years around the pubertal growth period, and estimated bone strength increases by approximately 50%, depending on sex and skeletal site [14–17]. By the end of adolescence, approximately 95% of adult bone mass has accrued [14]. As fracture risk during aging doubles for each standard deviation of bone lost from mean peak bone mass [18] and a 10% increase in peak bone mass is predicted to delay the onset of osteoporosis by 13 years [19], PA to increase peak bone mass during growth is advocated as a means of offsetting the increase in low-trauma fracture risk associated with aging [20–22].

Observational studies have demonstrated children and adolescents who lead more physically active lifestyles typically have 10–15% greater bone mass than their peers [14, 23, 24]. These data are supported by prospective randomized controlled trials which have demonstrated weight-bearing exercise in children and adolescents to increase bone mass at loaded sites (lower extremities and spine) by up to 5% in <2 years [25]. However, the skeletal advantage of exercising during adolescence has most eloquently been shown in the investigational model of racquet sport players.

Girls who began playing racquet sports before puberty had more than twofold greater differences in bone mass between their playing and nonplaying arms compared to those who began playing post puberty [26]. In support of this observation, Heinonen et al. [27] reported high-impact PA increased bone mineral accrual in premenarchal but not post-menarchal girls. Similarly, Ducher et al. [28] observed postpubertal racquet sport players had equivalent side-to-side differences in bone mass between their playing and nonplaying arms compared to peri-pubertal players, despite the former playing for longer. Although contrasting findings have been reported by other investigators [29–31], the cumulative findings suggest the presence of a "window of opportunity" during pre- and early puberty where the skeleton is most amenable to the mechanical loading associated with physical activity [32].

Physical Activity-Induced Optimization of Peak Bone Mass Is Not Maintained Long-Term

Although the skeleton appears most receptive to the benefits of PA during adolescence and particularly in the years leading up to and including the period of somatic maturation, reduced bone strength and the concomitant increase in the risk for low-trauma fractures is predominantly an age-related phenomenon. This observation raises the question as to whether PA-induced bone changes during growth persist into adulthood where they would be most advantageous in reducing fracture risk.

Numerous studies have explored the sustainability of PA-induced bone mass benefits acquired during adolescence. Prospective observational studies suggest some of the bone mass benefits of PA generated when young persist into early adulthood [33–38], and follow-up assessments of former participants in randomized controlled trials have documented that cessation of an osteogenic PA program is associated with some short-term maintenance of bone mass benefits [39–41]. However, the longevity of the benefits has been questioned.

Using a randomized controlled study design, Gunter et al. [40] demonstrated a jumping exercise intervention increased bone mass by 3.6% in their PA group compared to controls; however, this difference declined by over 60% (to 1.4%) in the first 7 years following intervention cessation. Similarly, cross-sectional studies suggest that the bone mass benefit of PA induced when young ultimately disappears, albeit it takes 30–40 years [12, 42]. In particular, Karlsson et al. [42] reported that PA in the form of soccer-playing conferred high peak bone mass, but its cessation resulted in accelerated bone loss during aging. Meanwhile, we showed that

throwing-to-non-throwing arm differences in bone mass observed within professional baseball players ultimately disappeared following cessation of throwing activities (i.e., unilateral dominant PA) [12]. The latter study is particularly convincing because the use of a within-subject controlled study design minimizes the influence of selection bias, with the unilateral upper extremity loading and adaptation associated with overhand throwing enabling the non-throwing arm to serve as an internal control site for inherited and other systemic traits.

Conventional Imaging Does Not Adequately Determine the Skeletal Benefits of Exercise

The ultimate loss of the bone mass seen once PA ceases makes evolutional sense considering humans have evolved for endurance [43], and it is not energy efficient for the skeleton to maintain its mass in excess of prevailing needs. It also suggests that skeletal changes generated by PA when young do not persist into adulthood where they may influence osteoporotic fracture risk. However, the latter conclusion is based on studies that used dual-energy x-ray absorptiometry (DXA) to assess bone status.

DXA is the "gold standard" in the clinical assessment of bone health and provides a picture of overall bone status; however, it has limitations in assessing bone strength and fracture risk. Considerable overlap in DXA-derived measures have been found between people who fracture and those who do not [44], and DXA-derived measures explain only a fraction of the observed reduction in the risk for fracture associated with osteoporosis drug therapies [45]. Thus, other factors beyond DXA-derived bone mass contribute to fracture risk.

As with any load-bearing structure, the strength of a bone is dependent not only upon how much material mass is present (i.e., quantity) but also the inherent properties of the material and how it is positioned (i.e., quality). DXA does not provide an adequate measure of bone structure as it provides a planar measurement with low-spatial resolution. These features allow DXA to provide a two-dimensional areal analysis of the bone; however, this areal analysis can lead to size-related artifacts when compared to a true three-dimensional analysis (Fig. 4.1) [46]. As DXA does not adequately assess bone structure, it is particularly limited when evaluating bone changes or their maintenance, induced by the mechanical loading associated with PA. Mechanical loading predominantly influences bone structure rather than mass to improve bone strength.

Fig. 4.1 (continued) strength (because of equivalent BMC) or that bone I is stronger (because of greater aBMD). (**c**) Bone II is bigger than bone I, as evident by its greater periosteal circumference (3.14 cm vs. 2.89 cm) and total cross-sectional area (0.78 cm^2 vs. 0.66 cm^2). Despite both bones having the same cortical area and BMC, the material in II is distributed further from the mechanical axes, as evident by its greater area moment of inertia (412.8 mm^4 vs. 320.4 mm^4). This results in bone II possessing 29% greater resistance to bending than that of bone I purely because of a difference in structure rather than mass (Reprinted from Warden and Fuchs [46]. With permission from Taylor and Francis Group, LLC)

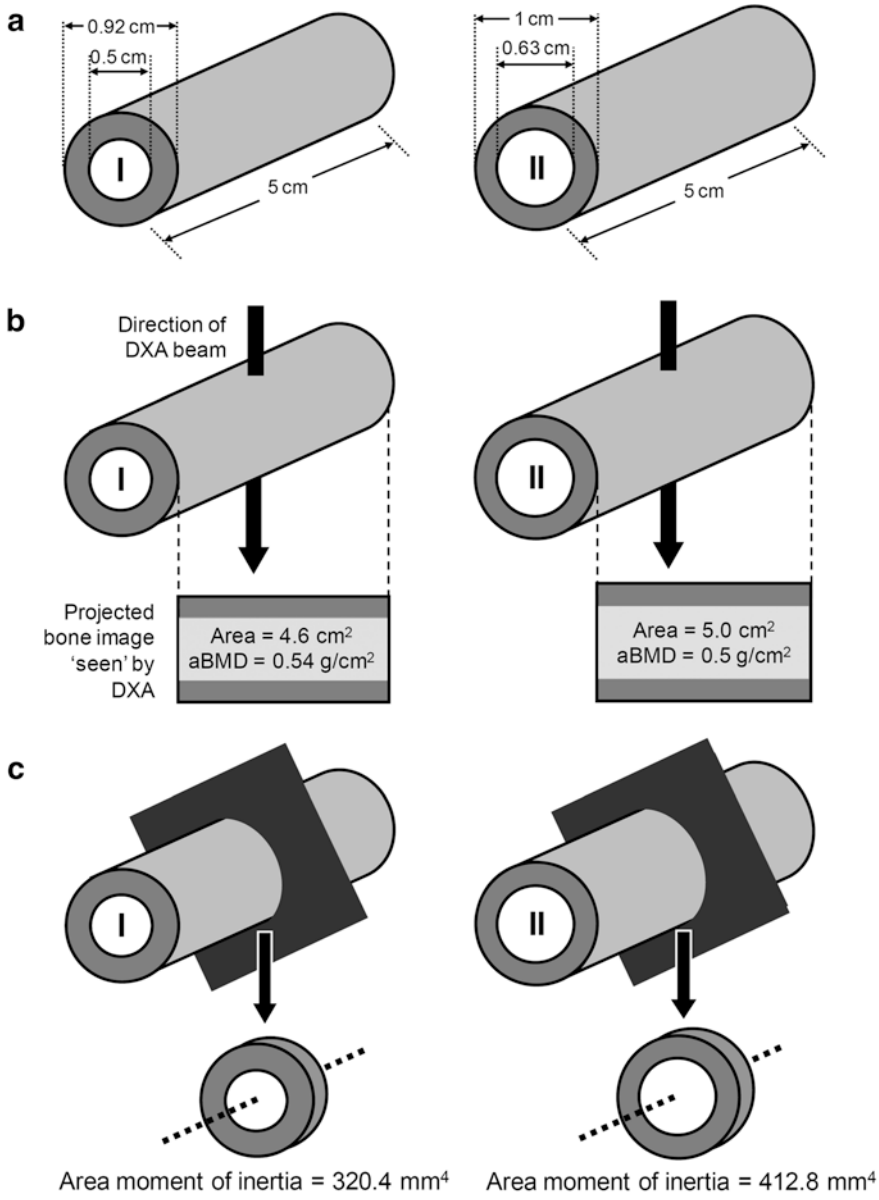


Fig. 4.1 Schematic illustration of the limitation of dual-energy x-ray absorptiometry (DXA) measures of bone and the influence of structural properties on bone strength. (**a**) Two bones (I and II) have the same mass (bone mineral content [BMC] = 2.5 g), volumetric bone mineral density (BMD) (1063 mg/cm^3), and cortical area (0.47 cm^2). The only difference between the bones is their structure, with bone II being larger. (**b**) DXA assessment would indicate that the bones have equivalent BMC (2.5 g) and that bone I has a higher areal BMD (aBMD). The latter results from bone I having a smaller projected bone area on DXA and DXA-derived BMD being derived as BMC divided by projected bone area. Thus, it may be concluded these two bones have equivalent

Physical Activity During Growth Encourages Structural Optimization

PA during growth adds extra material to loaded sites to effectively increase the quantity of bone present; however, mechanical loading associated with PA generates disproportionate increases in bone strength. For instance, studies in animal models have demonstrated that very small (<10%) changes in bone mass generated via mechanical loading result in very large (>60%) increases in skeletal mechanical properties [47, 48]. The disparate increase in strength relative to gain in mass results from structural optimization due to site-specific deposition of new bone tissue to regions where mechanical demands are greatest.

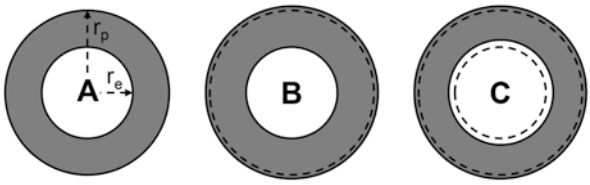
Most long bones are curved and bend and twist when loaded. During these motions, the greatest tissue stresses and strains occur in the regions furthest from the axes around which the bone is bending and/or twisting. This corresponds with the outer periosteal surface of the bone. Site-specific deposition of new bone on the outer periosteal surface leads to disproportionate increases in strength for the gain in mass as strength is more influenced by periosteal rather than endocortical surface changes (Fig. 4.2).

PA-induced structural optimization of bone by site-specific deposition of new material to the periosteal surface has been confirmed in clinical populations, with PA during adolescence causing new bone to be preferentially laid down on the outer periosteal surface of loaded bones [28, 49, 50]. Overall, bone strength changes in studies of the skeletal benefits of PA during adolescence have been reported to be mostly accompanied by gains in bone structure rather than mass [51].

Physical Activity-Induced Structural Optimization Lasts Lifelong

The surface-specific accrual of new bone is functionally important as the disproportionate increase in bone strength for the gain in mass helps the skeleton meet the dual needs of being strong to resist injury but lightweight to permit energy efficient locomotion. Importantly in terms of the lifelong skeletal benefits of PA during adolescence, specific mechanisms exist for PA-induced structural benefits to remain intact until senescence where they may have anti-fracture benefits even in the absence of persistent bone mass benefits [52].

PA during adolescence and age-related bone loss has contrasting surface-specific effects on bone. In contrast to the PA-enhanced periosteal bone formation during adolescence, age-related cortical bone loss is principally from the inner endocortical region and is mediated by intracortical remodeling within the cortex adjacent to the medullary cavity (Fig. 4.3a) [53]. The remodeling thins the cortex from within by forming cavities that coalesce and leave cortical remnants that look similar to trabeculae (a process referred to as cortical trabecularization). During aging, there is progressive bone apposition on the outer periosteal surface which causes the cross-sectional dimensions of the bone to ever increase [54]. However, the circumferential periosteal gain of tissue is unable to sustain bone mass as it occurs at a



Bone property	A	B	C
Periosteal radius (r_p)	1.00	1.05	1.05
Endosteal radius (r_e)	1.00	1.00	1.15
Bone mineral content	1.00	1.15	1.00
Polar moment of inertia	1.00	1.24	1.16

Fig. 4.2 Physical activity when young induces site-specific deposition of new bone on the outer periosteal surface leading to disproportionate increases in strength for the gain in mass. (**a**) The polar moment of inertia (i.e., strength) of a bone is proportional to the radii of its outer periosteal (r_p) and inner endocortical (r_e) surfaces according to the relationship $\pi(r_p^4 - r_e^4)/2$. This relationship illustrates that periosteal surface changes have a greater influence on strength than changes on the endocortical surface. (**b**) For example, a 5% increase in r_p (equating to a 15% increase in bone mineral content [i.e., mass]) results in a disproportionate 24% increase in strength, assuming constant bone material properties (i.e., volumetric bone mineral density) and an initial r_p-to-r_e ratio of 1.8. (**c**) If the same mass of bone added to the periosteal surface was simultaneously removed from the endocortical surface, r_e would increase by 15%, but the bone would still be 16% stronger than the bone with same mass in (**a**) because of its greater size (i.e., 5% greater r_p). Broken lines in (**b**) and (**c**) indicate the original bone surfaces in (**a**)

lesser rate than the intracortical bone loss, particularly during the menopausal transition. The net result is progressive thinning of the cortical shell and weakening of the skeleton during aging. As PA during growth primarily encourages new bone to be added to the outer periosteal surface and aging is not associated with loss of bone from this surface, the enhanced structure induced by PA during growth has the potential to remain intact and to have anti-fracture properties later in life (Fig. 4.3b).

The lifelong sustainability of the structural benefits of PA on the skeleton was initially observed in animal models [55–57]. Bones adapted to external mechanical loading when the animals were young lost their bone mass benefits when assessed during senescence; however, there was no loss of the bone size (total cross-sectional area) benefits. Destructive mechanical tests confirmed that the enhanced structure of the previously externally loaded bones contributed to greater resistance to fracture, despite the loss of the bone mass benefits.

It is valid to question the translatability of the animal study findings to humans as rodents rarely experience intracortical remodeling, the principal mechanism for age-related bone loss in humans. To explore whether the same phenomenon occurs in humans, we compared throwing-to-non-throwing arm differences in former professional baseball players to dominant-to-nondominant arm differences in control subjects. In addition to reducing the influence of selection bias (as indicated earlier), the study of baseball players reduces secular variations in PA levels, as individuals who reached this level of professional baseball typically threw with high volume from a young age, with throwing being the primary unilateral dominant training modality. Another distinct advantage of studying former professional players is that

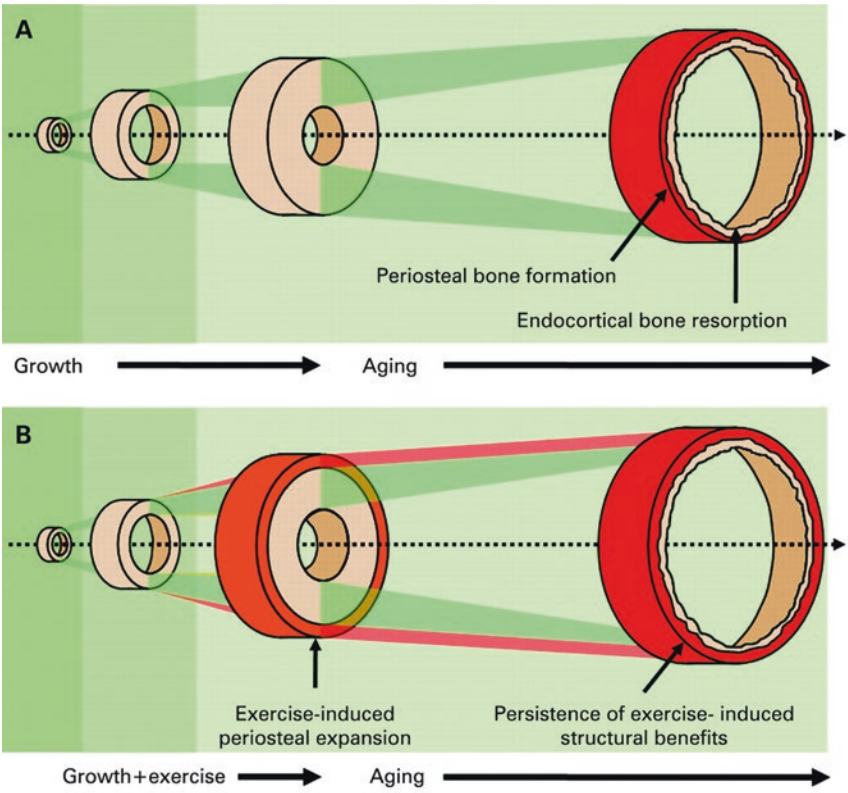


Fig. 4.3 Bone structural changes associated with aging and exercise. (**a**) Bone loss during aging occurs primarily via bone resorption on the endocortical surface. There is concomitant bone formation on the periosteal surface, which helps to maintain bone structure, but this is insufficient to maintain bone mass. (**b**) Exercise during growth facilitates periosteal bone formation, which optimizes bone structure. As bone loss during aging occurs from the inside out, the enhanced structure induced by exercise during growth has the potential to remain intact irrespective of age-related changes in bone mass (Reprinted from Warden and Fuchs [52]. With permission from BMJ Publishing Group Ltd.)

they often retire completely from throwing activities once they cease professional play, enabling the skeletal benefits of unilateral dominant PA to be explored long-term following return to habitual loading. By comparing throwing-to-non-throwing arm differences in throwing athletes to dominant-to-nondominant arm differences in age-matched controls, the skeletal benefits of unilateral dominant PA can also be isolated from differences due to the elevated habitual unilateral loading associated with simple arm dominance.

As indicated earlier, the bone mass benefits of unilateral upper extremity loading associated with overhand throwing ultimately disappeared following cessation of professional play (Fig. 4.4b). The progressive and eventual loss of the bone mass benefit resulted from accelerated age-related bone loss (medullary expansion and

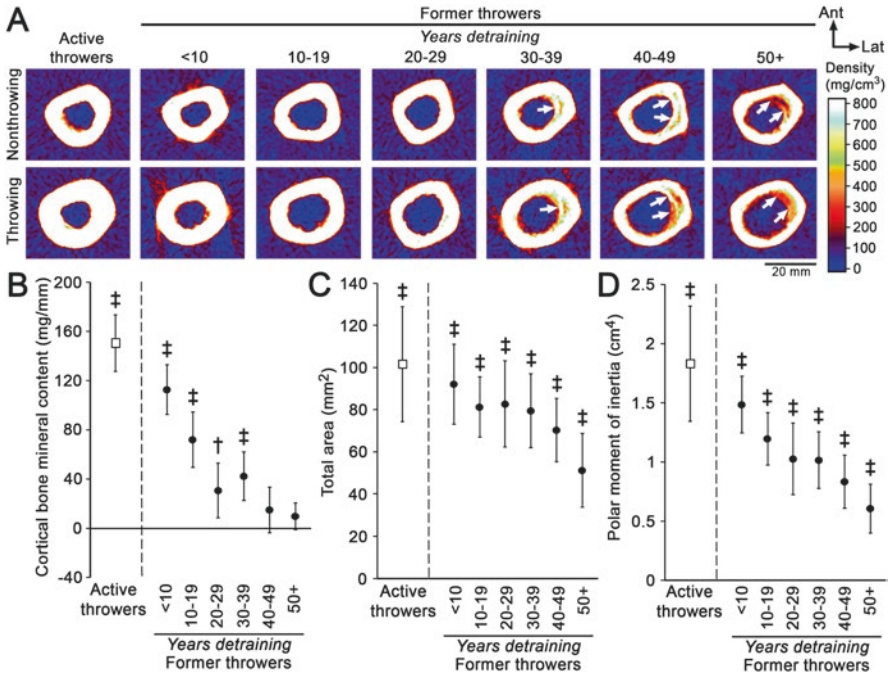


Fig. 4.4 Exercise when young had lifelong benefits on cortical bone size and strength, but not mass. (**a**) Quantitative-computed tomography images of the midshaft humerus in representative former throwers showing accelerated medullary expansion and intracortical trabecularization (arrows) in the throwing arm with increasing years detraining but maintenance of exercise effects on overall bone size. The graphs show loss of the throwing effect when young on (**b**) cortical bone mineral content and partial maintenance of the throwing effect on (**c**) total area [bone size] and (**d**) density-weighted polar moment of inertia [bone strength]. Data show mean difference and 95% CI between the throwing-to-non-throwing arm in active and former throwers normalized to dominant-to-nondominant differences in controls. 95%CIs greater than 0% indicate greater throwing-to-non-throwing arm difference in throwers than dominant-to-nondominant arm differences in controls ($^{\dagger}P < 0.01$ and $^{\ddagger}P < 0.001$, unpaired t-test) (Reprinted from Warden et al. [12]. Copyright [2014] National Academy of Sciences)

cortex trabecularization) (Fig. 4.4a). In contrast, over half of the bone total cross-sectional area/size and one-third of the bone strength benefits of throwing-related PA persisted lifelong (for 50+ years after unilateral dominant PA completion and into the ninth decade of life) (Fig. 4.4c, d). These data indicate that the old adage of "use it or lose it" is not entirely applicable to the skeleton and that PA should be encouraged when young for lifelong bone health, with the focus being optimization of bone size and strength as opposed to the current paradigm of increasing mass.

Section Summary

1. The period up to and including the pubertal growth period represents a "window of opportunity" to take advantage of the skeletal benefits of PA.
2. PA during adolescence increases bone mass, size, and estimated strength.
3. The increase in bone size contributes to a disproportionate increase in estimated bone strength relative to the gain in bone mass.
4. The bone mass benefits of PA completed when young are progressively lost in the absence of ongoing elevated PA during aging.
5. Some of the bone size and strength benefits of PA completed when young are maintained lifelong.
6. PA when young should be encouraged to enhance bone size and strength, as opposed to the current paradigm of increasing peak bone mass.

Designing Physical Activities to Enhance Bone Adaptation

Mechanotransduction and Osteocytes

In order to design activities that promote structural optimization of the skeleton when young, it is important to understand how bone tissue responds to mechanical loads and the features of the mechanical stimulus that promote adaptation. The precise mechanisms underlying skeletal adaptation to PA-associated mechanical stimuli at the cellular and molecular levels remain to be fully elucidated; however, it is accepted that it involves mechanotransduction [58]. Mechanotransduction refers to the conversion of a biophysical force into a cellular and molecular response, which results in subsequent tissue adaptation.

Mechanotransduction requires a mechanical signal that is transmitted to the cellular level and cellular machinery to sense the signal. Muscles generate large forces on the skeleton as they work to resist gravity and produce motion during PA [59]. Muscle and gravitational generated forces combine to cause fluid flow within the bone matrix which triggers the adaptive response by bone cells [60, 61].

Bone is a porous tissue consisting of a network of lacunae/spaces interconnected by an elaborate network of tunnels called canaliculi. The lacunocanalicular network houses an abundant number of osteocytes and their dendritic processes, with the latter connecting to adjacent osteocytes and bone surface cells to form a network capable of transmitting intercellular messages from deep within the bone matrix. Surrounding the cell bodies and processes is interstitial fluid which has a baseline pressure and flow due to extravascular pressure. Deformation of a bone as a result of an applied force causes intramedullary pressure to increase and push interstitial fluid from areas of high (matrix compression) to low (matrix tension) pressure within the lacunocanalicular network. The fluid shear stresses sensed by the osteocytes is converted into a biochemical response that is then transmitted to effector cells (osteoblasts and osteoclasts) on the bone surface to bring about an adaptive response [62].

Bone Adapts Better to Dynamic Rather than Static Loads

Using the knowledge of fluid flow and bone cell response to mechanical stimuli, it is possible to predict what type of physical activities bone best responds and adapts to. As the mechanotransduction process requires active fluid movement through the lacunocanalicular network, bone responds better to dynamically applied loads rather than loads of the same magnitude that are held statically [63, 64]. Applying a static load causes fluid to shift during load application; however, fluid movement and its stimulation of mechanosensitive cells cease once the peak load is reached and held. In contrast, cyclically applying load to the same magnitude causes fluid to shift in one direction during each load application and relax and flow in the reverse direction during each load removal. The result is the introduction of repeat stimuli at the cellular level and a potentially greater adaptive response.

Bone Adaptation Increases with Increasing Load Magnitude

Bone cells do not respond to all applied loads. In order for mechanosensitive cells to respond and initiate an adaptive response, fluid flow needs to be elevated a certain amount compared to the usual baseline flow within the lacunocanalicular network. This means that there is a certain load threshold above which bone cells sense the presence of a stimulus to which they subsequently respond [65, 66]. With increasing load magnitude, and subsequent fluid flow, beyond the threshold level, there is a greater adaptive response. Thus, activities which introduce loads of greater magnitude to the skeleton have the potential to induce greater adaptation.

Bone Adaptation Increases with Increasing Loading Rate

Bone's adaptive response to loading is also influenced by how fast loads are introduced [67–69]. Loads introduced at a faster rate cause more rapid fluid flow within the lacunocanalicular network and a greater stimulus to mechanosensitive cells. Thus, activities which introduce loads over a short period of time induce greater adaptation than if the same load magnitudes are introduced more slowly. The net result is that the threshold for an adaptive response to loading is determined by the product of both loading magnitude and rate. Increasing the speed or rate at which a load is introduced reduces the load magnitude required to surpass the threshold for a bone adaptive response.

Bone Adaptation Is Enhanced with Novel Mechanical Loading

The identification of threshold-related bone adaptation to mechanical stimuli led some to suggest that a negative feedback loop (referred to as Frost's mechanostat theory) exists where bone is maintained such that everyday stimuli fall between

two effective levels [70]. Mineral homeostasis was suggested when stimuli fell within the "physiological window" between the two loads, whereas loads below and above the window were suggested to result in net mineral loss and gain, respectively [70, 71].

Frost's mechanostat theory provided an important advance in understanding bone adaptation to loading, yet it is not without limitations [72, 73]. In particular, the theory assumed bone cells were somehow preprogramed with a set threshold for a skeletal response to mechanical loading. However, the threshold must vary both between and within bones; otherwise relatively non-loaded sites (such as the cranium) and regions (such as near bending axes where tissue loads are low) would constantly be losing bone. Such loss of bone tissue does not occur because bone cell mechanosensitivity is plastic and cells accommodate to their usual environment.

Plasticity forms the foundation of the cellular accommodation theory which argues that the threshold above which a mechanical signal elicits a cellular response is not a set value and is rather the product of local loading history [73]. The theory assumes that when the threshold is surpassed the mechanosensory cells gradually accommodate or get used to the new state. The net result is that the bone response is proportional to the "error" or difference between the new load and an ever-changing threshold [74]. This means that adaptation to mechanical loading is greatest when loads differ most from usual loads and that it takes a greater stimulus to activate cells that are routinely exposed to higher loads because they have accommodated and their threshold to respond is elevated. Evidence to support the cellular accommodation theory has been provided experimentally with bone formation in a mechanical loading study closely resembling the theory's predicted results, but not those predicted by Frost's mechanostat theory [75, 76].

Bone Adaptation Is Greatest with Brief, Yet Often Mechanical Loading

The accommodation of bone cells to mechanical stimuli occurs on different time scales from seconds to months. On the short end of the time scale, the mechanosensing mechanism in bone cells desensitizes to repeated cycles of loading during a bout of PA, and the bone formation response tends to fade as loading duration increases. The decline in adaptation fits a logarithmic relationship such that after only 20 back-to-back loading cycles bone has lost more than 95% of its mechanosensitivity and extending the duration of loading does not yield proportional bone adaptation [77]. This indicates that PA programs targeting bone health need not be long to induce maximal adaptation.

The mechanosensing mechanism in bone cells gradually resensitizes to mechanical stimuli so that bone cells can respond to future bouts of PA. The amount of rest time required between loading bouts depends on the nature of the loading stimulus. For instance, including a few seconds, rest between consecutive loading cycles can result in greater bone adaptation than if the same stimulus is introduced with no rests in back-to-back cycles [78, 79]. This implies that activities incorporating a

short break between repeat loading cycles (such as plyometrics with 5–10 s break between successive jumps) will induce greater adaptation than activities with more continuous jump loading cycles (such as repetitive jumping, like jump rope).

Similarly, resting for a few hours after a desensitizing bout of PA enables the system to regain responsiveness and greater adaptation to be induced. Animal model data suggests that resting for 4–8 h between repeat bouts of a desensitizing mechanical stimulus is sufficient to restore 95–100% of mechanosensitivity and causes more bone adaptation than if the same stimulus is introduced all at once in a single bout [47, 80, 81]. Thus, breaking up PA into multiple bouts throughout the day has the potential to induce more bone adaptation than if the same activity is performed all at once one time per day.

Finally, continuous loading over a period of weeks to months causes resident bone cells to desensitize as they get progressively "bored" with persistent stimulation. Introducing a "rest" phase or period every few weeks or months can promote bone cell resensitization by allowing the cells to readjust back to a lower loading stimulus. Rest does not require a period of physical inactivity but can consist of activities that load alternate skeletal sites or the performance of alternate conditioning activities (such as cycling and swimming). When elevated loading is reintroduced after the rest phase, the difference between the resting loading stimulus and the elevated PA loading stimulus is now larger than if the elevated PA loading stimulus were introduced continuously. The net result is greater bone adaptation than if loading were continued without the incorporation of a rest period [82].

Bone Adaptation Is Highly Site-Specific

The bone adaptive response to loading is highly site-specific with elevated fluid flow and subsequent adaptation only occurring in the bones that were exposed to elevated loading. This has been confirmed in individuals playing sports exposing their dominant upper extremity to elevated mechanical loading, with the loaded bones in the dominant arm demonstrating considerable adaptation compared to the bones in the contralateral nondominant arm [12, 83–86]. However, the site-specific nature of bone adaptation to mechanical loading can be localized further than to the individual bone level. As long bones twist and bend when axially loaded, different regions within the bone cross-section are exposed to different levels of loading and subsequent fluid flow. The net result is that bone adaptation to loading has directionality, with mass being added to strengthen the bone in the direction of loading but less so in alternate directions. The clinical implication is that in order to strengthen the skeleton to a specific fracture, the bone in question needs to be loaded and adapted in the direction that strength is required during an injurious event. This has become an issue at the proximal femur where age-related osteoporotic fractures often occur as a result of a sideways fall onto the greater trochanter and overloading of the superolateral cortex of the femoral neck, whereas weight-bearing PA predominantly induces adaptation within the load-bearing inferomedial femoral neck [87].

Clinical Implications of Mechanical Loading Features Influencing Bone Adaptation

Using the knowledge of the loading characteristics conducive to bone adaptation enables the development of appropriate PA aimed at optimizing skeletal health [88, 89]. Current PA guidelines in the United States recommend adolescents complete 1 h of moderate-to-vigorous PA each day, which should include muscle- and bone-strengthening activities at least 3 days per week [90, 91]. Moderate and vigorous PA refers to activities with energy expenditures of 3.0–5.9 METs and >6 METs, respectively [90, 92]. While it is clear that adolescents participating in greater amounts of moderate-to-vigorous PA have greater bone size than those with less exposure, it is also clear that not all moderate-to-vigorous PA is equally beneficial to the skeleton [51]. For example, participating in swimming offers negligible skeletal benefit despite being a vigorous PA (9.8 METs; fast freestyle lap swimming), whereas participating in gymnastics is highly osteogenic despite only representing a moderate PA (3.8 METs) [93–95].

The reason for the contrasting skeletal benefits of different types of PA relates to the skeletal loading associated with each activity and the mechanical stimuli to which the bone best responds and adapts. The preceding section indicates that bone adaptation to PA is optimal when a specific skeletal site is exposed to novel, high-magnitude, and rapid loading. This means that activities requiring substantial muscle power are the most osteogenic, with muscle power being the ability to generate maximal muscle force in as short a time as possible. Using this idea, several investigators have developed scales or indexes to quantify the osteogenic or bone formation potential of different activities. For instance, using peak ground reaction forces and rates of force development to estimate lower extremity bone loading, Weeks and Beck [96] developed effective load ratings for common sports and activities (Fig. 4.5). Gymnastics presented the greatest effective bone loading, whereas swimming presented a negligible load. These data are consistent with clinical data demonstrating adolescent gymnasts have bone properties well above age and maturity expected normal values, while adolescent swimmers have equivalent bone properties to sedentary individuals [93, 97].

The bone loading estimates developed by Weeks and Beck [96] are generally consistent with actual bone loading data acquired by invasively attaching measuring devices directly to bone surfaces and with bone adaptation data. For instance, we know from studies attaching gauges to the bone surface that loading magnitudes and rates are greater in sprinting than jogging, with jogging in turn being greater than walking [98]. Similarly, from bone health studies we know that sprinters have greater bone mass than distance runners who in turn have greater bone mass than non-runners [99]. By breaking down the activities in Fig. 4.5 into component parts, it is clear that activities that are weight bearing and incorporate some form of impact loading have the greatest osteogenic potential. In particular, the activities with the highest effective load ratings all require some degree of intermittent, explosive jumping and/or sprinting with rapid changes in direction.

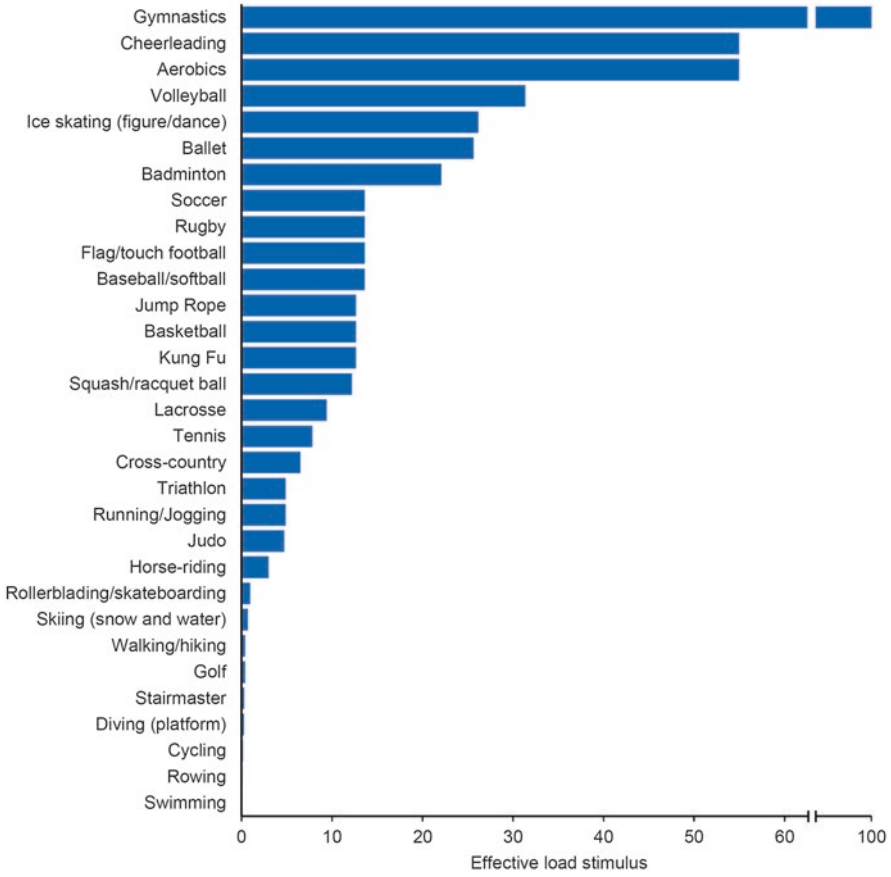


Fig. 4.5 Lower extremity effective load ratings for common physical activities, with higher load ratings being representative of a greater bone adaptive stimulus. Effective load ratings were estimated from the magnitude and rate of ground reaction force generation during representative actions (or similar actions when reaction forces could not be directly measured) (Based on data from Weeks and Beck [96])

Jumping activities and exercises have clearly been shown to the osteogenic during adolescence in randomized controlled trials [100–103]. They have the advantage over other forms of loading (such as running) of introducing higher magnitudes of load at higher rates of introduction and introducing the loads with variable periods of rest between repeat loading cycles. The latter takes into account cellular accommodation, with the short spacing of cycles and high number of repetitions associated with endurance activities (such as distance running) not providing an optimal osteogenic stimulus due to desensitization of the mechanosensing mechanism.

Activities targeting bone should be performed multiple times per week as the bone best responds to short bouts of loading rather one single long bout, with each

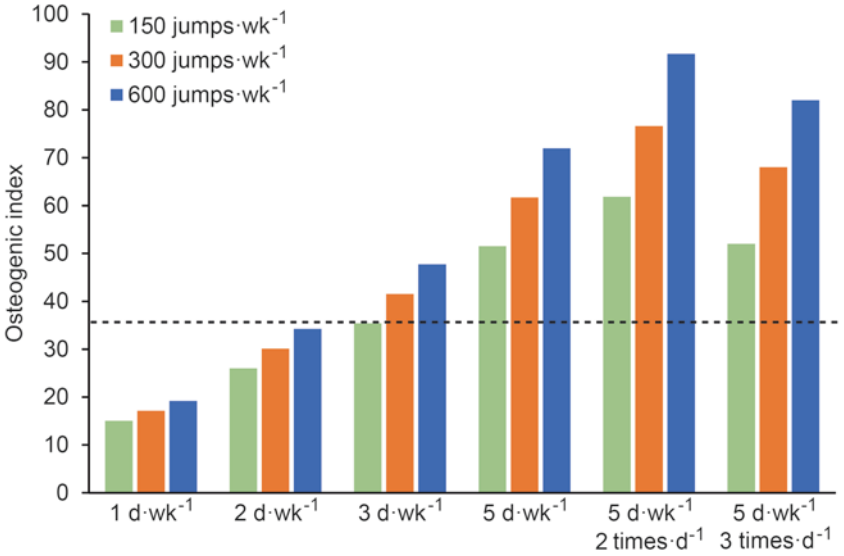


Fig. 4.6 Physical activities targeting the skeleton have the greatest efficacy when introduced, in short, frequent bouts. For the same number of jump repetitions per week, the osteogenic index (i.e., bone strengthening potential) for a mild-impact loading activity (i.e., jumping with three times body weight) is increased over threefold if repetitions are spread over 5 days rather all performed on 1 day. Separating the repetitions further into two bouts per day over 5 days results in a further 25% improvement in the osteogenic index compared to if the repetitions where performed in longer single bouts per day over 5 days. The dashed line indicates the osteogenic index for walking for 20 min per day, 5 days per week (Reprinted from Turner and Robling [88]. With permission from Wolters Kluwer Health, Inc.)

individual bout recruiting and stimulating a new group of bone cells that bring about adaptation [104]. To guide the dosing of PA specifically targeting bone health, Turner and Robling [88] modeled bone adaptation to various numbers of bouts and cycles of a jumping activity while taking into account cellular accommodation (Fig. 4.6). Greatest improvements in bone adaptation were predicted when more PA sessions per week were added rather than lengthening the duration of individual sessions. For instance, splitting 600 jumps/wk over 5 sessions/wk (120 jumps/session) was predicted to improve the osteogenic effectiveness by over 50% compared to the same number of jumps/wk performed over only 2 sessions/wk (300 jumps/session). By further splitting the 5 sessions/wk into 2 bouts/d (60 jumps/bout), the osteogenic effectiveness was further increased and was now more than double than if the same number of jumps was performed in one bout/d, 2 sessions/wk. Clinical evidence has provided initial support for the introduction of shorter but more frequent bouts of loading. In particular, Gabel et al. [105] most recently showed that bout frequency of vigorous PA was positively associated with estimated bone strength independent of the total amount of PA performed. Similarly, we previously observed in the setting of a randomized controlled trial that three bouts of a jumping exercise per week induced significant gains in adolescent bone health, whereas

similar gains were not observed when the jumping program was performed only twice per week [100, 106].

The final points to note from the preceding discussion regarding the mechanical stimuli to which the bone best responds are that adaptation is highly site- and direction-specific and that the bone responds best to novel loads. Due to the site- and direction-specific nature of bone mechanoadaptation and the need to develop bone size and strength to resist injurious loads coming from multiple directions when older, it is important that adolescents perform activities that load fracture prone sites and in the direction/s that the bones are loaded during fracture. As the direction of loading when a fracture occurs is not particularly predictable, the consequence is a need to strengthen the skeleton in multiple directions. Thus, activities that require jumping and landing activities in different directions or running with rapid changes in direction should be encouraged, such as it occurs during basketball, volleyball, soccer, and gymnastics, to name a few.

In terms of novel loads, bone requires periods of "rest" to allow the mechanosensing mechanism to readjust its threshold for a response back to a lower set point. By using a periodization approach wherein blocks of alternate forms or directions of loading are introduced, a greater osteogenic response can be achieved. This has implications for individuals participating in a year-round sports or who specialize in a single sport at a particularly young age. These individuals should be afforded "down periods" where they participate in other activities, not only for optimization of bone responses to mechanical loading but also to reduce the risk of musculoskeletal injury.

Section Summary

1. Mechanical loading causes fluid flow within bone which resident cells sense to initiate an adaptive response.
2. Activities causing greater loading and at faster rates cause more fluid flow to induce greater adaptation.
3. Loading magnitudes and rates are greatest during power-based activities, such as those requiring sprinting with rapid changes in direction and jumping and landing activities.
4. Power-based activities should be performed multiple times per day and multiple times per week and do not need to long in duration to induce adaptation (<10 min).
5. Adaptation only occurs in sites exposed to elevated loading relative to their usual loading.

How to Encourage Adolescents to Get Sufficient PA for Lifelong Bone Health

In the preceding sections, components for developing optimal PA prescriptions during adolescence to optimize lifelong bone health were introduced. Providing adolescents with the tools to understand how PA improves bone health during the critical growing years helps foster behaviors that may promote a lifelong commitment and awareness toward skeletal health. Working with individuals to meet the required PA guidelines for bone health is a team effort, with families, teachers, peers, and physicians working together. In general, activities should be developmentally appropriate, offer variety, and be enjoyable, with the goal of engaging in activities that incorporate varying bone loading activities depicted in Fig. 4.5 and performed a minimum of three times per week. Sedentary activities, such as television viewing, computer and telephone use, and inactive video games, should be discouraged and limited to <2 h per day as they are negative predictors of bone size during adolescence [107]. Below, we present a mini-vignette for a bone loading PA plan and how to engage an adolescent in activities that target the skeleton.

> *Alex is a 12-year-old boy who takes the bus to school and spends 3 hours per day on electronic devices. Alex has suffered fractures of both distal radii, and DXA assessments of bone mass revealed he has hip bone mass below normal for his age (Z-score = −1.1). Alex and his family do not participate in regular PA beyond activities of daily living; however, Alex meets daily recommend intakes for both calcium and vitamin D. Both of Alex's grandmother's suffered low-trauma proximal femur fractures.*

Despite a limited amount of time spent performing PA, engaging in some form of impact loading can offset Alex's sedentary lifestyle. For Alex, it will be important to select a variety of fun activities, working up to 60 min per day on most days of the week with the inclusion of bone loading activities. Stress that all activities performed during the day counts toward obtaining his daily PA goal. This will make attaining his goal feel more attainable. Alex can be provided an inexpensive step counter in order to monitor and motivate his performance of PA, although step counters do not provide an indication of accelerations and bone loading magnitudes or rates. Many current step counters synchronize with smartphones to provide alerts as to when it is time to stand up and move, as well as show when during the day PA and inactivity are most prolific.

In terms of bone loading activities, start by helping Alex and his family develop a list of activities that he and they find enjoyable. Compare those activities to those detailed in Fig. 4.5 in terms of their bone building potential. It will be important to engage Alex's family in the PA program so that they can work together to meet their goals and stay motivated. Strategies can be employed to encourage regular bouts of bone loading during activities of daily life, such as hopping or skipping to the bus stop, walking to school if possible and incorporating short sprints, parking further from the entrance of stores, and jumping or hopping over all cracks in the sidewalk, performing jumping in all directions during every advertisement break while watching television and running upstairs rather than taking an elevator.

Alex and his family can be encouraged to go the neighborhood park or field to climb and swing from bars for upper extremity musculoskeletal health and jump on and off play structures. Mini-obstacle courses or challenges can be developed whereby the family can "beat-the-clock" while running, jumping, and hanging to complete the course. Alex can be encouraged to explore local age- and ability-matched team sports to be exposed to a variety of multidirectional skeletal loading, such as soccer, basketball, and volleyball. Alternatively, these activities can be performed recreationally with friends or family. Similarly, participation in more individual sports such as track and field or one or more of the dance genres can be explored.

Overall Summary

The performance of appropriate PA during adolescence is important for lifelong bone health. The current paradigm is to perform PA during growth to increase peak bone mass; however, recent data suggests that its actually PA-induced optimization of skeletal structure that has lifelong consequences on bone strength. A combination of clinical and animal model-based studies provide insight into the types of PA to which the bone best adapts. Activities typically involve power-based movements, such as sprinting with rapid changes in direction and jumping and landing maneuvers. The movements do not need to be performed for long due to desensitization of the mechanosensory mechanism but should be performed multiple times each week and build up to multiple times per day. As only loaded bones and regions within those bones adapt, it is important to introduce loading in a variety of directions.

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The Bone Health History and Physical Examination in Adolescents

5

Alison M. Boyce

Introduction

The bone is a complex organ that may be impacted by a broad spectrum of biological, hormonal, and behavioral processes. The history and physical examination (H&P) is the clinician's best and most accessible tool to evaluate bone health in adolescents. While core elements of the H&P remain consistent across all patients, a bone-focused evaluation includes specific considerations to target the wide range of factors affecting skeletal health.

The primary objective in the bone-focused H&P is to identify patients with underlying skeletal pathology. Adolescent bone disorders fall broadly into two categories: (1) primary bone diseases, arising from congenital disorders that affect bone structure, and (2) secondary, or acquired bone diseases, which develop as a consequence of disorders affecting other systems [1]. Therefore, the bone-focused H&P must cast a wide net to identify a potentially broad array of pathology, ranging from primary skeletal dysplasias to nutritional disorders to underlying systemic diseases. Patients may have multiple coexisting risk factors, and clinicians must understand how these elements interact to affect the bone and overall health of the adolescent patient. The bone-focused H&P also provides an opportunity to promote skeletal health in adolescents. By evaluating modifiable lifestyle factors, the clinician can identify opportunities to optimize bone health and counsel patients on health-related behaviors.

This chapter will provide guidance to the primary care clinician in evaluating adolescents with known or suspected bone disorders, with an emphasis on recognizing features that contribute to skeletal disease and identifying opportunities to promote bone health.

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Fractures

Jackson is an 18-year-old soccer player who has sustained two metatarsal fractures, a left radius fracture, and a tibial stress reaction in his lifetime. What more do you need to know about these fractures to determine if they are "normal" or not?

Clinicians are often prompted to evaluate bone health in adolescents who present with fractures. A detailed fracture history is important to distinguish typical traumatic fractures, which occur commonly in adolescents, from fractures that arise due to skeletal fragility. This should begin by determining a patient's total number of lifetime fractures and the ages at which each fracture occurred. Asking the patient to describe the mechanism of injury may reveal whether the fracture is out of proportion to the degree of trauma. For example, vertebral compression fractures and femur fractures should be considered pathological in any child or adolescent outside of a severely traumatic event, such as a motor vehicle accident or fall from greater than standing height. Conversely, the small bones of the hands and feet are often injured from relatively minor trauma such as trips and falls from standing height, making them an unreliable indicator of bone fragility. A detailed history should also include how the fracture was diagnosed and treated. Patients and families may report multiple fractures treated with short-term immobilization; however, review of the radiographs may reveal that some injuries were sprains treated with splinting. Recurrent or non-healing stress fractures may indicate overexercise and/or poor bone health in athletes. Non-accidental trauma should always be considered in patients with repeated injuries, fractures that appear inconsistent with the reported history, and fractures in immobile patients.

Growth and Development

Growth is an important indicator of overall health, and both primary and acquired skeletal disorders may lead to abnormalities that can be identified through careful assessment of the growth curve (Fig. 5.1). Growth velocity is frequently affected in connective tissue disorders and other skeletal dysplasias. This may result in growth deceleration, leading to short stature (Fig 5.1a), or growth acceleration with resulting tall stature (Fig 5.1b) [2]. Systemic disorders typically lead to growth deceleration; this may be an early manifestation with onset even prior to the development of clinical symptoms (Fig 5.1c) [3–5]. Nutrition is a strong determinant of growth, with obesity characteristically leading to linear growth acceleration and inadequate caloric intake resulting in slowed linear growth [6, 7]. Linear growth in the absence of underlying pathology is determined primarily by genetic factors, and it is, therefore, important to consider parents' heights and ethnic/cultural norms when interpreting a growth curve [8]. Parental and familial growth patterns, such as early or delayed puberty, may also provide helpful information.

Obtaining a developmental history may provide clues to the presence of underlying disorders. Pregnancy history, birth history, and developmental milestones through

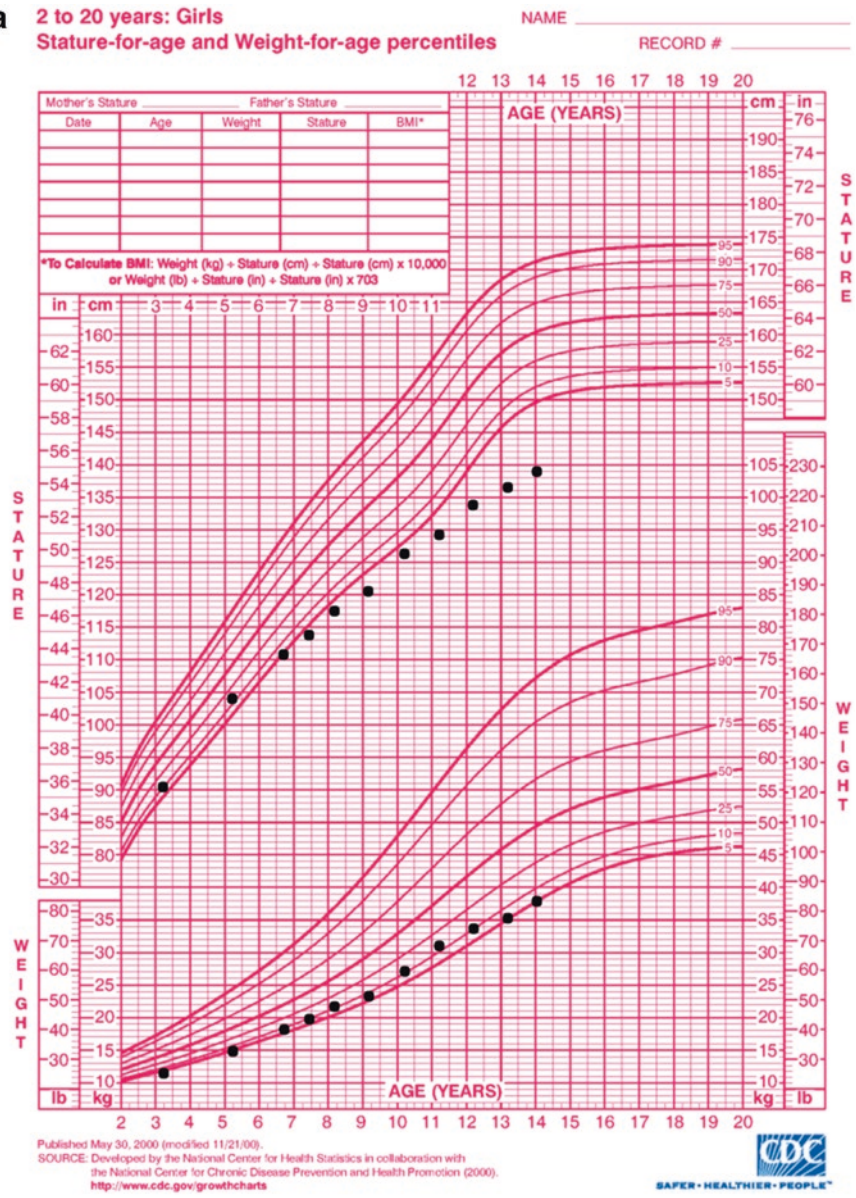
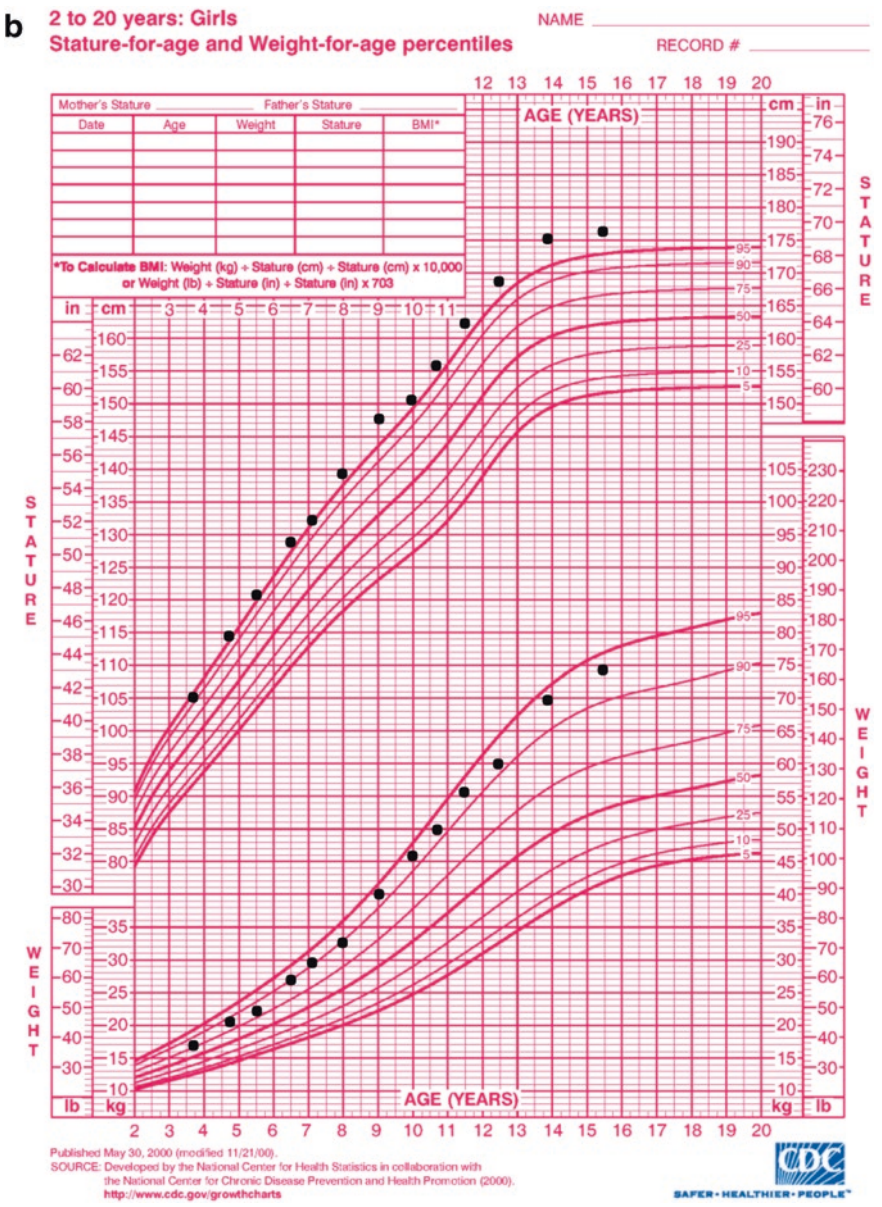


Fig. 5.1 Representative growth charts in skeletal disorders. (**a**) An adolescent with osteogenesis imperfecta type 1 shows typical linear growth deceleration, which occurs in proportion to weight. (**b**) A patient with Marfan syndrome shows tall stature with consistent linear growth velocity. (**c**) Following a period of normal growth in early childhood, an adolescent with Crohn disease develops deceleration in weight, which proceeds to a subsequent deceleration in linear growth



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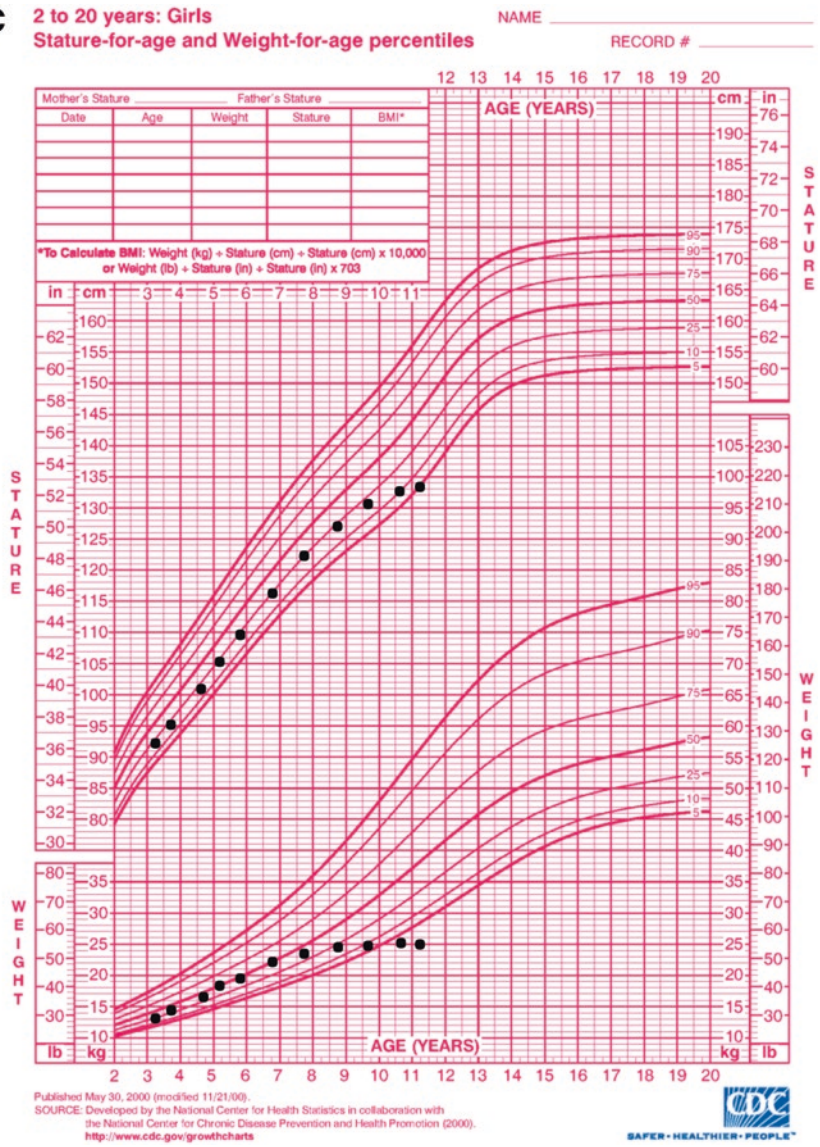

Fig. 5.1 (continued)

infancy and early childhood should be assessed. School performance and social functioning provide important insights into the development of school-aged children and adolescents. Growth and development are greatly impacted by both physical and psychosocial stressors; clinicians should, therefore, inquire about childhood illnesses, hospitalizations, and medications and take a detailed social history.

The physical examination should include assessment for skeletal dysplasias. These disorders affect the sizes and shapes of growing bones and may result in disproportionate growth between body segments [9]. Anthropometric parameters of interest include head circumference [10], arm span [11], and upper to lower segment ratios [12]. Fingers may be abnormal in length (arachnodactyly or brachydactyly). Patients may present with subtle or overt craniofacial abnormalities, including facial dysmorphism, blue- or gray-colored sclera, a high-arched palate, and dental abnormalities [13]. Soft tissue manifestations of primary bone disorders may include joint hyperextensibility, reduced muscle tone, soft and hyperelastic skin, chest wall deformities such as pectus excavatum or carinatum, and pes planus (flat feet) [13]. The Beighton score is a generalized measure of hypermobility that may be helpful in evaluating patients with these findings [14]. Deformities of the trunk and long bones may result from primary bone disorders or from longstanding metabolic abnormalities affecting bone strength and integrity. These include scoliosis, bowing of the long bones, and widening of the wrists and knees (the latter frequently seen in rickets).

Pubertal development is an important determinant of bone density. Skeletal mass approximately doubles between the onset of puberty and young adulthood, primarily due to effects of sex steroids [15–17]. Delayed puberty is, therefore, a potential risk factor for bone health in adolescents and may arise due to genetic, nutritional, or systemic factors [18]. Menstrual history is a key component of the adolescent H&P and should include age at menarche, date of last menses, cycle length, and frequency of menses. The average age at menarche is 12–13 years, and menses may occur at irregular intervals for the first 2 years due to anovulatory cycles. Menses that are delayed or consistently irregular may signal the presence of an underlying disorder, including absence of menses 3 years after thelarche, absence of menses by 15 years of age (primary amenorrhea), absence of menses for $\geq$3 months in post-menarchal girls (secondary amenorrhea), or $\leq$4 total menstrual periods in the preceding year in post-menarchal girls (oligomenorrhea). Pubertal onset in boys typically occurs between ages 9 and 14 and may also be affected by underlying disorders. The physical exam for all adolescents should include assessment of pubertal status, including Tanner staging [19, 20] (Fig. 5.2).

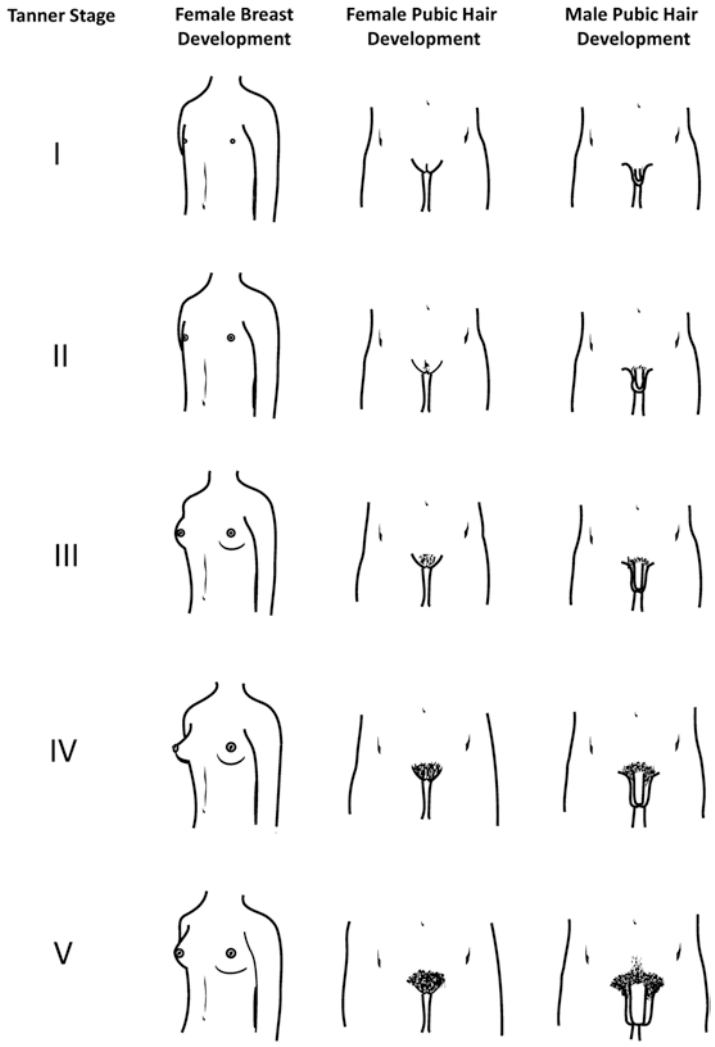

Fig. 5.2 Illustration of Tanner staging for females and males. Tanner stage 1 breast development is prepubertal with no glandular tissue and flat areolae following the contour of the chest. Tanner stage 2 breast development is characterized by formation of breast buds, which include widening of the areolae and small amounts of glandular tissue limited to the area beneath the areolae. Tanner stage 3 breast development includes elevation of the contour of the breast with extension of glandular tissue beyond the areolar border. The areolae continue to enlarge and remain in contour with the breast. In Tanner stage 4 breast development, the areolae and papillae form a secondary mound that projects above the contour of the breast. Tanner stage 5 breast development is fully mature, with the areolae returning to the contour of the breast. Tanner stage 1 is prepubertal with absent pubic hair. Tanner stage 2 is characterized by a small amount of slightly pigmented pubic hair, typically limited to the labia majora or base of the penis and scrotum. In Tanner stage 3, pubic hair becomes darker, coarser, and extends laterally in distribution. Tanner stage 4 is characterized by adult-type hair extending across the pubis but not reaching the medial thighs. Tanner stage 5 is fully mature with extension of pubic hair beyond the pubis to the inner thighs and abdomen

Nutrition

Nutritional assessment should be a routine component of the adolescent H&P, particularly when evaluating bone health. Both malnutrition and excess adiposity have been shown to be detrimental to bone health, leading to decreased bone density and increased fractures [21, 22]. Determining general nutritional status involves asking about overall caloric intake and daily eating habits. Clinicians should inquire if patients have undergone any intentional or unintentional changes in weight and if they are following any specific diets, avoiding any foods, or taking any dietary supplements. Dietary calcium and particularly dairy intake should be an area of focus, as consumption has been linked with bone density and fracture risk in children [23–25]. Vitamin D is essential to promote absorption of dietary calcium, and clinicians should assess risk factors for vitamin D deficiency, including dark skin, increased latitude, indoor sedentary behavior, and lack of vitamin D supplementation [26, 27]. Protein intake is also a nutritional determinant of bone density in adolescents [28, 29]. Clinicians should be aware of risk factors for poor nutrition, especially those that impact calcium and protein intake, such as strict veganism [30].

The physical examination focuses on identifying signs of malnutrition, nutrient deficiencies, or nutrient toxicities [31]. Body mass index should be calculated and compared to age and sex-adjusted norms. Clinicians should assess for overall body fat and muscle mass, as well as strength and tone. Signs of generalized malnutrition include sparse or dull hair, pale mucous membranes, dry skin, and brittle, ridged nails. Severe malnutrition may be associated with bradycardia, hypothermia, and orthostasis. Long-standing deficiencies in calcium and vitamin D in growing children may result in rickets, which typically presents with poor linear growth, bowing of the lower extremities, and widening at the wrists and knees.

Physical Activity

Mechanical loading is a key driver of bone mass acquisition in children and adolescents, as is expanded upon in Chap. 4 [32]. Weight-bearing exercises that generate high-intensity loading forces have been shown to enhance bone mass accrual [33, 34]. Patients with mobility impairments may have defects in bone modeling, leading to the formation of bones that are abnormally slender and prone to fracture [35]. Clinicians should be aware that even subtle impairments in children with cerebral palsy and other neuromuscular disorders may have significant detrimental effects on bone density. Periods of immobilization in otherwise mobile children, such as extended hospitalizations, illnesses, and treatments for fracture, result in increased bone resorption and decreased bone density [36]. If mobility is restored to baseline, these changes may be transient, with improvement or resolution of bone deficits [37]. The physical exam should include an overall assessment for strength, tone, and muscle bulk. Functional assessment should include observation of the patient's gait to assess coordination and patterns of weight bearing.

Excessive physical activity may lead to a state of low energy availability, resulting in decreased bone density and increased fracture risk. This may be compounded by restricted or disordered eating, which further increases the nutritional deficit. Patients who participate in activities that are affected by weight and/or appearance (such as dance, wrestling, or gymnastics) should be questioned about nutrition and restricted eating behaviors. The energy deficient state is frequently associated with hypogonadism, which contributes to the decline in bone density in these patients. Primary or secondary amenorrhea is a common presentation in adolescent girls with energy deficits, while boys may have more subtle signs of stalled or delayed puberty. These complex interactions between energy intake, expenditure, and development highlight the importance of taking a thorough history, including menstrual history and performing a pubertal exam in all adolescents at risk for poor bone health.

Mental Health

Evaluating mental health is an integral component of caring for patients of all ages. Several elements of mental health may impact on skeletal health in adolescent patients. As mentioned above, disordered eating is a risk factor for bone health. This may present with restricted intake or in episodes of overeating (bingeing) followed by compensatory purging through vomiting, use of laxatives, enemas, fasting, or exercise. Clinicians should be aware that some patients may maintain a normal body mass index despite disordered eating behaviors. Use of illicit substances, such as tobacco, alcohol, and anabolic steroids, may also be detrimental to bone density.

Review of Systems

Felicia is a 16-year-old with weight loss, abdominal pain, hematochezia, and oral ulcers. Why would you also be worried about her bones?

Because many organ systems may impact the skeleton, a thorough review of systems is an important part of the bone health H&P. This should focus particularly on identifying symptoms of potential underlying systemic disorders. Additional areas of focus are highlighted below.

The musculoskeletal evaluation should evaluate for the presence of acute and chronic injuries. Stress fractures and other injuries may be evidence of excessive exercise and/or impaired capacity for healing. Multiple joint injuries and chronic musculoskeletal pain may also be associated with some connective tissue disorders. Clinicians should inquire directly about the presence of back pain, because this may reflect spinal pathology such as vertebral compression fractures. Underlying inflammatory and arthritic disorders may present with muscle pains, joint pain, stiffness, or swelling.

Gastrointestinal disorders can have substantial effects on bone density, resulting from chronic inflammation which directly impacts skeletal turnover and bone density

or from malabsorption which may contribute to nutritional deficiencies. A detailed review of upper and lower gastrointestinal symptoms is therefore particularly important when evaluating bone health. Patients with underlying gastrointestinal diseases may develop impaired bone health even in the absence of clear gastrointestinal symptoms, which may lead to delayed or missed diagnoses [38, 39].

Additional symptoms of inflammatory disorders and other systemic disease include constitutional symptoms such as fatigue, changes in weight, appetite, weakness, fevers, and frequent infections.

Medications

Patients who take chronic medications rely on primary care clinicians to understand the interactions and systemic effects of these treatments. A growing number of medications have been recognized to impact bone health. Included below are brief summaries of those commonly encountered in adolescent patients, which should be highlighted during the bone health-focused H&P (Table 5.1).

Medications used for treatment of inflammatory disorders frequently impact bone metabolism. Long-term oral glucocorticoid use has direct inhibitory effects on osteoblasts and have been clearly demonstrated to decrease bone density and increase fracture risk, in addition to other deleterious effects on growth and metabolism [40]. Inhaled glucocorticoids have considerably less systemic availability than oral formulations; however, long-term, high-dose use has been associated with decreased bone density in children [41]. Methotrexate has deleterious effects on bone formation and resorption, and high dose regimens have been shown to negatively impact bone density [42]. It should be noted that uncontrolled chronic inflammation from any cause is highly associated with bone loss and that the therapeutic effects of these anti-inflammatory medications generally outweigh their negative effects on bone health [40].

Table 5.1 Medications that may adversely impact bone health

Medication	Common indications	Mechanism for skeletal effects
Glucocorticoids	Anti-inflammation	Decreased bone formation (long term), increased bone resorption (short term)
Medroxyprogesterone acetate (depot)	Contraception	Decreased sex steroids
Gonadotropin-releasing hormone agonists	Precocious puberty, endometriosis	Decreased sex steroids
Antiepileptic drugs	Epilepsy, neurologic disorders, psychiatric disorders	Increased vitamin D catabolism
Loop diuretics	Edema, hypertension	Urinary calcium loss
Heparin	Anti-coagulation	Decreased bone formation, increased bone resorption

Medications that inhibit sex steroid production may negatively impact bone density. Gonadotropin-releasing hormone agonists are used for treatment of precocious puberty and gynecologic conditions such as endometriosis. These medications induce a hypogonadal state which may be detrimental to bone health in adolescents with long-term use [43]. Depot formulations of medroxyprogesterone acetate are frequently used for contraception in adolescent girls and have been associated with decreased estrogen levels and bone loss [44]. In healthy girls, these effects are generally minor and insufficient to prevent use of this medication, particularly as bone loss is typically recovered after completion of therapy [44, 45]. However, in patients with altered mobility, chronic illnesses, and other risk factors for bone health, effects of these medications may be sufficient to significantly increase fracture risk. Adolescent patients whose history includes potential threats to bone health should be monitored on this contraceptive agent with caution.

Antiepileptic drugs have been associated with alterations in bone and vitamin D metabolism, leading to decreased bone density and increased fracture risk [46]. These effects may be partially related to vitamin D deficiency, making a nutritional history particularly important for these patients. The bone effects of antiepileptic drugs may be particularly detrimental in patients with associated comorbidities that impact bone health, such as neuromuscular disorders.

Multiple additional classes of medications may affect bone density, particularly in patients with chronic disease. Anticoagulants such as chronic heparin therapy have been associated with impaired bone density [47]. Loop diuretics increase urinary calcium excretion and have been associated with increased fracture risk in adults [48, 49]. Proton pump inhibitors may lead to a potential decrease in intestinal calcium absorption due to decreased acid secretion; however, clinical studies have been mixed, and at this time there is no clear association between use of these medications and impaired bone health [50].

Past Medical History

The bone-focused H&P should include standard elements such as pregnancy history, birth history, and any medical illnesses, hospitalizations, or surgeries. Clinicians should inquire about periods of immobilization or non-weight bearing and determine if they have any relationship with fractures. For example, patients may develop an additional fracture in a previously injured bone shortly after cast removal, due to decreased bone density related to immobilization. Repeated prolonged hospitalizations may contribute to low bone density in patients with chronic illnesses.

Family History

Genetic factors play an important role in determining bone density and may independently contribute to fracture risk [51–53]. Obtaining a family history should include questions about relatives with osteoporosis, osteopenia, or frequent fractures.

Family history of autoimmunity, inflammatory disorders, or gastrointestinal disease provides information about risks for underlying systemic disease. In patients with delayed or stalled puberty, clinicians should inquire about pubertal timing in parents, including maternal age of menarche and family history of menstrual disorders.

Social History

Matthew is a 14-year-old with two lifetime fractures who was noted to have below-average bone density for age by DXA. On social history you discover his family struggles with food insecurity, he spends 8 hours each day watching television, and he does not play outside because of community safety concerns.

Social factors frequently impact bone health, making this an essential element of a bone-focused H&P. Families with scarce resources may have limited access to healthy foods, resulting in either undernutrition or obesity. Opportunities for physical activity may vary greatly depending on available family and community resources. For example, adolescents who lack transportation may be unable to participate in group sporting activities, and those living in unsafe neighborhoods may avoid exercising outdoors. Barriers to healthcare access or financial coverage may negatively affect a family's and clinician's ability to control underlying chronic illnesses that affect bone health.

Social and cultural pressures may affect an adolescent's attitudes toward nutrition, exercise, and body image. Idealization of certain aspects of appearance such as "thinness" or "muscularity," and narrow definitions of beauty that exclude persons of different weights, shapes, races, or ethnicities, increasingly contribute to poor body image in adolescents. A history of bullying (particularly based on weight) may contribute to poor self-esteem and increase risk for disordered eating. Adolescents with a history of neglect and physical or sexual abuse are at higher risk for eating disorders and substance abuse.

Physical Examination

As always, the physical examination is guided by the history and review of systems. In addition to the aforementioned evaluations, some bone-specific assessments should be conducted. The Adams forward bend test should be performed to assess for spinal abnormalities, including lordosis, kyphosis, and trunk asymmetry [54]. Palpation of the vertebral bodies may reveal tenderness associated with vertebral compression fractures. In evaluating the skin, multiple café au lait spots could indicate the presence of neurofibromatosis or McCune-Albright Syndrome, both of which are associated with bony deformities. Physical signs of systemic disease may include the pallor that accompanies anemia of chronic disease.

Conclusions

Bone health in the adolescent patient is affected by multiple interrelated factors that contribute to overall health and development. Targeting bone health in adolescents therefore requires clinicians to elicit complex information about physiologic, genetic, and behavioral factors and to understand how these factors contribute to skeletal health. The bone-focused H&P is the clinician's best tool for identifying underlying skeletal pathology, as well as for providing an opportunity to promote skeletal health in adolescents.

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Bone Health Laboratory Assessments

6

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Introduction

Laboratory investigations are an important component of bone health evaluations. The most commonly obtained laboratory assessments are serum calcium, phosphorus (measured as inorganic phosphate), 25-hydroxyvitamin D (25(OH)D), and total alkaline phosphatase. These assessments provide a quick snapshot of mineral status, vitamin D status, and bone turnover. In selected circumstances, additional assessments related to calcium homeostasis (e.g., PTH, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$)) or bone turnover (e.g., bone-specific alkaline phosphatase and serum or urine measures of collagen telopeptides) may be helpful. In children who have suspected or confirmed osteoporosis, laboratory screening for secondary causes of low bone mass, including celiac disease and inflammatory bowel disorders, may also be warranted.

Specific information about commonly available laboratory measures used for bone health evaluations, including factors that influence the observed values and the utility of each, is provided below.

General Laboratory Assessments

Calcium

Adolescence is a key time for total body calcium accrual, with at least 40% of skeletal calcium stores laid down during adolescence. Calcium is consumed enterally

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through dietary sources (mostly milk and milk-containing foods), absorbed through the gut mucosa, stored in the bone, and excreted into the urine. The average adult human body contains ~1000 grams of this mineral. More than 99% is stored in the skeleton in the form of hydroxyapatite; some is found in teeth, and less than 1% is found in the plasma and interstitial fluids. Only 700 mg of total body calcium is found in extracellular fluids and 350 mg circulates in the serum. One-third of the circulating calcium is bound to albumin/globulin. The rest is diffusible, of which 80% is ionized. Ionized calcium is essential for muscle contraction, neural transmission, and protein secretion [1].

Both the bound and free forms of calcium are readily measured in the blood, either as serum total calcium or as ionized calcium. Since most circulating calcium is bound, low serum albumin concentrations lead to low measured total calcium even when the ionized calcium is normal. It is, therefore, important to account for albumin when interpreting total calcium measurements. The formula is measured total calcium (mg/dL) + [(4.0 – serum albumin (g/dL)) × 0.8]. Alternatively, in cases of albumin deficiency, ionized calcium may be preferentially measured [2].

Ionized calcium values are very tightly regulated by the calcium-sensing receptor (CaSR) and parathyroid hormone (PTH). Hypocalcemia stimulates PTH secretion. PTH then stimulates bone resorption, increases renal calcium reabsorption, and stimulates $1,25(OH)_2D$ production which will increase intestinal calcium absorption. Hypercalcemia, conversely, inhibits PTH secretion. Ionized calcium values are affected by pH and will be higher with acidosis and lower with alkalosis [1]. Potassium ethylenediaminetetraacetic acid (EDTA) is a sample tube anticoagulant used in many laboratory tests. Since it binds cations, gross sample contamination with EDTA may lead to factitious hypocalcemic measurements [3].

Urinary calcium can be readily measured and provide a means to assess calcium throughput. The gold standard assessment is 24-h urine calcium/creatinine clearance, with hypercalciuria defined as greater than 4 mg/kg/day of calcium excretion [4, 5]. However, in children, it is often difficult to get a 24-h urine sample, due to both practicability and accuracy of sample collection. Therefore, currently it is more common in pediatric practice to obtain a spot urine calcium/creatinine ratio (UCa/Cr). Most, but not all studies (conducted in adults), suggest that these spot values are highly correlated with 24-h values [4–6]. Normal urinary calcium excretion varies with age, with higher values seen in very young children [7]. Although age-adjusted normal ranges are available for this test, there is variability in the cutoffs for normal values. For older children and adolescents, a typical cutoff is <0.2 mg/mg [8]. Since urinary calcium is normalized to urine creatinine, in children with low muscle mass (such as those with Duchenne muscular dystrophy), urine Ca/Cr ratios will often overestimate the calcium excretion due to decreased urine creatinine excretion. For these patients, a random urine calcium/osmolality (UCa/Osm) ratio is used instead of a random UCa/Cr ratio [4]. In patients with decreased muscle mass, UCa/Osm (x10) ratio > 0.25 was found to be sensitive (100%) and specific (93%) for identifying hypercalciuria [4]. Alternatively, a 24-h urine collection for calcium can be performed. Normal serum values can be found in Table 6.1.

Table 6.1 Sample normal serum values (values will vary based on laboratory assay used, always consult local reference values when available)

	Conventional units	SI units
Total serum calcium	8.5–10.5 mg/dL	2.1–2.6 mM
Ionized serum calcium	4.4–5.2 mg/dL	1.1–1.3 mM
Urine Ca/Cr (>6yo)	<0.2 mg/mg	
Total serum phosphorus		
10–15 years	3.3–5.4 mg/dL	1.07–1.74 mM
>15 years	2.4–4.4 mg/dL	0.78–1.42 mM
Alkaline phosphatase		
12–14 years	74–397 U/L	74–397 U/L
14–18 years	48–277 U/L	48–277 U/L
Serum magnesium	1.6–2.9 mg/dL	0.7–1.1 mM
Serum PTH	10–65 pg/mL	1.1–6.9 pM
Serum 25-hydroxyvitamin D	30–80 ng/mL	75–200 nM
Serum 1,25-dihydroxyvitamin D	19.9–79.3 pg/mL	52–206 pM

Phosphorus

Like calcium, phosphorus is taken enterally, absorbed in the intestine, stored in the bone, excreted into the urine, and readily measured in the blood. Inorganic phosphate is crucial for bone matrix mineralization [9]. Most total body phosphorus is stored in the skeleton (85%) as part of hydroxyapatite. Fourteen to fifteen percent of total body phosphorus is found in the soft tissue and <1% in the blood. Phosphorus circulates in the blood as both organically bound phosphoric acid (70%) and inorganic phosphate ions (30%). Inorganic phosphate is what is measured with a serum "phosphorus" concentration [1]. These ions are comprised of a central phosphorus atom surrounded by four oxygens (PO_4^{3-}) and coupled to hydrogen depending on acidity.

Serum phosphorus concentrations are primarily regulated by the kidneys. Most filtered phosphate is reabsorbed in the tubules (mainly in the proximal tubule). Fibroblast growth factor 23 (FGF23), PTH, and $1,25(OH)_2D$ all play roles in phosphate homeostasis, although FGF23 serves the primary role. FGF23 decreases phosphorus in part by decreasing synthesis and increasing metabolism of $1,25(OH)_2D$. Both PTH and FGF23 directly increase urinary phosphate excretion [1, 10]. PTH also works through the receptor activator of nuclear factor-κB ligand (RANKL)/RANK/osteoprotegerin (OPG) system to enhance phosphorus release from the bone (via osteoclasts) and through $1,25(OH)_2D$ which increases intestinal phosphate absorption.

An important aspect of the evaluation of hypophosphatemic or hyperphosphatemic states is a TmP/GFR (tubular reabsorption of phosphate adjusted for glomerular filtration rate) which can be calculated from simultaneous fasting serum and urine measurements of phosphate and creatinine (using the second morning void or a 2-h urine collection). The TmP/GFR can also be found using a nomogram after

measuring the same values [11]. For both the equation and the nomogram, the TRP must be calculated first. The equation for TRP is 1-[(urine phosphate)/(plasma phosphate) x (plasma creatinine)/(urine creatinine)]. If the TRP is ≤0.86, then phosphate reabsorption is maximal and TmP/GFR = TMP × [plasma phosphate]. If TRP is >0.86, then TmP/GFR = 0.3 × TRP/(1 − (0.8 × TRP)] × [plasma phosphate] [11, 12]. TmP/GFR assesses whether the patient is reabsorbing an appropriate amount of phosphorus in the context of the serum phosphorus [1, 11]. A urine phosphorus can also be collected (as a 24-h or random sample) to access phosphorus excretion. This value also needs to be interpreted in the context of the serum phosphorus and the clinical context.

Circulating phosphorus concentrations change significantly with age during childhood. Infants have the highest levels, likely due to increased need associated with skeletal and cellular growth. Phosphorus levels then decrease gradually as the child ages to the normal adult ranges [1]. It is important to recognize that many clinical laboratories do not provide age-specific ranges when reporting phosphorus levels, leading commonly to a misidentification of a low phosphorus level as "normal." Since phosphate is very important for bone health, especially during times of growth, it is critical to assess the value in the context of age.

Magnesium

Magnesium is an essential ion for hundreds of enzymatic reactions. It plays an important role in bone health and is critical for brain, heart, and skeletal muscle function. Only 1% of total body magnesium is in the extracellular space; the rest is stored intracellularly (50–60% in bone, with the remainder in muscle soft tissues) [13].

In the serum, magnesium acts as a calcium antagonist. Low circulating magnesium acutely increases PTH release, but chronic magnesium deficiency suppresses PTH release by changing CaSR activation and induces end-organ resistance to PTH, and may be associated with refractory hypocalcemia [14]. Until the magnesium is replenished, calcium normalization may not be possible.

In the bone, magnesium ions are bound to hydroxyapatite where they increase phosphate and calcium ion solubility and change crystal size [13]. Magnesium also influences osteoblast proliferation and pro-inflammatory cytokine release; low magnesium levels may predispose to brittle bone and fracture.

Sixty percent of circulating magnesium is in the free, ionized form (active form), 10% complexed to serum anions, and 30% albumin bound [15]. Total serum magnesium is a readily available test and is currently the standard means of assessing magnesium status. Unlike calcium, ionized magnesium levels are not generally available. Since only 1% of the total body magnesium is in the extracellular space, serum magnesium may be normal despite profoundly decreased total body stores [16]. As for calcium, gross sample contamination with EDTA may lead to factitious hypomagnesemia [3]. Also since circulating magnesium is bound to albumin, if the

patient has low albumin levels, the magnesium may erroneously appear low [16]. Unlike for calcium, usually the serum magnesium concentration is not adjusted for serum albumin.

Vitamin D and Its Metabolites

Jennifer is a healthy 14-year-old athlete who was told she had low vitamin D2, but vitamin D3 of 50ng/mL. Her mother asks if she needs to take a D2 supplement.

Vitamin D and its metabolites are critical for calcium metabolism and bone health. Ergocalciferol (vitamin D_2) is intestinally absorbed from plant sources, while cholecalciferol (vitamin D_3) can be endogenously produced (from 7-dehydrocholesterol in skin exposed to UVB light in the range of 295–300 nm) or intestinally absorbed from animal-derived sources (Fig. 6.1). The difference between vitamin D_2 and vitamin D_3 is the structure of their side chains. Once absorbed or produced, vitamin D (D_2 or D_3) is transported to the liver, where it is hydroxylated to form 25(OH)D. This 25(OH)D is then converted in the kidney by the enzyme 1-α-hydroxylase to $1,25(OH)_2D$ which then circulates and acts on different tissues through the vitamin D receptor. 1-α-hydroxylase is also found in skin keratinocytes, osteoblasts, and certain immune system cells (including monocytes and macrophages). The conversion of 25(OH)D to $1,25(OH)_2D$ is usually highly regulated in all tissues, predominately by PTH.

25-Hydroxyvitamin D

If there is clinical concern for vitamin D deficiency or overall bone health, 25(OH)D should be measured to assess vitamin D stores. Guidelines suggest that serum vitamin D levels > 30 ng/mL (75 nmol/L) are optimal, especially for children and adolescents with a chronic disease [17, 18]. However, recent international guidelines suggest that the sufficient circulating concentration of 25(OH)D necessary to prevent rickets is >20 ng/mL (50 nmol/L), with insufficiency being 12–20 ng/mL (30–50 nmol/L) and deficiency <12 ng/mL (30 nmol/L) [19].

25(OH)D (calcifediol) is a stable metabolite of vitamin D. It is the most appropriate metabolite to measure when assessing total body vitamin D status. There are a number of different laboratory methods for measuring 25(OH)D concentrations. Most assays measure both vitamin $25(OH)D_2$ and $25(OH)D_3$. Treatment with D_2 or

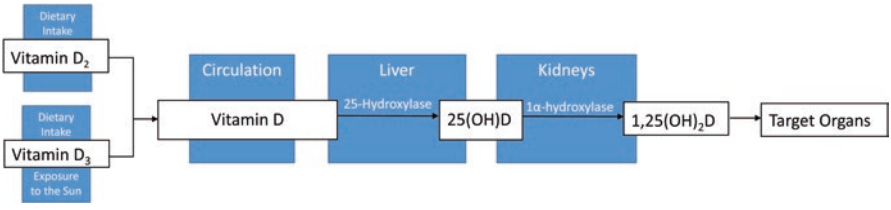

Fig. 6.1 Vitamin D metabolism

D_3 is thought to be equally effective. However, as a single large dose, vitamin D_3 would be preferable, because D_3 has a longer half-life and appears to have enhanced potency [19]. Data suggest that vitamin D_3 supplementation is associated with greater increases in total and free 25(OH)D_3 than an equivalent dose of vitamin D_2 supplementation [20]. When assessing vitamin D status by measuring 25(OH)D, if the values are reported separately, both D_2 and D_3 components are added to assess whether an individual is considered vitamin D "sufficient," "insufficient," or "deficient" [18]. As the number of guidelines on this topic suggest, the 25(OH)D concentration that translates to optimal health represents an area of ongoing controversy.

There are three different ways to measure 25(OH)D, including immunoassays, HPLC, and liquid chromatography-tandem mass spectrometry (LC-MS/MS) [21, 22]. Laboratories commonly use immunoassays for several reasons, including them being easily automated and available at a low cost. However, initially the accuracy and precision of these assays had been suboptimal. Recently, they have improved. However, it is important to know the limitations of the assay being used. Questions also remain about the reliability for low 25(OH)D concentrations <8 ng/mL (<20 nmol/L)) [22].

LC-MS/MS works well for high volume reference laboratories; it has greater specificity and measures both 25(OH)D_2 and 25(OH)D_3, although the instrument cost is greater [[21]. Historically, there was great variability in 25(OH)D measurements performed in different labs. There has been a significant decrease in variation between different laboratories using liquid chromatography-tandem mass spectrometry with application of National Institute of Standards and Technology (NIST) standard reference ranges [17, 19, 21, 22]. Recently the accuracy of 25(OH)D assays has improved in part through the Vitamin D standardization program [19, 23].

It is not recommended that clinicians screen for vitamin D deficiency routinely when assessing overall health in children [17, 19]. Measuring 25(OH)D as a general population screening practice would be expensive, require the burden of a venous blood draw for all children, and have a low positive predictive value. Recent Global Consensus Recommendations recommend adopting appropriate prevention strategies to lower the overall likelihood of vitamin D deficiency (including food fortification and supplementation) and to only screen those individuals who are at high risk [19].

1,25(OH)$_2$D

1,25(OH)$_2$D (calcitriol) is the "active" form of vitamin D, and, through actions on the vitamin D receptor, 1,25(OH)$_2$D stimulates calcium and phosphorus absorption in the proximal small intestine, renal calcium absorption, and bone resorption. Although serum concentrations of 1,25(OH)$_2$D can be measured, they mainly reflect acute changes due to fluctuations in PTH in response to overall circulating calcium concentrations. Therefore, they are not useful to assess overall vitamin D stores [1]. 1,25(OH)$_2$D has been historically a difficult analyte to measure. Although there have been improvements, further standardization is required to improve assay

accuracy and comparability [24]. In general practice, $1,25(OH)_2D$ concentrations should only be measured in situations when patients are hypercalcemic with suppressed PTH or have renal insufficiency [25].

Parathyroid Hormone (PTH)

PTH is made and secreted by the parathyroid glands and is a critical and rapid regulator of calcium concentration. PTH works to increase calcium by stimulating calcium resorption from the bone, by increasing renal reabsorption of calcium, and by stimulating $1,25(OH)_2D$ production.

When calcium levels fall, PTH secretion is stimulated, and, conversely, when calcium levels rise, PTH is inhibited. This relationship is important to keep in mind when interpreting PTH in the context of the ambient calcium level [1] (Table 6.2).

PTH is an 84 amino acid peptide hormone, with the first 34 amino acids providing its biological activity. It circulates in many different forms and is readily measured clinically. The first-generation radioimmunoassays (RIA) have been replaced by second- and third-generation immunometric assays (IMAs). The second-generation assay (also known as intact PTH assay) initially was thought to measure only PTH (1-84) but was found to also measure other PTH fragments [26]. The third-generation assay (whole/bioactive PTH assay) was also initially thought to only detect PTH (1-84), but it was found to react with another N-form of PTH [27]. Patients with renal failure accumulate more PTH fragments; therefore, it is important in those patients to use more sensitive assays to be able to assess the biologically active fraction [27].

Recombinant forms of PTH are used for treatment of osteoporosis and, less commonly, hypoparathyroidism, although a black box warning due to an observed increase in osteosarcomas noted in growing rats generally precludes their current use in children.

PTH-Related Peptide (PTHrP)

PTHrP is a hormone with paracrine and autocrine actions [28]. Unlike PTH, which is only made in the parathyroid gland, PTHrP is made in many different tissues. Both PTH and PTHrP bind to the G-protein-coupled type 1 parathyroid hormone

Table 6.2 Interpretation of calcium in the context of PTH

	Calcium		
PTH	Decreased	Normal	Increased
Decreased	Primary hypoparathyroidism		PTH-independent hypercalcemia (includes malignancy)
Normal		Normal	
Increased	Pseudohypoparathyroidism	Secondary hyperparathyroidism	Primary/secondary hyperparathyroidism

receptor. Like PTH, the biological action of PTHrP at this receptor is imparted by the first 34 amino acid residues.

It has many different functions, the most important of which is regulation of endochondral bone formation and mineralization. PTHrP also appears to play a role as a cellular cytokine that influences cell growth and differentiation. It also has a paracrine regulatory role in smooth vascular muscle. It plays a role in calcium regulation and can be measured in the blood. PTHrP is also important for transferring calcium from the mother to the fetus, during both pregnancy and lactation [1].

In the context of malignancy, PTHrP can be elevated and lead to hypercalcemia, although this scenario is rare in children. It is important to note that the PTHrP assays are currently limited in sensitivity and can miss PTHrP-producing tumors [29]. It is generally only measured in children who have cancer and hypercalcemia, but a low circulating PTH concentration.

Bone Formation Markers

Bone is constantly being remodeled throughout the lifetime. In children, new bone is also being formed and modeled. There are many commercially available laboratory markers to assess rates of bone formation and bone resorption (Table 6.3) [10]. It is important to interpret these values in the context of the patient's growth and pubertal status. In particular, during puberty, a time of rapid bone growth, many of the markers of bone metabolism increase.

Alkaline Phosphatase

Alkaline phosphatase is an enzyme that is important for bone formation and mineralization. It helps to maintain serum phosphate levels by cleaving phosphorus to form beta-glycerol phosphate [9]. When circulating phosphorus is low, alkaline phosphatase enzymatic activity increases to increase phosphate availability. When there is sufficient phosphorus available, it normalizes.

Table 6.3 Measures of bone formation/resorption

Bone formation	Bone resorption
Serum alkaline phosphatase	Collagen-derived Serum/urine C-terminal cross-linked telopeptide (CTX) Serum/urine N-terminal cross-linked telopeptide (NTX)
Serum bone-specific alkaline phosphatase	[a]Urine deoxypyridinoline (DPD)
[a]Serum osteocalcin	[a]Urine pyridinoline (PYD)
[a]Serum C−/N-terminal collagen propeptides (P1CP and P1NP)	[a]Tartrate-resistant acid phosphatase 5b (TRAP5b)

[a]Available, but not generally measured clinically

Total alkaline phosphatase is present in a number of tissues, primarily in the bone and liver, but also in the intestine, kidneys, leukocytes, and placenta, each producing different isoforms. Its circulating concentrations are therefore influenced not only by bone disease but also by hepatobiliary disorders. Since alkaline phosphatase rises with bone growth, serum alkaline phosphatase concentrations are 1.5–2.5 times higher in growing children than in adults. During the pubertal growth spurt, some adolescents have a greater alkaline phosphatase response than what is deemed "normal," and while this usually resolves with the height plateau, it is reasonable to monitor. Children with early puberty may also have higher alkaline phosphatase values than is normal during their maturation and have values below the lower limit for age (although normal for bone age and normal for adults) after their pubertal growth spurt is complete.

Bone-specific alkaline phosphatase (BAP) is produced by osteoblasts and is important for bone matrix formation. As its name implies, it works best to facilitate bone formation at slightly basic pH concentrations. It counterbalances osteoclastic bone resorption by a tartrate-resistant acid phosphatase (TRAP) which works best in acidic environments.

Bone-specific alkaline phosphatase is readily measured clinically and may serve as a better and more specific marker for bone and phosphorus homeostasis than total alkaline phosphatase [9]. A number of methods are used to measure BAP including phenylalanine inhibition and heat activation techniques. Despite recent improvements, specificity in these BAP assays remains an issue [10]. However, in children with increased bone turnover (like 25(OH)D deficient rickets) who do not have liver disease, the liver isoform contribution is small enough that the measurement of BAP may not offer any additional benefits over following total alkaline phosphatase concentrations. There are also fewer normative reference data for BAP beyond total alkaline phosphatase.

Alkaline phosphatase concentrations are generally elevated in children with rickets/osteomalacia [10]. With therapy, concentrations tend to initially rise as bone formation increases with metabolic bone recovery and then decrease as bone remodeling normalizes over time. Low concentrations of alkaline phosphatase are seen in a variety of disorders, including the rare inherited disease hypophosphatasia [30]. Alkaline phosphatase concentrations are also useful for monitoring the effects of therapy with antiresorptive treatments such as bisphosphonates.

Osteocalcin

Osteocalcin is a small 49 amino acid protein. Like bone-specific alkaline phosphatase, osteocalcin is also produced by osteoblasts. Since it is more specific to bone cells than alkaline phosphatase, it should be the best marker for assessing osteoblast activity. However, it has not been as useful clinically due to the instability of the molecule and difficulty distinguishing between its different forms. Recent studies have shown that it may be involved in energy metabolism. At this time, we would not recommend measuring osteocalcin in a general practice [10].

Collagen Propeptides

Type 1 collagen begins as procollagen type 1 which is the most common protein made by bone osteoblasts and fibroblasts. After procollagen is secreted, the procollagen type 1 carboxy- and amino-terminal propeptides (P1CP and P1NP) are cleaved off and released during the conversion to collagen. Circulating concentrations of these propeptides reflect osteoblast function and the synthesis of collagen type 1, which is an important step in bone formation [31]. There are enzyme-linked immunosorbent assays (ELISAs) and radioimmunoassays available to measure serum PICP and PINP [31]. P1NP is more stable and has a longer serum half-life than P1CP, so it may be a more useful measure [28]. At this time, although following trends in these measures (particularly P1NP) may useful in certain limited clinical scenarios, we would not recommend measuring these in a general practice, in part because of a paucity of pediatric reference data.

Bone Resorption Markers

Most of the markers used clinically to assess bone resorption are derived from assays of degradation products formed during post-translational modification of bone-derived type 1 collagen. These markers are released when the bone matrix is broken down during the process of osteoclastic bone resorption. These include pyridinoline (PYD), deoxypyridinoline (DPD), N-terminal cross-linked telopeptide (NTX), and C-terminal cross-linked telopeptide (CTX). Another marker of bone resorption is tartrate-resistant acid phosphatase 5b (TRAP5b) which is derived from osteoclasts. Both urine and serum NTX and CTX are available, although urine NTX and serum CTX are more commonly used. The values vary with age and pubertal stage, have limited clinical utility, and need to be followed over time. In general, they are only useful clinically for monitoring during therapy with antiresorptive agents. There is no role for assessing them in general adolescent clinical care [10].

FGF23

FGF23 is a peptide hormone mainly made by osteocytes. FGF23 is important in the regulation of phosphate homeostasis and vitamin D metabolism [1, 32]. Like PTH, FGF23 is a "phosphatonin" that decreases serum phosphate concentrations. Unlike PTH, FGF23 also decreases $1,25(OH)_2D$ concentrations [33]. Only the intact form of FGF23 exerts biological effect [34]. Diseases such as X-linked hypophosphatemic rickets that are associated with excess FGF23 lead to hypophosphatemia and osteomalacia, causing rickets in growing children. Diseases characterized by decreased FGF23 lead to hyperphosphatemia which results in ectopic soft tissue and vascular calcifications [1, 32]

There are two commonly used commercially available enzyme-linked immunosorbent assays (ELISA) for measurement of FGF23 concentration in research

settings. An intact ELISA (iFGF23) recognizes the full FGF23 prior to cleavage. The C-terminal ELISA (cFGF23) assays both the intact hormone and the C-terminal fragment. Some conditions result in elevations of both intact and C-terminal FGF23, while others lead to elevations only of the inactive C-terminal FGF23 measurement [35]. The results of the two types of assays are not interchangeable, and the choice of assay depends on various considerations, most important of which is on clinical situation [34]. Additional ELISAs for iFGF23 using automated platforms have been developed but are not yet in common use, and the normal ranges differ with each assay. At this time we would not recommend ordering FGF23 levels in a general practice and only in very unique clinical cases.

Suggested Initial Laboratory Evaluations in Selected Clinical Situations

Samuel is a 13-year-old with milk allergy who does not meet the RDA for calcium intake. His mother is reassured by the fact that his serum calcium level is normal. Should she be?

Hypocalcemia

When enteral calcium intake is suboptimal, the body will increase intestinal calcium absorption and also maintain normocalcemia at the expense of bone mineral density. Therefore, it should not be assumed that hypocalcemia is due to insufficient calcium intake, just as it should not be assumed that normocalcemia reflects adequate enteral calcium intake. A normal serum calcium level does not necessarily imply adequate dietary intake due to these compensatory mechanisms. When total serum calcium is found to be low, an assessment of ionized calcium should be done unless circulating albumin concentrations are already known to be normal. If hypocalcemia is confirmed, the next step is to measure PTH. In order to interpret the PTH concentration, a serum phosphorus and creatinine should be obtained.

If PTH is high (usually >65 pg/mL) in the context of hypocalcemia, the differential diagnosis includes secondary hyperparathyroidism due to vitamin D deficiency or chronic kidney disease. The laboratory evaluation of suspected vitamin D deficiency is discussed below. Pseudohypoparathyroidism, characterized by resistance to PTH, is also possible, although rarer. Individuals with pseudohypoparathyroidism have high PTH and low calcium with high phosphorus concentrations. Many will have evidence of other hormone resistance, and those with pseudohypoparathyroidism type 1a manifest physical features of Albright hereditary osteodystrophy, including short stature, round facies, and brachydactyly [36]. Children with suspected pseudohypoparathyroidism should be referred to an endocrine specialist.

Table 6.4 Hypercalcemia with an elevated/inappropriately normal PTH: common disorders and labs

	Primary hyperparathyroidism[a]	Familial hypocalciuric hypercalcemia (FHH)[a]
PTH	*Increased*	Normal/slightly increased
Phosphate	Decreased	Normal/decreased
Urine calcium	Decreased[b]/normal/increased	Decreased
25(OH)D	Normal	Normal
$1,25(OH)_2D$	Increased	Normal

[a]Can be difficult to distinguish between the two diagnoses
[b]In mild primary hyperparathyroidism

Table 6.5 Hypercalcemia with a low PTH: common disorders and labs

	Immobilization	Granulomatous disease	PTHrP-mediated malignancy	Vitamin D intoxication
Phosphate	Increased	Increased	Decreased	Increased
Urine calcium	Increased	Increased	Increased	Increased
25(OH)D	Normal	Normal	Normal	Increased
$1,25(OH)_2D$	Decreased	Increased	Normal, increased, or decreased	Increased
PTHrP	Normal	Normal	Increased	Normal

If PTH is normal (inappropriately) or suppressed and the patient has hypocalcemia, the differential diagnosis would include a variety of forms of hypoparathyroidism, including inherited forms such as DiGeorge (22q11.2 deletion) syndrome. After treating the acute complications of hypocalcemia, rapid endocrine referral is warranted.

Hypercalcemia

Hypercalcemia is relatively uncommon in adolescents [37] and often associated with an underlying known clinical disorder, such as immobilization or malignancy. Whenever an adolescent presents with an elevated serum calcium, a PTH (along with phosphorus and creatinine) should be obtained. If PTH is frankly high for the serum calcium, the most likely diagnosis in this pediatric age range is primary hyperparathyroidism (Tables 6.4 and 6.5). In children, this can be due to an isolated adenoma (more rarely carcinoma), but can also reflect a first manifestation of multiple endocrine neoplasia, types 1 or 2b. Endocrine referral is warranted in either setting. In the context of kidney disease, tertiary hyperparathyroidism should be considered.

If PTH is inappropriately normal or modestly high and calcium is just above the normal range, a 24-h urine calcium or a spot urine calcium/creatinine ratio can be obtained to assess for possible familial hypocalciuric hypercalcemia (FHH), as

urinary calcium excretion would be lower [38]. It may be prudent to test other family members' calcium levels, as well, as FHH is an autosomal dominant disorder. Genetic testing for this condition is also readily available. It is important to note that urine calcium is not necessarily increased in primary hyperparathyroidism. In mild primary hyperparathyroidism, urine calcium is low and the biochemical findings are indistinguishable from FHH [39]. If total calcium is high, it may also be prudent to check a serum albumin and an ionized calcium, as increases in serum albumin can be associated with "pseudohypercalcemia."

If the PTH is suppressed, the differential diagnosis then includes excessive vitamin D or (more rarely) calcium intake, malignancy (in which case PTH-related peptide should also be measured), granulomatous diseases (in which case $1,25(OH)_2D$ is also elevated), and immobilization. Rarely hyperthyroidism, adrenal insufficiency, and pheochromocytoma are associated with hypercalcemia. Some drugs are also associated with hypercalcemia, including lithium, thiazides, systemic retinoids, and theophylline. In these cases, clinical correlation/endocrine referral is warranted [40, 41].

Hypophosphatemia

As noted previously, it is critical that serum phosphate concentrations be assessed using age-appropriate normal ranges, as phosphorus values decrease during childhood, and use of adult normal ranges will lead to a failure to recognize hypophosphatemia in children. The first step would be to measure calcium, PTH, and alkaline phosphatase. A secondary evaluation performed by an endocrinologist may include a TmP/GFR and urine phosphorus. The TmP/GFR can help determine if renal losses are causing the hypophosphatemia [11].With an elevated PTH, and elevated calcium, the differential diagnosis would include hyperparathyroidism. With a low calcium and elevated PTH, vitamin D deficiency/rickets needs to be considered. With a normal serum calcium, normal or mildly elevated PTH, elevated alkaline phosphatase (but not as elevated as would expect in vitamin D deficient rickets), low/normal $1,25(OH)_2D$, and normal 25-OH vitamin, X-linked hypophosphatemic rickets (XLH) needs to be considered, even in the absence of a family history, as sporadic cases often occur. A diagnosis of XLH requires evidence of urinary phosphate wasting and thus requires a TmP/GFR [11, 42].

Hyperphosphatemia

The most common reason for hyperphosphatemia is renal failure causing decreased phosphate excretion. More rarely hyperphosphatemia is due to other causes related to excessive intake, reduced excretion, or shifting of intracellular phosphate to the circulation (such as with muscle injury due to crush trauma or rhabdomyolysis, hemolysis, or tumor lysis). The first step in work-up of hyperphosphatemia is to consider the clinical context and assess renal function. If further "bone-related"

work-up is desired, the next measurements would be of calcium, alkaline phosphatase, and PTH.

If the PTH is suppressed and the calcium is high, the differential diagnosis would include vitamin D toxicity (particularly if excess calcitriol is consumed).

If the PTH is normal or suppressed, and the calcium is low, the differential would include hypoparathyroidism.

If PTH is high and calcium is low, the differential would include pseudohypoparathyroidism as outlined, and the patient should be assessed for phenotypic features of Albright's hereditary osteodystrophy.

It is important to note that spuriously high-serum phosphate concentrations (pseudohyperphosphatemia) can be obtained if blood is taken from a line containing heparin or a sample is grossly hemolyzed. Very rarely, high-serum paraprotein concentrations, hyperbilirubinemia, and hyperlipidemia can be associated with falsely high-serum phosphate concentrations due to interference in the sample measurement assay. Recently, pseudohyperphosphatemia has been reported to be associated with amphotericin use [43].

Vitamin D Deficiency/Rickets/Osteomalacia

Laboratory evaluation may include serum calcium, phosphorus, alkaline phosphatase, PTH, 25(OH)D, $1,25(OH)_2D$, and urine calcium/Cr ratio. Typical findings would include a low 25(OH)D, serum calcium, serum phosphorus, and urine calcium and an elevated PTH and alkaline phosphatase [19]. The serum calcium (and, less commonly, phosphorus) can be normal depending on the degree of deficiency and degree of PTH elevation [41]. Laboratory testing alone may not differentiate whether the primary cause is from vitamin D deficiency or dietary calcium deficiency, because commonly you may have both [19, 44].

Evaluation for Secondary Causes of Low Bone Mass

When a patient presents with low bone mass or fragility fracture without any known underlying cause, we would recommend beginning a laboratory assessment with general screening for secondary causes for osteoporosis [45]. A reasonable first lab panel would include serum total calcium, albumin, phosphate, creatinine, alkaline phosphatase, PTH, 25(OH)D, complete blood count, erythrocyte sedimentation rate or c-reactive protein, alanine aminotransferase (serum glutamic pyruvate transaminase), thyroid-stimulating hormone, tissue transglutaminase IgA antibody (for celiac disease) and total IgA, and a spot urine calcium/creatinine. If there are concerns about pubertal progression, one could consider additionally measuring testosterone (males) and follicle stimulating hormone/estradiol (females). If there is consideration to begin antiresorptive therapies for osteoporosis, a referral to a pediatric metabolic bone specialist should be strongly considered.

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Imaging to Evaluate Bone Health

7

Heidi J. Kalkwarf

Introduction

Adolescents experience diverse chronic medical conditions or may receive treatment with pharmaceutical agents that result in bone loss or affect bone accretion, preventing them from reaching their genetic potential for peak bone mass. Low BMC or BMD is associated with increased fracture risk in children and adults, and poor bone accrual during growth may affect lifelong bone strength [1, 2]. The goal of bone densitometry is to identify individuals at risk for skeletal fragility and determine the magnitude of bone deficits in order to guide and monitor treatment. The current clinical standard for assessment of bone health and bone fragility across all ages is dual-energy x-ray absorptiometry (DXA) given its speed, precision, safety, low cost, and widespread availability.

Principles of DXA

DXA yields estimates of bone density by measuring the transmission of x-rays through the body. DXA uses high- and low-energy x-rays, allowing for the discrimination between soft tissue and bone. Low-energy x-rays are attenuated by soft tissue, whereas high-energy x-rays are attenuated both by bone and soft tissue. Subtraction of the two attenuation values yields a measure of the amount of bone in the x-ray path on a pixel-by-pixel basis (e.g., grid-like). Software algorithms define bone edges based on the attenuation in each pixel. Bone area (cm^2) is calculated by summing the pixels within the bone edges as defined by the software. Attenuation values for each pixel within the bone map are converted to bone mineral density

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(BMD, g/cm^2) by comparison to a bone density phantom. DXA is characterized as a two-dimensional imaging technique owing to its projectional nature that does not account for the depth of bone. Bone density measured by DXA is often called "areal" BMD, or aBMD, as it is not a true volumetric density (i.e., g/cm^3) measurement. Bone mineral content (BMC, *g*) is calculated by multiplying the mean aBMD by the bone area.

Types of DXA Scans

There are four types of dedicated DXA scans (whole body, spine, hip, and forearm scans) and a customized scan of the lateral distal femur that are commonly used to assess bone health in clinical practice. The choice regarding what scans and skeletal sites to measure is influenced by age of the patient, underlying disease condition, whether there are conditions precluding the ability to obtain an adequate scan of a certain region (e.g., indwelling hardware, skeletal deformity, contractures), and availability of reference data to interpret scan results. Regardless of the scan performed, attention must be given to appropriate positioning of the individual during scan acquisition, examination of the scanned image to ensure that there are no artifacts, and assessment of the regions of interest for accurate analysis. Poor positioning and foreign artifacts can invalidate scan results. Movement-related artifacts are common in young children but can occur at any age.

Radiation Exposure

Cynthia is a 15-year-old with premature ovarian insufficiency following her bone marrow transplant. In conjunction with starting hormone replacement therapy, you order DXA scans to assess her baseline bone density. Her mother expresses concerns about radiation exposure given the amount she has received to date.

DXA scans involve a small amount of radiation exposure to the patient. The DXA operator's manual often provides the radiation exposure from DXA scans as the "entrance dose" in *millirems* (*mrem*) as it is easy to measure from the machine. However, the entrance dose does not consider the amount of radiation reaching specific tissues nor the radiosensitivity of the tissue exposed. Radiation safety experts prefer to express radiation exposure as the "effective dose" as it considers the biological effects of radiation on radiosensitive tissues. Also, it can be compared across other types of procedures involving radiation exposure. The effective dose of DXA scans vary according to three factors: (1) the part of the body being scanned determines which organs are exposed, and each organ has different radiosensitivity; (2) the size of the individual (corresponding to age), which affects the proportion of an organ present in the scan field and exposed to radiation, and the amount of x-ray attenuation by soft tissue before reaching radiosensitive organs; and (3) the scan mode, which affects skin entrance dose. Slower scan modes have higher entrance

doses. For DXA scans performed on Hologic machines using default scan modes, the effective dose of a whole-body scan is 4.8 *microsieverts* (*μSv*), a spine scan is 12.1 μSv, and a hip scan is 6.2 *μSv* in a 10-year-old child [3]. In adults, the respective amounts are 4.2 *μSv*, 7.4 μSv, and 5.0 μSv [3]. For comparison, the radiation exposure associated with a chest or abdominal x-ray in an adolescent using modern equipment and procedures is about 100 *μSv* [4]. The average annual background radiation exposure (originating from soil, rocks, outer space) in the United States is about 3000 *μSv* a year or about 8 *μSv* a day. The health risks associated with the very low level of radiation from DXA scans have been difficult to extrapolate from studies involving much higher levels of radiation exposure. Current studies have not been able to establish an association between health risks and the low levels of radiation exposure typical with DXA. The National Council of Radiation Protection and Measurements states that an annual effective dose of 10 *μSv* is considered a negligible individual dose [5].

Recommended DXA Scans

Terry is a 17-year-old with cerebral palsy, seizure disorder, status post spinal fusion, and bilateral hip hardware given prior fractures. Should she undergo DXA scans?

The International Society of Clinical Densitometry (ISCD) recommends the whole-body and spine scans for clinical bone health assessment in children and adolescents owing to their good precision, easily identified landmarks, and abundant reference data [6]. Furthermore, these measures have been shown to be sensitive and specific for identifying vertebral fractures in children with chronic medical conditions [7]. The spine is also a recommended site for bone health assessment in adults. The hip scan is not recommended by the ISCD for monitoring bone health in children as the skeletal landmarks in the hip region that assure accurate positioning are not well developed until mid-adolescence. Hip scans are recommended however as a standard assessment site for adults, and obtaining a hip scan can eventually be helpful to obtain in older adolescents to enable a smooth follow-up as they transition to adulthood with provision of health care at adult health-care facilities. The precision of DXA scans in adolescents is similar to that of adults [8].

The whole-body scan provides information about the mineral content and density of the whole skeleton, as well as for specific subregions (Fig. 7.1). The whole body less head region, which excludes the skull, is recommended by ISCD for assessing bone health in children and adolescents [6]. The rationale for excluding the head is that it contributes a varying proportion of the total skeletal mass as children grow, and the skull is not responsive to physical activity. Because the whole-body scan provides information on lean and fat mass as well as bone, it is useful in situations involving malnutrition or muscle deficits and in situations where changes in lean mass are helpful for interpreting bone results (e.g., immobilized patients). Common artifacts in a whole-body scan include the movement of the arm or leg and the presence of orthopedic rods or pins, ports, IV contrast material,

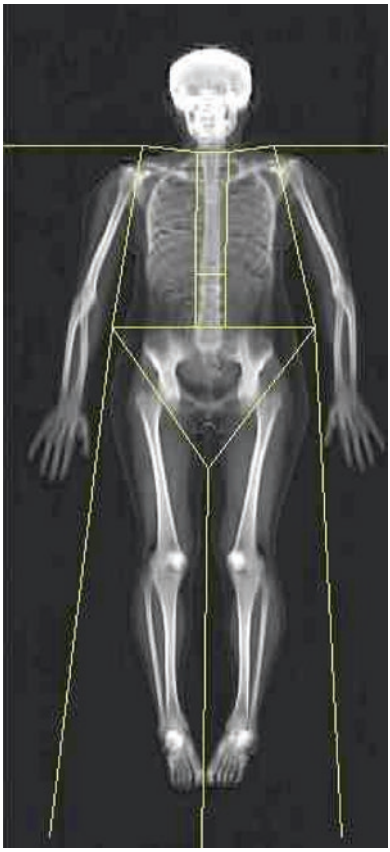

Fig. 7.1 Whole-body DXA scan image of a healthy 15-year-old girl

buttons and metal on clothing or undergarments, and items in pockets. Ideally the patients should be wearing scrubs, gown, or light clothing without metal or thick plastic that would interfere with the scan image. DXA scans should not be obtained within 7 days of the patient having had an x-ray with contrast material or within 3 days of nuclear medicine studies.

The spine scan measures bone area, BMC, and aBMD of L1-L4 (Fig. 7.2). Although data are reported separately for each vertebra and for the total L1-L4 region, information for the total L1-L4 region is typically used for assessing results as the larger, combined bone area has better precision than a single vertebra. Some studies reported the aggregate values for L2-L4. It is important to note the region being reported upon on the DXA report as L1-L4 and L2-L4 results differ and are not interchangeable. Results for bone area, BMC, and BMD typically increase moving from L1 to L4. Notable deviations from this may indicate the presence of an artifact or vertebral fracture. Common artifacts in the spine scan include rods, umbilical piercings, and undissolved calcium supplements within the intestine. Vertebral fractures may be suspected if the vertebra has a shorter height, smaller

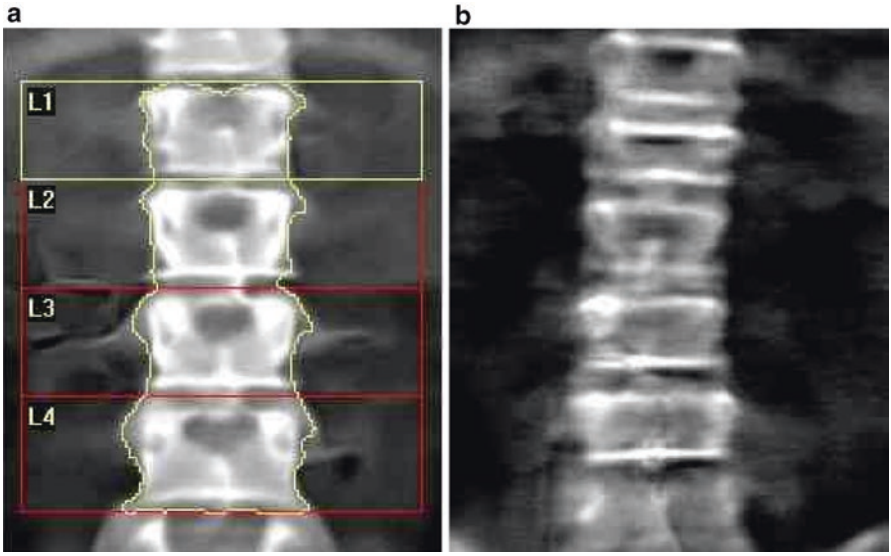

Fig. 7.2 Lumbar spine DXA scan images: (**a**) healthy 15-year-old girl; (**b**) 14-year-old boy with multiple vertebral fractures

bone area, nonparallel end plates, and areas of extreme density on the vertebral end plates (Fig. 7.2).

The hip scan provides bone results for the total hip and the femoral neck subregion (Fig. 7.3). Other subregions such as Ward's triangle are not recommended for clinical use. In very obese individuals, a panniculus may overlie the hip region and affect results. The patient should be asked to lift the panniculus away from the scan region before scanning. Other artifacts that commonly occur in the hip region include pins in the femoral neck, coins in pockets, and buttons or metal on clothing or undergarments.

BMC and aBMD values from the ultra-distal and one-third radius regions of the forearm scan (Fig. 7.4) can also be used for bone health assessments, although its use is less common. It can be of great value, however, when it is not possible to perform scans of other skeletal sites due to contractures, indwelling hardware, or for patients who exceed the weight limit of the table. The forearm scan may be of high interest in the patient who has experienced multiple forearm fractures. aBMD at the one-third radius site has been associated with forearm fractures in several studies [9–12]. Scans should not be performed on forearms with indwelling hardware, casts, or splints or if a cast or split has recently been removed since values may be lower due to recent immobilization.

The lateral distal femur scan (Fig. 7.5) is a customized scan developed for patients who have indwelling hardware, multiple vertebral fractures, or contractures preventing comfortable positioning for other scans [13, 14]. It is also useful for

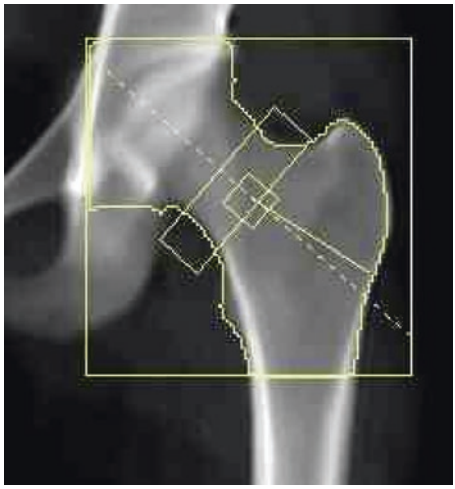

Fig. 7.3 Hip DXA scan image of a healthy 15-year-old girl

Fig. 7.4 Forearm DXA scan image of a healthy 15-year-old girl

assessing bone health in non-ambulatory patients as aBMD at the lateral distal femur is a strong predictor of femur fractures in these patients [15]. Analysis of lateral distal femur scans is achieved by creation of three regions of interest. aBMD results for each region can be compared to published sex- and age-specific reference ranges [14, 16]. aBMD results from lateral distal femur scans have been found to have good reliability [17].

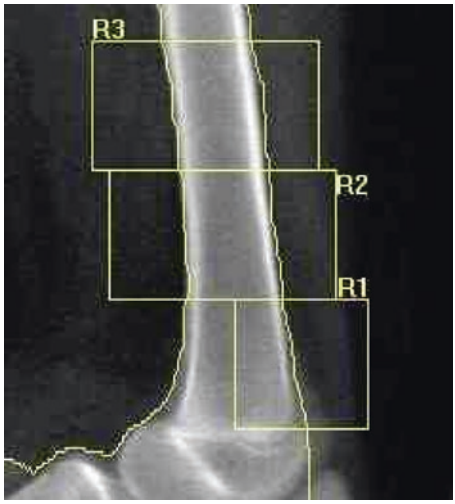

Fig. 7.5 Lateral distal femur scan

Interpretation of DXA Results

Peter is a 14-year-old with short bowel syndrome, short stature, and delayed puberty. His spine Z-score by DXA is reported as −2.4, but the height-for-age-adjusted Z-score is −1.4, and his bone age-adjusted Z-score is −1.0.

BMC and aBMD increase during growth and maturation, and bone mineral accrual trajectories differ between males and females. Sex differences in BMC and aBMD are pronounced with the onset of puberty, making it important to have sex-specific reference data in older children, adolescents, and adults. BMC and aBMD also vary by population ancestry. Higher BMC and aBMD values are evident in Black (African ancestry) compared to non-Black children by 5 years of age, and these differences increase in adolescents and adults [18–21]. Comparisons among other population ancestry or ethic groupings are smaller. The clinical interpretation of a BMC or aBMD results requires knowing if the value obtained for a patient is similar to what is expected for their age, sex, and population ancestry. As such, BMC and aBMD results are expressed as Z-scores (the number of standard deviations above or below the median according to age-, sex-, and ancestry-specific norms). Under no circumstance should T-scores (comparison to peak bone mass, assumed to occur by age 30 years) be used in pediatric densitometry assessments. Reference data used to calculate Z-scores are specific for the type of densitometer used (e.g., Hologic vs. GE Lunar) as bone density values from different manufacturers are not interchangeable [22]. Reference data for aBMD of the whole-body, lumbar spine, hip, and forearm scans are incorporated in the machine's software, and Z-scores are automatically generated when the scan is analyzed.

Interpretation of BMC and aBMD results can be erroneous in situations when the patient has altered growth or maturation. BMC and aBMD are positively associated with weight and height throughout childhood and adolescence [23, 24], due in part

to age-related increases in body size, bone thickness, and volumetric BMD (vBMD). As discussed above, DXA measures of aBMD (e.g., g/cm^2) are inherently influenced by bone size due to the two-dimensional nature of DXA. Thus, some means of adjustment of BMC and aBMD for bone size is necessary in situations of advanced or delayed skeletal growth relative to peers to prevent erroneous interpretation of bone mineral status. This is of great importance for adolescents with chronic diseases complicated by poor growth or those receiving glucocorticoid therapy resulting in short stature – aBMD Z-scores may overestimate bone deficits in these patients. Often, these are the patients that are referred for bone health assessments.

Different strategies have been proposed to account for or remove size-related effects on DXA results to enable a more appropriate bone health assessment of children and adolescents. Some have expressed BMC as a function of height or bone area rather than age, and others have calculated Z-scores using height age rather than chronological age [7, 25]. Height age is the age at which the child's height was the median value for height from growth charts. A disadvantage of these approaches is that it compares a child who is short for age to a younger, less mature child of similar height.

One size-adjustment approach that is gaining support is to calculate bone mineral apparent density (BMAD, g/cm^3), an estimate of volumetric BMD from lumbar spine DXA measures. BMAD is calculated by dividing BMC by the projected bone area to the power of 1.5 [26]. Crabtree et al. recently published age-, sex-, and ancestry-specific reference data for spine BMAD for individuals aged 4–20 years for scans acquired on both GE Lunar and Hologic DXA scanners [22]. Notably, BMAD values were about 30–40% higher from GE Lunar scanners than from Hologic scanners. BMAD values increased with age, and sex differences were apparent after the onset of puberty with females having higher BMAD values than males. Similar to aBMD, ancestry differences in spine BMAD are evident with Blacks and South Asians having higher values than Whites of the same age and sex. The clinical value of BMAD was recently demonstrated. Among several size-adjustment techniques for spine DXA measurements, it was the best at predicting of fracture in a large ($n = 450$) clinical sample of children [7].

Another bone size correction approach that seems promising is to adjust BMC and aBMD Z-scores for height-for-age Z-score (HAZ) via regression models [21, 25]. The rationale for this approach is that it simultaneously considers both height and age. Zemel et al. tested different height adjustment strategies and found that adjusting BMC and aBMD Z-scores for HAZ was more effective in reducing height-related biases than using height age, BMC for height, or BMAD (Fig. 7.6) [25]. The diagnostic performance of HAZ-adjusted aBMD Z-scores for fracture prediction has not been established. Currently, DXA software does not generate HAZ-adjusted aBMD Z-scores, but they can be calculated using a website calculator for aBMD measured on Hologic densitometers (https://bmdcs.nichd.nih.gov/zscore.htm).

Advanced or delayed skeletal maturation may occur along with advances or delays in skeletal growth. As such, some clinicians may find it useful to calculate aBMD Z-scores using bone age instead of chronological age, especially when the bone age is

2 or more standard deviations above or below a patient's chronological age. This is accomplished by entering a pseudo birth date (i.e., the birth date assuming the bone age was chronological age) into the DXA scanner so that the "bone age Z-score" can be calculated. This approach has not been evaluated relative to actual reference ranges created as a function of bone age, as they have not been developed to date.

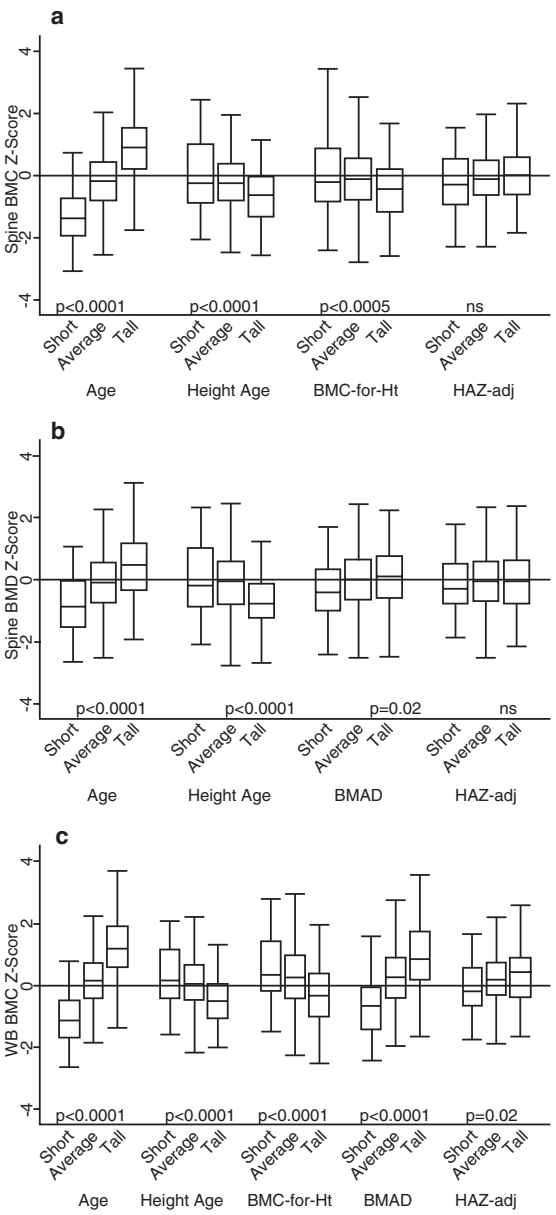

Fig. 7.6 Comparison of height adjustment strategies from Zemel et al. [25]. (**a**) Spine BMC and (**b**) spine BMD Z-scores for age, compared with Z-scores calculated using height-for-age, BMC-for-height, BMAD, and HAZ-adjusted (HAZ-adj) Z-scores for short (HAZ < −1), average (−1 ≤ HAZ < 1), and tall (HAZ > 1) children. (**c**) Whole-body BMC Z-scores for age, compared with BMC Z-scores height-for-age, BMC for height, BMAD, and HAZ-adj for short, average, and tall children. An unbiased adjustment methods will have a similar Z-score distribution among short, average, and tall children (Reprinted from Zemel et al. [25]. With permission from Oxford University Press)

In older children and adolescents, consideration of body composition, especially lean mass, may be useful when interpreting whole-body BMC measures [23, 27]. During growth, muscle and bone mineral accrue in concert owing, in part, to hormonal signals regulating growth of these tissues. In addition, muscle contractions place strains on bone that, in turn, stimulate bone formation and affect bone mass, density, and geometry. This phenomenon known as the "mechanostat hypothesis" was put forth over two decades ago [28]. Research studies have demonstrated that accounting for lean body mass along with BMC is better than BMC alone in predicting fractures [7, 29]. The way to operationalize this knowledge for clinical practice is not entirely clear. Some advocate that evaluation of the bone-muscle unit may enable clinicians to distinguish primary bone deficits from those due to a deficit in muscle forces on bone [28]. A primary bone deficit would be suspected if BMC was lower than expected for lean mass or muscle size. A muscle deficit would be suspected if lean mass (muscle size) was too low for height. Reference data on lean mass for height have been published for healthy children and adolescents enabling this type of evaluation [30].

Follow-Up Scans

Healthy children and adolescents generally maintain the same aBMD Z-score over time as they grow and gain bone mass and density. In other words, aBMD Z-scores track over time, similar to what is seen with gains in height along a growth curve [31, 32]. Follow-up DXA scans help clinicians determine whether bone accrual during the interval was the amount expected for the patient's age (e.g., Z-scores stays the same), if bone accrual was less than expected or lost since the prior scan (e.g., Z-scores would decline), or if bone accrual was greater than expected for the patient's age (e.g., Z-scores would increase). Follow-up scans are critically important to monitor effectiveness of bone therapies or when clinical disease activity has changed.

Determining whether a real change in aBMD has occurred depends on the precision or reproducibility of the measurements. The concept of least significant change (LSC) was developed to define statistically when a real change may have occurred given the known precision of the measurement in a given population. Precision of BMC and aBMD measurements varies across skeletal sites, clinical populations, and DXA centers; thus, the LSC varies across these as well. The ISCD recommends that each DXA center determine the LSC values for their DXA technicians to enable interpretation of changes in aBMD measures [33]. Namely, a real change in aBMD has occurred if the interval change in aBMD is greater than the LSC. Interpretation of follow-up scans for pediatric patients is a two-step process: determining whether a real change in aBMD occurred (e.g., relative to the LSC) and if the change was greater or less than expected for age (e.g., change in Z-scores).

The optimal frequency of obtaining follow-up scans is often questioned. Clinicians and patients want to know if a treatment is effective as soon as possible. However, bone accrual and response to treatment are slow processes, and gains in BMC or aBMD may be small relative to the precision of measurement. The concept

of a monitoring time interval (MTI) was developed to help shed light on the minimum time interval for obtaining follow-up scans that considers the expected growth-related gains in aBMD in children and adolescents [8]. The MTI is the time between two aBMD measurements during which 50% of the population changes more than the LSC. The MTIs vary by age given that the expected change in aBMD differs greatly as a function of age [8]. MTIs are ≤0.5 years for the spine, whole body, and hip during rapid pubertal growth. In general, MTIs are shortest for the spine (0.2–1.1 years) and longest for the femoral neck and distal one-third radius (0.6–4.3 years). Current guidelines are that DXA scans should be repeated at most every 1–2 years for clinical purposes. It may be helpful to repeat scans after 6 months when therapy with bone-altering agents is initiated and large increases in aBMD are expected.

Common Challenges with DXA

In addition to growth and maturational delays described above, there are a variety of other situations in which interpreting DXA results is challenging. When foreign bodies (e.g., orthopedic rods, ports, belly button rings) are present in the region of interest, it is wise to obtain a scan of an alternate skeletal site. The presence of a vertebral fracture, foreign body, or severe scoliosis in the L1–L4 region invalidates results from affected vertebra. These artifacts may be identified by examining the image and the aBMD results. The aBMD should increase progressively from L1 to L4. A vertebral fracture or foreign body may be present if one of the vertebrae is excessively dense. Some DXA software will report Z-scores for each lumber vertebra, but many times this option is not available. In these cases, the DXA technologist can exclude the affected vertebra from the region of interest and recalculate the total BMC or aBMD. This manuever is helpful when there are follow-up scans so that the rate of change can be calculated the following year. If a vertebral fracture is suspected, the clinician ordering the DXA scan should be alerted so that spine radiographs can be obtained as part of that patient's clinical care.

Vertebral Fracture

Although DXA has replaced radiography for assessment of bone density, spine radiographs play an important role in bone health assessment when a vertebral fracture is suspected. Vertebral fractures are rare in healthy children or adolescents in the absence of severe trauma. However, vertebral fractures are more common than previously appreciated among children with chronic inflammatory or disabling conditions and those receiving prolonged treatment with glucocorticoids. A vertebral fracture should be considered in situations of unexplained back pain. Despite growing awareness of vertebral fractures in specific pediatric chronic disease populations, a large proportion of vertebral fractures are missed as the patient is

asymptomatic. Studies in children report that only about half of vertebral fractures identified via imaging are symptomatic and come to clinical attention [34]. Early identification of vertebral fracture is useful for guiding initiation of pharmacologic therapies especially since there is evidence for normalization of vertebral morphology with treatment in prepubertal children [35].

Vertebral fractures are typically determined by visual inspection of lateral spine radiographs. The height of a given vertebra is compared to the height of adjacent vertebra. Height reduction can occur in the anterior, posterior, or mid-vertebral locations giving rise to anterior wedge, posterior crush, or biconcave fractures. Fractures also may be identified by comparison of heights within a given vertebra (e.g., anterior vs. posterior heights). A skilled reader can distinguish vertebral deformities due to fracture from normal variants or pathologies. The vast majority of spine fractures in children are anterior wedge fractures. The distribution of fractures along the spine is bimodal with peak fracture occurrence at T6-T7 and L1-L2 regions in adolescents [36, 37]. This fracture pattern may result from the mechanical forces induced by natural kyphosis and lordosis. The severity of fractures is often graded using a semiquantitative classification scheme, such as that proposed by Genant et al. [38]. Height reductions of >20% to <25% are considered mild fractures, height reductions of 25 to <40% are moderate fractures, and height reduction of ≥40% are severe fractures. Other classification schemes have been proposed but have not been used as widely in pediatric populations.

Lateral spine imaging for vertebral fracture assessment (VFA) is possible on some DXA devices. Advantages of VFA are the lower radiation exposure compared to spine radiographs (≈42 μSv vs. ≈ 97 μSv) [36] and the convenience of obtaining a bone density measurement and fracture assessment with the same device. VFA images are evaluated and rated like that of conventional lateral spine radiographs. The ISCD endorses VFA for detecting vertebral fractures in older adults (women ≥70 years and men ≥80 years), individuals with historical height loss of ≥1.5 inches, or individuals who had glucocorticoid therapy equivalent to ≥5 mg prednisone per day for ≥3 months [39]. VFA has not been used widely in pediatrics owing to early studies finding poor performance in children [40]. Recent studies using newer DXA systems with better image resolution, however, have found that VFA is as good as conventional radiography in identifying moderate to severe vertebral fractures in children and adolescents [36, 41, 42].

A quantitative morphometric analysis of DXA VFA images can also be performed, although the accuracy, and therefore the utility, of this technique is still being determined in children and adolescents. To do so, the operator places 6 points on each vertebra corresponding to the four corners of the vertebral body and the midpoints of the vertebral end plates. The software determines vertebral heights for each vertebra and compares it to adjacent vertebra. Similar to the Genant semiquantitative approach, height ratios are used to classify the severity of fractures as mild, moderate, or severe deformity. Despite the quantitative nature of this technique, it is not a recommended stand-alone technique for detection of vertebral fracture in adults or children [39]. Compared to an expert radiologist evaluating spine

radiographs, the morphometric analysis overestimates the prevalence of mild vertebral fractures in children and adolescents, and there is only moderate concordance (kappa = 0.69) in detection of moderate and severe fractures [36].

QCT

Quantitative computed tomography (QCT) is another technique for measuring bone density that does not suffer from the two-dimensional limitations of DXA. QCT is a three-dimensional technique that quantifies true volumetric BMD in mg/cm^3 and is independent of bone size. QCT can measure cortical and trabecular bone compartments separately, which is an advantage as trabecular bone turns over more rapidly than cortical bone and may be a better marker of metabolic perturbations in some clinical conditions. In addition, QCT can assess geometric aspects of bone that may contribute to its strength. QCT devices include general-purpose whole-body scanners to measure vBMD of the trabecular compartment in the lumbar spine and hip (axial sites) and special peripheral QCT (pQCT) and high-resolution pQCT (HR-pQCT) scanners to measure cortical and trabecular compartments in the arms and legs (peripheral sites).

Studies involving QCT, pQCT, and HR-pQCT have provided more in-depth understanding of changes apparent by DXA as well as those related to specific disease conditions and therapies. HR-pQCT quantifies several trabecular (thickness, number, and connectivity) and cortical (vBMD, porosity, and thickness) measures, thereby providing insight into discrete components of bone strength. In addition, it yields micro-finite element analysis of failure load, a measure of biomechanical competence. Studies of HR-pQCT have shown impaired bone strength (failure load) and low total vBMD, bone volume ratio, trabecular thickness, and cortical area of the radius to be associated with low-energy forearm fractures [43, 44].

Axial QCT is largely a research tool in children and adolescents owing to the greater radiation exposure and lack of reference data needed to interpret scan results. The ISCD found no preferred QCT methodology for clinical application in children [45]. Different medical conditions require the use of different quantitative techniques to adequately characterize bone deficits. For many medical conditions, no comparative studies of different techniques have been performed. Major components needed to justify recommending clinical application of QCT are absent, such as consensus on optimal measurement sites, normative ranges, precision and accuracy errors, and how well it predicts risk of fracture. QCT, pQCT, and HR-pQCT are primarily research techniques used to characterize bone deficits in children.

Summary

DXA scans of the spine and whole body are recommended for bone health assessments in children and adolescents due to their low radiation exposure, speed, precision, widespread availability, and abundant reference data. Large strides have been

made to identify appropriate size-related adjustments of aBMD Z-scores to prevent erroneous interpretation of results in children and adolescents with growth delay. Follow-up DXA scans at 1- to 2-year intervals may aid clinical management. Recent advances in VFA by DXA are encouraging, and VFA may prove to be an efficient method for detecting moderate to severe vertebral fractures in children and adolescents. Although QCT, pQCT, and HR-pQCT have yielded deeper insights into bone changes with growth and disease, they remain research tools in children and adolescents.

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Bone Health in Adolescents with Multiple Fractures

8

Kristen Miller Nathe and Jaime Rice Denning

Incidence of Adolescent Fractures

A 13-year-old female presents having sustained her third lifetime fracture. She has broken her tibia at 8 years old when playing basketball, her right forearm at 10 years old when she slipped and fell while ice skating, and her left wrist this year in a soccer game. Her mother wonders if there is something wrong with her bones.

There are a few large epidemiological studies regarding how common fractures are during childhood and adolescence. One British study using the General Practice Research Database from a cohort of 7,000,000 residents between 1988 and 1998 found that the incidence of sustaining a fracture between the ages of 0 and 17 was 133.1/10,000 person-years. This translates to approximately one-third of children in the population sustaining a fracture before adulthood. The incidence of fractures peaked at age 14 for boys and age 11 for girls. The most common site of fracture was the radius and ulna, accounting for 30% of all fractures recorded [1]. In a study including a single university hospital serving northern Sweden from 1993 to 2007, the accumulated risk of sustaining a fracture between ages 0 and 17 was 34%, with peak incidence at age 13–14 for boys and 11–12 for girls. The most common fracture site was the distal radius and ulna [2]. The reported risk of sustaining a fracture between ages 0 and 16 in another Scandinavian study of fracture epidemiology was 42% for boys and 27% for girls, and distal radius fractures were the most common location [3]. Although these large studies, and others not detailed above, varied in geographic location, climate, and demographics, the incidence of fractures, peak age for sustaining a fracture, and most common site of fracture were very consistent among studies.

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The peak incidence for fractures seems to coincide with the pubertal growth spurt (peak height velocity) likely because there is a rapid and complex shift in bone length, bodily calcium requirement, and bone turnover [4–7]. Specifically, there is a relative decrease in bone mineral density transiently as the bone increases in length, and there is insufficient mineralization until the bone has reached its final length [8]. These skeletal changes are occurring at a time when patients are commonly participating in sports and recreational activities that may result in falls on an outstretched arm [6, 9, 10].

From 1998 to 2007 in the Hedstrom study cited above, there was a 59% increase in the incidence of fractures, which the authors attribute to multifactorial causes including a known increase in daily physical activity/organized sports among some Swedish children and a higher prevalence of overweight children in northern Sweden over that time period [2]. Both increased sporting activity and increased BMI are associated with higher rates of fractures [11, 12]. Although exercise is associated with increased bone mineral density (BMD), the higher BMD is not protective against the increased incidence of fractures associated with sports-related injuries. Children who participate in daily physical activity have double the fracture risk than children who do 3 or fewer days of physical activity per week [13]. In an American population-based study over different time frames, there was 32% greater incidence of distal forearm fractures among male children in 1999–2001 compared with 1969–1971 and 56% greater incidence of fractures among female children over the same time periods. The greatest increase in incidence occurred between ages 11 and 14 in boys and 8 and 11 in girls [14].

What Is Abnormal?

Multiple fractures are not uncommon in the pediatric population. In a birth cohort of 1037 children, 10.2% of children who fractured a forearm between 0 and 18 years old sustained two or more fractures at the distal forearm [15]. In large population-based studies including bones aside from distal forearms, the rates of multiple fractures are even higher, with 16–25% of pediatric patients sustaining more than one fracture during childhood [3, 16]. Since fracture risk comprises three main factors, it is logical to look for outliers among these three risk factors to help define what is abnormal when it comes to multiple fractures. The three risk factors include amount of force sustained at the time of injury, exposure to trauma, and bone density/quality. Additionally, the location of fracture (which bone is fractured) can help determine what is abnormal.

Any bone could break if there is a large enough force imparted upon it. Low-impact fractures are defined as fractures that occur with no trauma or from a fall no higher than standing height [17]. These low-impact fractures may signal poor bone health and should lead the clinician to obtain further history about the mechanism of injury and any previous fractures [18].

Regular vigorous exercise in children is associated with a two-fold higher fracture risk than less active age-matched children [13]. Thus, pediatric patients who are

Table 8.1 Definition of abnormal fracture history

Abnormal fracture history: One or more of the following in the absence of local disease or high severity trauma
≥ 2 arm or leg fractures by age 10
≥ 3 arm or leg fractures by age 19
≥ 1 vertebral compression fracture (>20% vertebral body height loss)

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active in sporting activities are exposed to more frequent situations that could result in fractures. It is the patients who have low physical activity and sustained fractures that should be more carefully monitored for repeat fractures or underlying lower BMD [19].

Lower bone mineral density (BMD) and its relationship with incidence of fractures/fracture risk in pediatric population have been the focus of several studies [20]. While lower BMD seems to correlate with increased fracture risk in children, the association between BMD and fracture risk is not as strong as it is in adults [21]. Risk factors for low BMD include low dietary calcium intake, including dairy allergy [20, 22, 23], and high body weight [20, 23, 24].

Isolated wrist or peripheral skeleton fractures are less likely to cause concern for bone health, but hip or spine fractures, especially in the setting of low-impact fractures, should urge the clinician to evaluate for underlying bone pathology [18].

As a summary of what is abnormal based on available evidence in children, the following three criteria (in the absence of high-energy trauma or local disease) define an abnormal fracture history: two or more long bone fractures by age 10, three of more long bone fractures by age 19, and one or more vertebral compression fractures with greater than 20% vertebral height loss. See Table 8.1 for the definition of abnormal fracture [25].

Work-Up for Multiple Fractures

When multiple fractures occur or are found to be abnormal in nature as described above, it is essential to understand the next steps. A thorough work-up may be warranted to investigate further and establish baseline data. Figure 8.1 provides an algorithm for evaluation of the adolescent with multiple fractures. The most important initial consideration is a comprehensive history and physical examination. The history should include both medical and nutritional histories and a detailed history of physical activity [18, 25]. The patient should also be assessed for their height, weight, and pubertal stage with attention paid to their growth charts. A deviation from the normal growth curve can signal that there could be a nutritional deficiency, metabolic process, hormone deficiency, or other medical problem contributing to an increased fracture risk resulting in multiple fractures. Physical activity history is significant because it has been noted that there is a decreased bone mineral density for adolescents with low physical activity and, on the opposite end

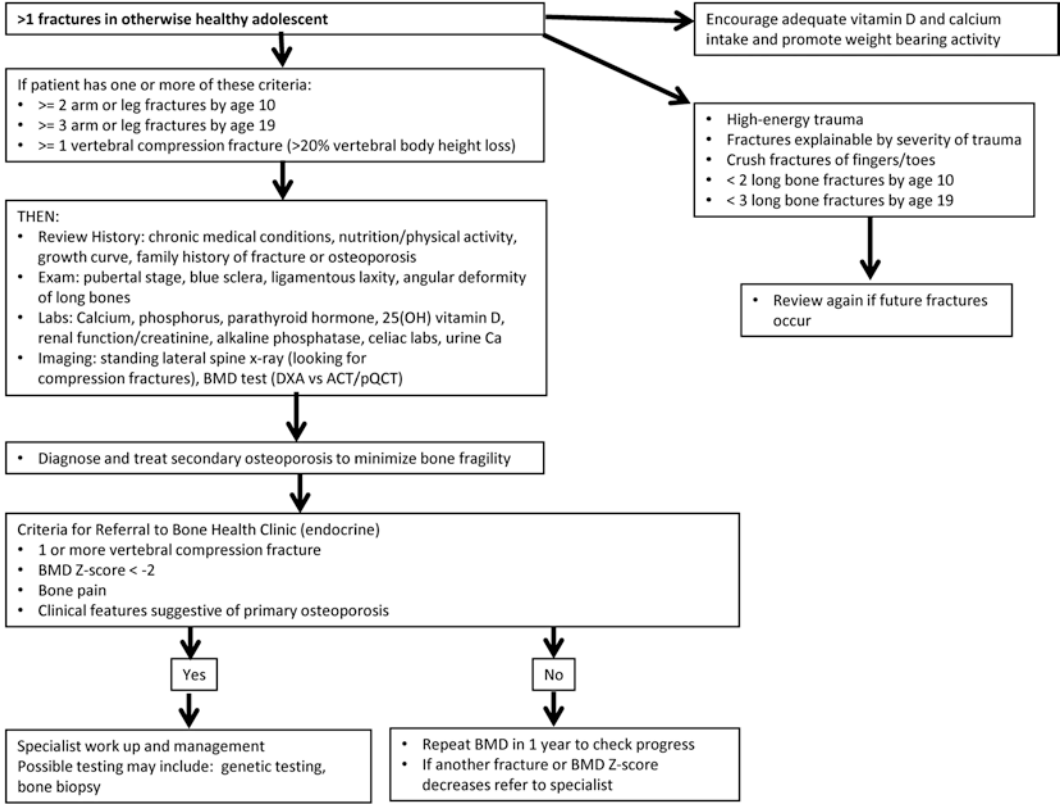

Fig. 8.1 Algorithm for the evaluation of an adolescent with multiple fractures (Reprinted from Ref. [25] with permission from Elsevier)

Table 8.2 Risk factors for multiple fractures

Nutritional deficiency/malnutrition
Low dietary calcium and/or vitamin D intake
Chronic inflammatory diseases
Medications
History of >3 fractures or axial skeletal fracture
Early age of first fracture
High body weight
Low physical activity
Lifestyle (e.g., smoking, soft drinks, reduced sun exposure)

Table 8.3 Differential diagnosis of primary disorders causing osteoporosis

Primary disorders	
Cause of osteoporosis	Disease
Impaired collagen	Osteogenesis imperfecta
Impaired collagen cross-link formation	Bruck syndrome
Connective tissue defects	Ehlers-Danlos syndrome
	Marfan syndrome
	Homocystinuria
Defective bone mineralization from low alkaline phosphatase activity	Hypophosphatasia
Impaired cell signaling and osteoblast function	Osteoporosis-pseudoglioma syndrome
	Idiopathic juvenile osteoporosis

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of the spectrum, increased fracture risk with adolescents involved in high demand or dangerous physical activities [13, 19].

Once it has been documented that a patient has risk factors (Table 8.2) for multiple fractures or meets the criteria for abnormal fractures, further investigation is performed. Several laboratory studies, such as nutritional and hormonal analyses, should be checked to rule in and out possible etiologies (Tables 8.3 and 8.4). Nutritional assessments done as a screening test are not normally recommended in the general adolescent population. However, in a patient as described above, physiologic stores of vitamin D should be checked by measuring a serum 25-hydroxyvitamin D (25[OH]D) concentration [26–29]. Levels at or greater than 50 nmol/L (30 ng/mL) are optimal for adolescents with a history of multiple fractures [25]. Calcium and phosphate homeostasis should be assessed by ordering serum calcium, phosphate, creatinine, parathyroid hormone, alkaline phosphatase (total), and urinary calcium excretion [25]. Bone turnover markers such as bone-specific alkaline phosphatase and cross-linked telopeptides are more useful when measuring response to treatment than for diagnostic purposes and can be challenging to interpret in growing children and adolescents [25]. Hormonal deficiencies

Table 8.4 Differential diagnosis of secondary disorders causing osteoporosis

Secondary disorders	
Causes of osteoporosis	Disease/medication
Medication induced	Glucocorticoids
	Antiepileptics
	Anticoagulants (heparin)
	Methotrexate
	Cyclosporine
Neuromuscular disorders: Reduced weight-bearing activity or muscle bulk	Duchenne muscular dystrophy
	Cerebral palsy
	Prolonged immobilization
Infiltrative conditions	Leukemia
	Thalassemia
Chronic inflammatory conditions	Juvenile idiopathic arthritis
	Inflammatory bowel disease
Endocrine abnormalities	Hypogonadism
	Growth hormone deficiency
	Hyperparathyroidism
	Hypercortisolism
	Juvenile diabetes mellitus
	Cushing syndrome
	Hyperprolactinemia
Vitamin and nutritional deficiencies	Vitamin D deficiency
	Celiac disease
	Anorexia nervosa
	Bulimia
	Cystic fibrosis
Renal disease	Chronic renal failure with secondary hyperparathyroidism
	Idiopathic hypercalciuria

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need to be investigated depending on the history and physical examination. Estrogen deficiency in adolescent girls can manifest as a decline in bone mass of 3–5% per year [30].

After the initial assessment has been performed, it can be helpful to gain more information from appropriate imaging modalities. Children and adolescents who have underlying bone fragility should be evaluated with a standing lateral spine radiograph [25]. It is not uncommon for adolescents with bone fragility to have vertebral body height loss or compression, but the compression is considered significant when the vertebral body height loss is greater than 20%. Up to 50% of these vertebral body compressions are asymptomatic and can simply be unnoticed [25]. The standing lateral spine radiograph allows a global overview of deformity such as increased kyphosis, as well as for measurements to be taken of vertebral body height.

When there is a suspicion of low bone mineral density as is the case for adolescents with a history of abnormal fractures or medical conditions associated with reduced bone mass, dual-energy X-ray absorptiometry (DXA) scans should also be performed as a baseline assessment [26, 29]. DXA, which provides a two-dimensional evaluation of bone, is considered a rapid, safe, and widely used method to detect areal bone mineral density [31]. Reference data for DXA have been collected for healthy children and adolescents; however, sparse data exist for adolescents with chronic illness and children younger than 5 years of age [31]. Interpretation of Z-scores in the adolescent by DXA can be challenging as this imaging modality can be confounded by bone size [31]. Normal DXA results can be found in adolescents with a history of multiple fractures; therefore, findings from a single DXA scan cannot be used in isolation to confirm or refute a diagnosis of bone fragility [26]. Studies suggest that bone mineral density in adolescents should be monitored no more frequently than yearly, but noting trend over 6 months may be useful in some clinical scenarios [29].

Recent literature has also reported the use of quantitative computed tomography (QCT) as a way to measure bone mineral density. QCT is a fast, noninvasive bone mineral density test performed on a computed tomography (CT) scanner most commonly examining the hip and spine [32]. A peripheral quantitative computed tomography, pQCT, is a type of QCT used for determining volumetric bone mineral density, the stress-strain index (SSI), and bony geometry in a peripheral part of the body, like the forearm or lower leg. The dose of radiation of a spinal QCT is higher than for a DXA, comparable to a spinal radiograph performed for patients suspected of having osteoporosis [32]. Peripheral QCT produces a negligible dose of radiation which is preferable in the adolescent population [32]. Currently QCT and pQCT are used more for research purposes than for routine clinical care, and their availability is often limited to academic research centers.

Lastly, referral to an endocrinologist or bone health clinic may be warranted for further work-up of multiple fractures. Referrals are advocated for adolescents with symptomatic bone pain or clinical features suggesting primary osteoporosis [25]. After initial work-up, a bone mineral density Z-score less than −2 or vertebral fractures seen on radiographs should initiate a referral for further evaluation and possible pharmacologic treatment [25]. Rarely, a patient may need genetic testing, as in the case of osteogenesis imperfecta, to look for the presence of the COL1A1 or COL1A2 gene mutations. Reserved for the most complex cases, a bone biopsy (usually trans-iliac) can also be performed to detect overall bone quality and turnover [25].

Differential Diagnosis for Multiple Adolescent Fractures

A history of multiple fractures in an adolescent that seems to conflict with the circumstances, such as the exposure to trauma or severity of trauma, may benefit from further exploration for any underlying condition contributing to bone fragility. Refer to the work-up as described above for adolescents with multiple fractures that are

suspicious for fragility fractures. Bone fragility can be the result of either a primary disease affecting bone or as an outcome to follow for an adolescent with a secondary disease or chronic medical condition. Tables 8.3 and 8.4 provide information on the most common diseases affecting bone health.

Primary osteoporosis can be caused by genetic conditions that encompass bone cell signaling, bone cell function, or bone matrix homeostasis defects. Secondary osteoporosis can be triggered from a combination of factors, including certain medication classes, long-term use of glucocorticoids, conditions causing increased inflammatory cytokines, inadequate nutrition, physical activity, and muscle bulk [33–35]. Rarely, a history of multiple fractures may be the initial presentation for an otherwise clinically silent disease, again signifying the importance of risk stratification and performing a proper work-up for those outside the norm [25].

Fracture Healing

Once a fracture has occurred, it initiates an intricate and sequential regenerative process in response to the injury. The injured bone can be healed by two mechanisms, primary or secondary healing. Primary healing occurs through intramembranous means where new bone is laid down without a cartilaginous intermediate forming a hard callus. Secondary healing involves enchondral healing with the assistance of the periosteum and surrounding soft tissues. Most fractures heal through secondary healing, unless they are rigidly fixed, usually via surgical intervention. In secondary healing, immature and disorganized bone forms between fragments, termed soft callus [36–39].

Fracture repair progresses through three closely integrated stages. The initial stage is considered inflammation because bleeding from the damaged tissues causes a hematoma at the fracture site which serves to stop blood loss and recruit growth factors and cytokines needed for healing [40]. Leukocytes, monocytes, macrophages, and multipotential mesenchymal cells reach the fracture site through increased endothelial vascular permeability [40]. Growth factors released at this time promote differentiation of the mesenchymal cells into osteoblasts and fibroblasts (bone-forming cells) [41–45].

In the repair stage, primary callus forms within the first 2 weeks after fracture. Secondary or enchondral ossification converts the soft callus to hard callus (woven bone). Callus formation within the medullary canal also supplements the bridging soft callus to increase the strength and stability. Early in fracture healing, type II collagen (cartilage) is produced, followed by the appearance of type I collagen (bone). The amount of callus is inversely proportional to the extent of immobilization. The closed treatment of fractures in a cast will typically result in a moderate amount of callus formation.

The last stage, remodeling, lasts long after the fracture is clinically healed. Remodeling involves incremental changes to the damaged skeletal segment until it regains its original shape and size [37, 39, 46]. Mechanically unnecessary portions of the callus are resorbed in remodeling, and the orientation of trabecular bone

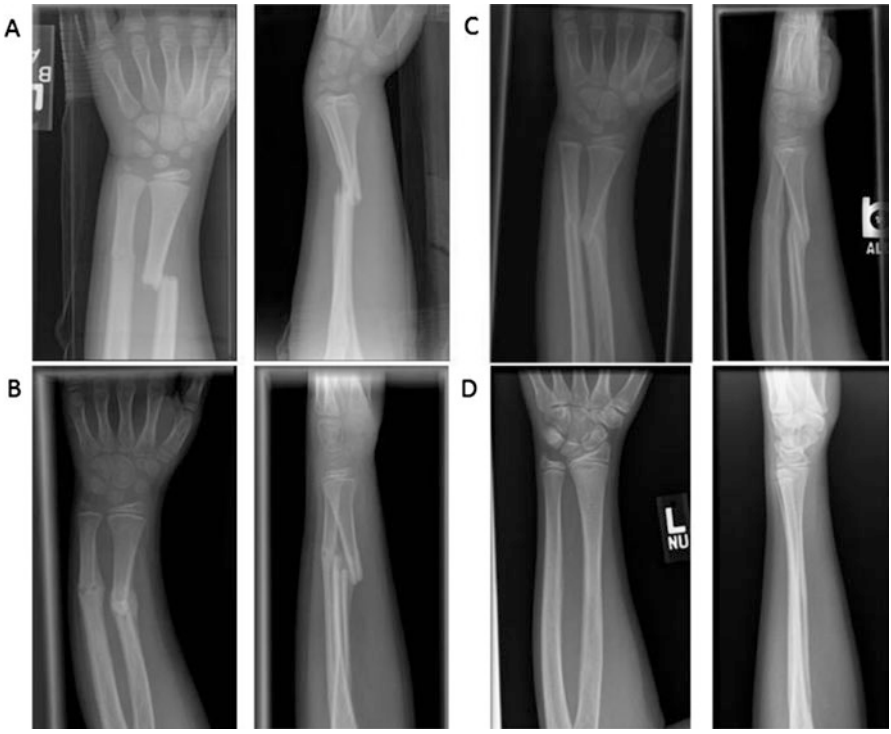

Fig. 8.2 Demonstration of bone healing and remodeling in adolescents. (**a**) Anterior-posterior and lateral radiographs depicting initial injury of a distal radius and distal ulna fracture with shortening and angulation. (**b**) Early healing with callus formation. (**c**) Late healing with remodeling. (**d**) Fully healed and remodeled with no evidence of prior fracture

subsequently forms along the lines of stress. The new bone shape is in response to Wolf's law stating that the bone remodels in response to mechanical stress. During this time, the cartilage that was laid down during enchondral ossification is calcified, new blood vessels invade the forming bone, and the bone is remodeled by the coordinated activity of osteoblasts (bone-forming cells) and osteoclasts (bone-resorbing cells). Figure 8.2 provides a radiographic depiction of bone healing and remodeling in the adolescent population.

Intrinsic mechanical properties of the bone, as well as how the tissue is organized, determine the strength of the bone. During bone healing, callus is weaker than intact bone, but because the callus is further from the center of the deforming force, the moment of inertia is increased, in turn causing an increase in the strength of the bone [47]. The bone of a child or adolescent has a thick periosteal layer that helps in widening the callus, causing children to form a callus of larger diameter than adults. The larger-diameter callus and the fact that children form new bone faster than adults allow children's bone to recover its original strength much earlier following a fracture than adults [47].

In adolescents with multiple fractures, many variables exist that can affect fracture healing and, subsequently, bone strength. Bone healing can be affected by intrinsic variables such as blood supply to the bone, head injury, and mechanical factors. Blood supply is the most important variable to bone health, and after initial flow disruption following the fracture, blood flow increases and peaks around the 2-week point and normalizes by 3–5 months [48]. An increased osteogenic or bone-forming response can occur with a brain or spinal cord injury. This response can happen at the site of a concomitant fracture that occurred at the time of the head injury or at uninjured sites (usually around large joints like elbow or hip). The etiology and pathophysiology of this increased bone formation in the setting of head injury are unknown but likely involve a still-unidentified inducing agent causing osteoblastic stem cells to activate [49]. Mechanical factors influencing fracture healing include bony soft tissue attachments, mechanical stability (can be impacted by the type of fracture immobilization), location of the injury, amount of bone loss, and fracture pattern.

Individual patient factors can also interfere with fracture healing such as diet, diabetes, nicotine use, HIV, certain medications, and chronic medical conditions. Nutritional deficiencies, specifically calcium and vitamin D, can be contributing factors to bony nonunion [18, 29]. Patients with diabetes mellitus have a fracture healing rate that is 1.6 times longer than patients without this disease [50] through decreased cellularity of the callus, diminishing the strength of the callus, and delaying enchondral ossification. Nicotine use inhibits the invasion of new blood vessels into newly forming bone, decreasing the rate of healing as well as the strength of the fracture callus [51]. HIV can be associated with a higher prevalence of fragility fractures with associated delayed healing. Medications that influence fracture healing include bisphosphonates (long-term use has been associated with osteoporotic fracture and increased healing times), corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs) (prolonged healing time), quinolones (toxic to chondrocytes that are needed in repair of a fracture), and medroxyprogesterone [27]. However, the most recent data suggest that NSAIDs do not delay bone healing in children and adolescent patients [52, 53]. Tables 8.3 and 8.4 provide a list of chronic medical conditions that can cause increased fracture risk.

Risk of Repeat Fracture

There is a paucity of literature on repeat fracture rates in the pediatric and adolescent population. Most of the current literature is focused on the re-fracture risk related to forearm fractures within the pediatric population. Fractures of the radius and ulna are extremely common during adolescence, accounting for approximately 30% of all fractures [1]. The distal forearm is the most common site of fracture during childhood or adolescence [10, 54]. It has also been found to be the most common site of re-fracture in the pediatric population [54].

Re-fractures can occur in children's forearm fractures despite the extraordinary potential for rapid healing and remodeling [55]. There is a relatively low incidence

of re-fractures in children as compared to the adults. Multiple historic sources have established a pediatric forearm re-fracture rate of 4–8% [56–59]. More recently in a 2006 study by Ferrari et al. [60], only one case of forearm re-fracture, rate of 1.7%, was detected in 125 female children with 58 forearm fractures after being followed prospectively for 8 years. In 2015, Tisosky et al. [61] reported a re-fracture rate of 1.4%, or 36 repeat fractures in 2590 patients. The newer reported forearm re-fracture rates suggest that the historic data rate of 4–8% may be exaggerated.

In a study by Fung et al. [62], distal radius fractures in children were studied prospectively to assess the difference in bone mineral density (BMD) and bone mineral content (BMC) after casting to determine the overall change in bone health. This study found that there was no difference in BMD or BMC at the time the cast was taken off or at the 1-year point, but from cast off to 24 weeks, there was a transient elevation in both [62]. The site of fracture was found to be denser than the non-fractured arm within the first 3 months after a distal radius fracture suggesting that bone density improves quickly in children and may be stronger around the site of fracture [62]. White et al. [63] found that a fully healed fracture in a rabbit tibia will re-fracture at a location unrelated to the site of initial fracture. This suggests that callus formed during fracture healing may protect an area around the original injury from subsequent re-fracture [63].

The location of fractures along the bone can impact the likelihood of re-fracture at the same site of injury. For example, the location of the initial fracture along the radius and ulna can factor into the rate of repeat fracture. In the study by Tisosky et al. [61], the researchers found that the most common region of bone to re-fracture was the middle third comprising 78% of the documented re-fractures. Out of 36 re-fractures from 2590 initial fractures, 78% re-fractured in the middle third, 3% in the proximal third, and 19% in the distal third [61]. Bould et al. [56] established that a fracture of the diaphysis of the forearm is over eight times more likely to re-fracture than the distal forearm. Again, Baitner et al. who documented that the distal radius is less vulnerable to re-fracture as compared to the proximal radius corroborate this concept [55].

Many factors can contribute to the risk of repeat fracture in the adolescent population. Almost all of these factors are related to the initial injury in terms of fracture type, site of fracture, method or length of treatment, bony reduction, and bone healing. Greenstick fractures, or incomplete fractures due to bending of the bone, have led to repeat fractures due to healing with a less exuberant callus formation potentially decreasing the strength of the healed bone [56, 57, 64]. The location of injury, middle and proximal third shaft fractures, has been discussed previously as being a risk factor for forearm repeat fractures [54, 55, 61]. The method and length of treatment can increase the rate of re-fracture. For example, early cast removal before 6 weeks was found to contribute to re-fracture risk in forearm fractures [56, 64]. Inappropriate technique of cast immobilization can lead to a larger risk of re-fracture by inadequately holding the fracture alignment increasing the likelihood for malunion or noninion [64].

Bony alignment is another factor that increases the risk for repeat fractures. When speaking about forearm fractures in adolescents, many are displaced and

Table 8.5 Risk factors for re-fracture

Risk factors for re-fracture
Inadequate immobilization (early cast removal)
Incomplete bony union
Inadequate reduction (residual angulation)
Location – Middle and proximal one-third forearm fractures
Age – (skeletal immaturity, younger age)
Level of activity (higher impact activity/sports)

need to undergo a reduction. A reduction usually consists of a closed manipulation of the fracture performed under sedation to restore the anatomic bony anatomy. The alignment is then maintained by casting or splinting. Residual angulation in the bone from either an inadequate reduction or incomplete fracture remodeling has been described as a risk factor for re-fracture [55, 56]. In the forearm, residual angulation greater than 10° was found to be a risk of re-fracture by Tisosky et al. [61] In the distal humerus, another common site of fracture, residual cubitus varus was noted to increase the rate of re-fracture [64].

Fracture healing is another important risk factor for re-fracture. Baitner et al. [55] reported that of 63 forearm re-fractures, fracture line visibility of the radius was noted in 48%, and 67% had visibility of the ulnar fracture line at the latest follow-up. Incomplete bony consolidation on radiographs has been noted by multiple sources to contribute to re-fracture risk of forearm fractures [56, 57, 64]. Please see Table 8.5 for a list of the most common risks for bony re-fracture.

Re-fractures have been described in medical literature dating back to 1942. Blount et al. described re-fracture of bone can be common within the first 6 months after trauma [65]. Re-fractures in regions of incomplete bony unions have been found in subsequent studies to most commonly occur within 5 months of the initial fracture [64, 65]. For forearm re-fractures, literature varies on the average time to re-fracture. Schwartz et al. suggests that re-fracture of the forearm is seen at an average of 14 weeks after the primary fracture [57]. Meanwhile, Tisosky et al. reported that the average time to re-fracture after the initial fracture was declared "healed" was 14 weeks with 42% of the re-fractures within the first 6 weeks after clearance [61]. Bould et al. discussed that the risk of re-fracture of the forearm decreases with increasing time from removal of the cast and the risk plateaus at 16 weeks postfracture [56]. Overall, historical literature observes that only 5% of children who fracture their forearm will re-fracture within 18 months [56, 57].

Besides the forearm, fractures of the clavicle have been studied and show a re-fracture rate of 1.6% within 1 year following fracture [66]. The re-fracture rate for clavicle fractures was found to be higher at 26% when the initial angulation was less than 40°, compared to 6% with an initial angulation greater than 40°. This is similar to greenstick fractures of the radius and ulna [66]. In the same article, 18% of the 120 patients re-fractured the same clavicle and 4 patients had more than one re-fracture [66].

Patient age and activity level also relate to the risk of re-fracture in the pediatric population [55–57, 66]. Masnovi et al. [66] detail that re-fracture rates are higher in younger children and prove that the risk of re-fracture of the tibia was found to be

significantly higher for a younger age at time of surgery and continues to be higher until skeletal maturity. Fung et al. [62] observed a significant effect of age on the rate of change in bone mineral content: the older the patient, the greater the change in mineralization after a simple upper extremity fracture with casting. The nature and level of activity of the child have also been associated with risk of re-fracture, such as with more accident-prone children and children involved in competitive sports [55–57]. The lifestyle of the child should be taken into consideration when determining activity limitations and length of fracture protection to prevent re-fractures [55]. It is also important to recognize that some re-fractures may be completely unrelated injuries that no period of rest or protection may avoid [55].

Summary

Most fractures that occur during adolescence are considered a normal part of childhood and are not a cause for concern. However, it can be abnormal to present with multiple fractures during this period of growth and development, especially when the mechanism of injury is mild. It is important to be able to recognize and identify adolescents who warrant further work-up and evaluation. A definition of clinically significant fracture history and an algorithm for work-up is presented. Bone healing when a fracture arises is discussed, as well as the low repeat fracture risk in adolescents.

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Bone Health in Adolescents with Eating Disorders

9

Neville H. Golden

Jen is a 15-year-old female with anorexia nervosa who has been followed in your practice since early childhood. She has a 1-year history of anorexia nervosa, diagnosed after losing 20 lbs. in order to "become healthy." Her last menstrual period was 18 months ago. One month ago, she sustained a fracture of the forearm when she fell during a soccer practice. DXA measurements revealed a lumbar spine Z-score of −2.5 and a total hip Z-score of −2.0. She has been in treatment with a multidisciplinary team for the past year and has gained 12 lbs. However, she still has not resumed menses. Her BMI is 18.9 kg/m². What strategies would you recommend to optimize her bone health?

Eating disorders (EDs) are prevalent in adolescents with an estimated lifetime prevalence of 5.7% for adolescent girls and 1.2% for adolescent boys [1]. Onset is typically during adolescence [2], the period during which 40–60% of peak bone mass is accrued [3]. Multiple studies have demonstrated that both boys and girls with anorexia nervosa (AN) have reduced bone mineral density (BMD) at one or more skeletal sites compared with age-matched peers. Most of the research on bone health in adolescents with EDs has been conducted in patients with AN, but patients with other EDs can also have impaired bone health, especially if they are underweight or amenorrheic. Although some improvements in BMD can occur with weight restoration and resumption of menses, persistent deficits remain, and long-term fracture risk is increased. The aim of this chapter is to review how bone health is impaired in patients with EDs and to discuss current treatment approaches in this population.

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Table 9.1 Key features of *DSM-5* diagnostic criteria for feeding and eating disorders

Diagnosis	Key features	Body weight
Anorexia nervosa	Restriction of food intake leading to lower-than-expected body weight	Low
	Intense fear of gaining weight or becoming fat	
	Distorted body image	
Bulimia nervosa	Recurrent episodes of binge eating – Eating a large amount of food in a discrete period of time	Usually normal but may be high or low
	A perceived sense of lack of control during a binge	
	Unhealthy compensatory behaviors following a binge to prevent weight gain (e.g., self-induced vomiting, food restriction, excessive exercise, or use of laxatives, diuretics, diet pills, or other medications)	
	Behaviors occur at least once a week for 3 months	
	Self-worth is overly based on body shape and weight	
Binge eating disorder	Recurrent episodes of binge eating –eating a large amount of food in a discreet period of time A perceived sense of lack of control during a binge	Often overweight or obese
	Episodes are associated with at least three of the following: – Eating faster than normal – Eating until overly full – Eating large quantities of food when not hungry – Eating alone because of embarrassment about the quantity of food eaten – Feeling guilty after eating	
	Marked distress about binging	
	Episodes occur at least once a week for 3 months	
	Binging is not accompanied by unhealthy compensatory behaviors	
Avoidant/ restrictive food intake disorder	An eating disturbance where certain foods are avoided because of their taste, texture or color, or fear of choking or vomiting, resulting in failure to meet energy requirements for normal growth and development associated with at least one of the following: – Significant weight loss or failure to meet expected weight or height gain in children – Significant nutritional deficiency – Dependence on nonfood nutrition, such as nasogastric feeds or oral nutritional supplements – Interference with psychosocial functioning The problem is not related to lack of food availability There is no distortion in body image or fear of gaining weight The problem is not attributable to another medical or mental disorder	Low
Other specified feeding or eating disorder		

(continued)

Table 9.1 (continued)

Diagnosis	Key features	Body weight
Atypical anorexia nervosa	All criteria for anorexia nervosa but weight is normal	Normal
Bulimia nervosa (of low frequency and/or limited duration)	All criteria for bulimia nervosa except frequency	Usually normal but may be high or low
Binge eating disorder (of low frequency and/or limited duration)	All criteria for binge eating disorder except frequency	Often overweight or obese
Purging disorder	Recurrent purging in an effort to lose weight without binging	May be normal

Based on data from Ref. [4]

Diagnostic Categories of Eating Disorders

The revised 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* [4] includes several changes to prior versions that improve the clinical utility of the diagnostic categories for feeding and eating disorders. The ED diagnostic categories most frequently encountered clinically in adolescents include AN, bulimia nervosa (BN), binge eating disorder (BED), and avoidant/restrictive food intake disorder (ARFID) (Table 9.1).

The key features of AN are significant weight loss leading to a low body weight for age, distortion of body image, and preoccupation with shape and weight. In DSM-5, the revised criteria eliminated a specific low weight cutoff for "low body weight" and instead provided guidance that a body weight associated with a BMI for age < 5th percentile suggests a low body weight. In addition, the amenorrhea criterion was eliminated. As a result, patients who previously may not have met DSM-IV criteria for AN might meet DSM-5 criteria for this condition. In contrast to AN where weight is low, in BN, weight is usually normal. Key features of BN include recurrent episodes of binge eating accompanied by inappropriate compensatory behaviors such as self-induced vomiting, excessive exercise, periods of starvation, and use of diet pills, laxatives, and/or diuretics. In DSM-5, the frequency criterion for binging and purging episodes was decreased from twice per week in DSM-IV to once per week in DSM-5. Binge eating disorder describes those individuals who binge eat, but do not purge or compensate in any other way. Individuals with BED are usually overweight or obese. Avoidant/restrictive food intake disorder (ARFID), a new diagnostic category in DSM-5, describes those patients who avoid certain foods because of color, texture, or fear of choking or vomiting. There is no distortion in body image and no fear of gaining weight, but eating behaviors interfere with normal growth and development. In adolescents with ARFID, body weight is usually low [5].

Evidence for Reduced Bone Mineral Density in Adolescents with Eating Disorders

Most of the studies evaluating bone health in adolescents with EDs have used DSM-IV criteria for AN and few have used DSM-5 criteria. To date, no published studies have investigated bone health in patients with ARFID, and only a handful of studies have examined bone health in patients with BN.

In AN, studies have consistently demonstrated reduced BMD for age at one or more skeletal sites [6, 7]. Over 90% of adults with AN have a BMD of at least 1 standard deviation (SD) below the young adult mean (i.e., T-score < −1.0) at one or more skeletal sites, and 38% have a BMD score more than 2.5 SD below the young adult mean (i.e., T-score < −2.5) [8]. In adolescents with AN, low BMD is also seen. Adolescent girls with AN fail to accrue bone mineral at a time when healthy adolescents are rapidly accruing bone [6, 9]. One study found that >80% of adolescent subjects had a lumbar spine BMD Z-score < −1.0, with 32% having a Z-score < −2.0 [10]. The degree of reduction in BMD is directly proportional to both the degree of malnutrition (expressed either as BMI or percent median BMI) [7, 10–15] and, in girls, the duration of amenorrhea [7, 12–14, 16]. Both cortical and trabecular bones are compromised, and the lumbar spine is more profoundly affected than the hip [8, 14], probably because of the greater proportion of metabolically active trabecular bone in the vertebra compared to the hip, which contains mostly cortical bone. Recent studies utilizing high-resolution peripheral quantitative computed tomography (HR-pQCT) have demonstrated impaired trabecular microarchitecture in adolescent girls with AN, evidenced by lower total and trabecular volumetric BMD, higher cortical porosity, decreased trabecular thickness, and greater trabecular separation. Furthermore, estimated bone strength is reduced compared to controls [17]. Similar to girls with AN, boys with AN have significant deficits in areal BMD at the lumbar spine, total hip, femoral neck, and whole body, compared to healthy controls [15, 18, 19]. One study found that, in contrast to girls with AN, boys with AN had lower BMD at the hip and femoral neck than at the spine [19] although this finding has not been replicated by others after controlling for age, duration of illness, and degree of malnutrition [15].

Both intermediate [9, 10, 20, 21] and long-term studies [22–24] have demonstrated that the reduction in BMD seen with AN is persistent and may be irreversible despite full recovery from the ED. In adult women with active AN, the rate of decline of areal BMD is approximately 2.5% per year [25]. In women recovered from AN for an average of 21 years, BMD of the hip remained lower than controls, and a relatively high percentage of patients reported a history of pathologic bone fractures [22].

Some studies have shown that patients with bulimia nervosa and subclinical eating disorders can also have reduced BMD and increased fracture risk, especially if they have had a prior history of amenorrhea or AN [26, 27]. Using quantitative computed tomography to measure volumetric BMD and estimate vertebral strength, Bachmann et al. found that women with atypical AN (where BMI is in the normal range) can also have reduced BMD and estimated vertebral strength. Women with

AN had the lowest volumetric vertebral BMD and bone strength, but those with atypical AN had measures intermediate between those of low weight patients with AN and the healthy controls. In women with atypical AN, a prior history of low weight and present or past amenorrhea each independently predicted lower vertebral BMD [28].

Fractures in Patients with Eating Disorders

A past history of AN is associated with a two- to three-fold increased risk of fracture in adulthood [27, 29, 30]. In a large population-based retrospective cohort study in the United Kingdom, Nagata et al. found that the fracture incidence in females with AN was higher than in unexposed females across all age groups, with a higher risk of fracture at all anatomic sites and the greatest excess fracture risk at the hip/femur and pelvis. In males, incident fracture risk increased only in those >40 years of age with a significantly increased risk of vertebral fractures, but no increased fracture risk at other sites [30]. In a large Danish cohort study, fracture risk was increased two-fold in those with AN, but was not significantly increased in patients with BN. Patients with other EDs (previously called "Eating Disorder Not Otherwise Specified") also had an increase in fracture risk while lower than those with AN [27]. In the only study evaluating fracture risk during childhood and adolescence, the incidence of fractures (both stress fractures and nonstress fractures) was significantly higher in the 310 adolescents with AN compared to the 108 normal-weighted controls, and the incidence increased dramatically after the diagnosis of AN had been made. Fracture risk increased even in the presence of a normal areal BMD, supporting the concept that factors other than BMD contribute to fracture risk [31].

Determinants of Impaired Bone Health in Adolescents with Eating Disorders

Factors contributing to impaired bone health in adolescents with EDs include low body weight; changes in body composition; dietary deficiencies of protein, calcium, and vitamin D; and hormonal alterations including sex hormone deficiency, low insulin-like growth factor-1 (IGF-1) levels, and hypercortisolism. Prolonged bed rest, used in some inpatient programs to help stabilize vital signs and curtail physical activity, may further aggravate bone health in as rapidly as 5 days [32]. In contrast to adults with EDs who have decreased bone formation and accelerated bone resorption, adolescents with AN have suppressed markers of both bone formation and bone resorption [12].

Both BMI and lean body mass are important determinants of BMD. Mechanical loading during weight-bearing activities stimulates bone formation, and lower body weight reduces mechanical loading. Multiple studies have shown that in patients with AN, areal BMD is directly correlated with BMI [9–11, 13] and lean body mass [12, 13, 33]. In addition to low BMI, adolescents with AN have increased amounts

of bone marrow fat in both the central and peripheral skeleton despite the fact that subcutaneous fat is decreased. In patients with AN, bone marrow fat content is inversely proportional to BMD [34]. Increased amounts of bone marrow fat may contribute to reduced bone mass in AN [34–36].

Calcium is necessary for mineralization of the skeleton and acquisition of peak bone mass during adolescence. According to the Institute of Medicine and the American Academy of Pediatrics, the dietary reference intake for calcium in adolescents is 1300 mg per day [37, 38]. The major dietary source of calcium is dairy products. Milk consumption by adolescents has declined, and in 2011 only 9.3% of girls in the United States consumed three or more servings of milk per day (one 8 oz. serving of milk contains approximately 300 mg of calcium) [39]. Adolescent girls with EDs often avoid milk products considering them to be "fattening." Poor dietary intake of calcium may contribute to impaired bone health. Vitamin D is a fat-soluble vitamin necessary for absorption and utilization of calcium. Adequate vitamin D intake is essential for utilization of calcium. In 2011 the Institute of Medicine increased the Recommended dietary allowance (RDA) of vitamin D for adolescents to 600 IU/day [37]. Vitamin D deficiency is prevalent in northern climates and in individuals consuming low-fat diets. In adolescents with EDs, most studies show that approximately 30% of those who have not previously been supplemented with vitamin D have 25-hydroxyvitamin D levels <20 ng/mL, which is considered deficient [40–42]. One study of adolescents with AN, who were already in treatment for their ED, found only 2% of patients to be vitamin D deficient, compared to 24% of healthy controls. The investigators attributed the low incidence of vitamin D deficiency in this sample of adolescents with AN to the extreme compliance of these patients with prescribed medication which included a multivitamin-containing vitamin D [43].

Several hormones that can affect bone health are altered in patients with eating disorders. In AN, suppression of the hypothalamic-pituitary-gonadal axis results in low estrogen levels and amenorrhea in girls and low testosterone levels in boys. Estrogen deficiency is associated with increased bone resorption, potentially mediated in part by local inflammatory cytokines, and testosterone is a powerful stimulator of bone formation. Hypogonadism in AN is an independent contributor to impaired bone health in this condition. AN is also associated with relative growth hormone resistance, resulting in low IGF-1 levels [44, 45]. IGF-1 is a nutrition-dependent bone trophic factor that stimulates bone formation through its action on osteoblasts. Low IGF-1 levels in AN are positively correlated with BMD, independent of BMI. Hypercortisolemia is a well-recognized finding in AN, and spinal BMD has been found to correlate with urinary cortisol excretion [46]. Glucocorticoids have a deleterious effect on the bone by both suppressing osteoblast activity and increasing bone resorption. As the complex physiology of AN is better understood, the role of other hormones including insulin, ghrelin, leptin, amylin, and peptide YY on bone metabolism will be better understood [6].

Approximately 50% of adolescents with EDs are treated with psychotropic medications for comorbid psychiatric conditions such as depression, anxiety, and obsessive-compulsive disorder, with the majority being treated with selective

serotonin reuptake inhibitors (SSRIs) [47]. The long-term use of the SSRIs is associated with reduced BMD in adolescent girls with AN, independent of duration of illness and duration of amenorrhea [48]. Therefore, it is important to weigh the benefits of SSRI used for a given patient's mental health against the potential negative implications for his/her bone health.

Management of Impaired Bone Health in Adolescents with Eating Disorders

Treatment of the underlying ED with weight restoration, interruption of the eating disorder behaviors, and resumption of spontaneous menses is the most important strategy to improve bone health in adolescents with EDs. Weight gain is associated with improvement in BMD, but levels may not return to normal [20, 49, 50]. In adolescent girls with AN, weight gain without resumption of menses is not accompanied by significant increases in BMD [50]. Although weight gain leads to improvement in bone health, full weight restoration is difficult to achieve and sustain in this population and takes time. It is important to identify other interventions to optimize bone health. The ideal intervention would both increase bone formation and reduce bone resorption. In the adolescent age group, a safe therapeutic agent that has the ability to stimulate bone formation would be particularly advantageous.

Calcium and Vitamin D Supplementation

Although calcium and vitamin D supplementation increase BMD in healthy adolescents, no randomized controlled trials have been conducted in adolescents with EDs, and there is no consensus about optimal 25-hydroxyvitamin D (25-OHD) levels in this population. Many ED treatment centers screen for vitamin D deficiency, treat when deficiency is found, and aim for a 25-OHD level > 30 ng/mL. Optimal intake of calcium and vitamin D is preferable through the diet, but given the restrictive diet of this population, many programs routinely recommend supplementation to meet the Recommended dietary allowance (RDA) for both calcium and vitamin D (1000–1200 mg/day of elemental calcium) and prescribe vitamin supplements to achieve a total daily intake of at least 600 IU vitamin D a day [2].

Weight-Bearing Physical Activity

Mechanical loading promotes bone formation, and in healthy children and adolescents, weight-bearing activity increases BMD, improves bone microarchitecture, and increases bone strength [51, 52]. Adolescent athletes have higher BMD than sedentary controls provided they have regular menses. Once they become amenorrheic, the protective effect of exercise is lost [53]. However, a challenge for

clinicians is the fact that excessive exercise is used by many adolescents with EDs to burn calories in order to lose weight. The effect of targeted exercise protocols aimed at increasing BMD without compromising weight gain in AN remains unclear. One pilot randomized controlled study in hospitalized adolescents with AN, who were otherwise on bed rest, tested the hypothesis that a twice daily jumping activity would increase biomarkers of bone formation. This study failed to show significant changes in bone biomarkers during the hospital stay but resulted in more rapid stabilization of vital signs [54]. It is possible that this intervention was either too brief or of too low intensity to stimulate bone formation.

Anabolic Agents

Short-term parenteral administration of IGF-1, a potent anabolic agent, at a dose of 30 mcg/kg twice per day, increased markers of bone formation without altering markers of bone resorption in a sample of 23 adult women with AN [55]. The same investigators then randomized 60 adult women with AN to one of four treatment groups: recombinant IGF-1 alone, an oral contraceptive alone, the combination of IGF-1 and oral contraceptive, or placebo. Subjects were followed for 9 months. The investigators found that there was a modest increase in BMD of the lumbar spine in those administered with IGF-1 but that BMD increased to the greatest degree in those receiving combination treatment (mean increase of lumbar spine BMD of 1.8 ± 0.8%). Treatment with oral contraceptives alone did not have an effect, and treatment with placebo was associated with further bone loss [56]. IGF-1 has to be administered by subcutaneous injection twice a day and is not FDA-approved for use in AN.

Dehydroepiandrosterone (DHEA) is a precursor of both androgens and estrogens, and levels are low in AN. Theoretically, administration of DHEA could inhibit bone resorption and stimulate bone formation. Gordon et al. randomly assigned 61 adolescent women with AN to receive either 50 mg/day DHEA or a combination of estrogen and progestin pill. Total hip BMD increased 1.7% over 1 year in both groups, but after controlling for weight gain, no treatment effect was detected [57]. DiVasta et al. conducted an 18-month double-blind, randomized, placebo-controlled trial investigating the effects of oral DHEA combined with an oral contraceptive on bone health in young women with AN. The study found that compared to placebo, those who received the combination therapy were able to preserve spinal, hip, and whole-body BMD, whereas receipt of placebo led to further decreases in BMD [58]. The combination treatment also improved hip structural geometry and estimates of bone strength [59].

Teriparatide (recombinant human parathyroid hormone) stimulates bone formation and has been used to treat osteoporosis in adults. A randomized controlled trial of 21 adult women with AN treated with teriparatide and 11 healthy controls demonstrated that in the teriparatide group, lumbar spine BMD increased 6.0 ± 1.4% compared with a change of −0.6 ± 1.0% in the controls ($p < 0.01$) after just 6 months of treatment [60]. In the United States, teriparatide currently has a black box

warning from the FDA against its use in children and adolescents because of an increased incidence of osteosarcoma in rodents with open growth plates. Provision is also limited to 24 months of total lifetime use, resulting in its often being reserved for severe cases of adult osteoporosis.

Antiresorptive Agents

Estrogen replacement therapy in the form of a low-dose estrogen-progestin contraceptive pill has not been found to increase BMD significantly in adolescents with AN [10, 61–63]. Many providers discourage the use of oral contraceptive pills for this purpose because they have not been proven to be effective but also because they mask spontaneous resumption of menses, a sign of achievement of a weight associated with return to biological health. Exogenously induced menses may give a false sense of being cured and reinforce denial in those who are still of low weight. Oral estrogen-progestin preparations suppress hepatic synthesis of IGF-1. However, transdermal estrogen bypasses the liver, is delivered directly into the systemic circulation, and does not suppress IGF-1 production. One study found that physiologic doses of transdermal estrogen, coupled with oral progesterone to maintain a healthy uterine lining, increased spine and hip BMD compared to controls [64]. There have been no studies to date examining the bone health implications of the combined contraceptive hormonal patch (i.e., Ortho Evra) in subjects with EDs.

Bisphosphonates inhibit osteoclast-mediated bone resorption. In a 12-month double-blind randomized placebo-controlled pilot study of alendronate 10 mg daily in 32 adolescents with AN, femoral neck and lumbar spine BMD increased by 4.4 ± 6.4% and 3.5 ± 4.6%, respectively, in the alendronate group compared with increases of 2.3 ± 6.9% and 2.2 ± 6.1% in the control group. These between-group differences were not significantly different. However, within-group analysis revealed that both femoral neck and lumbar spine BMD increased significantly from baseline to follow-up in the alendronate group ($p = 0.02$) without a significant increase in those assigned to placebo [49]. In adult women with AN, Miller et al. found that 35 mg of risedronate administered weekly significantly increased lumbar spine and hip BMD compared to placebo. Lumbar spine BMD increased by 3%, and hip BMD increased by 2% compared to controls [65]. Direct translation to adolescents is not possible given the significant difference in bone physiology. While bisphosphonates have been found to increase BMD in adult patients with AN, the effect is modest, and they are not recommended for general use because of potential side effects and their long half-life.

Denosumab is a human monoclonal antibody that inhibits bone resorption by neutralizing RANKL, a key mediator of osteoblast formation and function. Denosumab has been used to treat postmenopausal osteoporosis [66]. A single case report describes a dramatic increase in lumbar spine BMD (14.8% from pretreatment levels) and a more modest increase of 1.8% in total hip BMD after 3 years of treatment with denosumab in a 29-year-old woman with a 17-year history of severe AN [67]. Of note, the patient had no weight gain during the 3 years of treatment, so

the improvement in BMD was not a result of weight restoration. To our knowledge, there are no other published data on the use of denosumab to treat low BMD in patients with EDs.

Summary

Bone health is impaired in adolescents with EDs, making them susceptible to fractures. Once established, low BMD is difficult to treat and only partially reversible. Unfortunately, optimal management of low BMD in adolescents with EDs remains challenging. Weight restoration with resumption of menses is the cornerstone of treatment, but attaining this benchmark is difficult and often a lengthy process. The potential benefits of weight-bearing activity must be balanced against the potential deleterious effects on weight restoration and resumption of menses. Many programs routinely recommend calcium supplementation in those whose diet does not contain at least 1300 mg of elemental calcium. Adolescents with EDs should have serum 25-OHD tested, and those with levels <30 ng/mL (75 nmol/L) should be treated with vitamin D 50,000 IU weekly or 2000 IU daily for 6–8 weeks [2]. Oral estrogen-progestin agents have not been found to increase BMD in AN, but physiologic doses of transdermal estrogen may have a role in some patients. The future role of anabolic agents, bisphosphonates, and other antiresorptive agents remains to be determined in adolescents with EDs. Current recommendations for low BMD in AN include weight restoration with resumption of spontaneous menses, optimal calcium (1300 mg/day of elemental calcium) and vitamin D (600 IU units/day) intake, and treatment of vitamin D deficiency.

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Bone Health of Adolescent Athletes

10

Kristin M. Ernest, Rebecca G. Martinie, Sarah Dobkins, and Albert C. Hergenroeder

A 14-year-old runner comes into your clinic for evaluation of lower leg pain for 1 month. She has recently increased her running after joining the cross country team. Initially pain was just with running but now has pain at rest. She has had nine menstrual cycles in the past 12 months, and her BMI is 19 kg/m² (50%). On examination she is tender to palpation over an area of 6 centimeters along the medial tibia. The differential diagnosis includes a medial tibial stress fracture.

Introduction

Bone health is an important component of adolescent athletes' overall health and sports performance. The goal of this chapter is for the readers to understand (1) the epidemiology, prevention, diagnosis, and treatment of stress fractures, (2) the relationship between exercise and bone health, and (3) the nutritional concerns in promoting bone health in adolescent athletes.

Background: Definitions, Epidemiology, and the Prevention of Stress Fractures

Definitions and Etiology

The Society for Adolescent Health and Medicine defines adolescents as individuals who are 10–25 years old [1]. Puberty is defined by the emergence of secondary sex characteristics and is characterized by periods of peak height and weight velocity

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[2, 3]. The most rapid periods of bone accrual are between ages 11 and 14 years for females and 13 and 17 years for males [4]. Between the ages of 12 and 16 years, females accrue approximately 40% of their adult bone mass [5]. The definition of an athlete is more elusive. For this discussion, an athlete is an individual who participates in one or more extracurricular sports outside of required physical education or is involved in regular training for a specific athletic competition. Regular physical activity and exercise are associated with higher bone mass and should be encouraged. Exercise has a positive effect on osteogenic activity leading to improved bone mineral content and density [6]. Female collegiate runners had greater bone strength compared to healthy, non-running controls, due to greater bone area; male runners had favorable bone geometry, but not strength, compared to controls [7]. When considering the contribution of calcium intake, oral contraceptive use, and exercise to bone mineral density (BMD) in adolescents, only exercise was associated with increased BMD and bone strength [5].

Stress fractures were first described prior to the invention of radiographs in military recruits in 1855 by a Prussian military doctor [8–10]. In athletes, they were initially reported in 1958 and continue to be a concern for athletes [8]. Bone stress injuries are defined on a continuum from stress reactions to stress fractures. Bones are in a constant flux of remodeling characterized by cycles of bone formation and resorption. In bone stress injuries, excessive mechanical stress overloads the repair mechanisms tipping the scale toward increased resorption and leads to weakened bones which become injured with continued loading from activity [11, 12]. This is often thought of as a fatigue curve, in which excessive impact force results in a breaking point [13]. Initially, there are microfractures which gradually coalesce, creating a clinically detectable injury. Stress reactions are the early result where bone has become weakened, but not physically disrupted, as is evidenced by edema on MRI [11, 13, 14]. Stress fractures can be further divided into fatigue fractures or insufficiency fractures. The majority of the stress fractures in adolescent athletes are fatigue fractures (i.e., injuries that occur in normal bones due to repetitive force exceeding the repair mechanism). The minority are insufficiency fractures that occur in abnormal bone as a result of an underlying disorder such as nutritional deficiency associated with an eating disorder [15, 16]. Insufficiency fractures that occur due to other pathological states such as tumors and genetic conditions such as osteogenesis imperfecta will not be discussed in this chapter.

Epidemiology

Initially stress fractures were conditions described in adults, but with the increasingly competitive and year-round training in youth sports, there has been an increasing trend of stress injuries in the pediatric population [15]. The reported prevalence of these injuries varies. The percentage of patients seen in sports medicine or orthopedic clinics range from 0.7% to 20% of visits [16, 17]. In the military, these fractures account for 3 to 9% of injuries, and in Division I NCAA athletes, they make up 1.4% of injuries [17]. In high school athletes, it is estimated that stress fractures

account for 0.8% of sports-related injuries at a rate of 1.54 per 10,000 athlete exposures (A-E) [17]. However, when examining certain populations, these estimates drastically increase. In general, the prevalence is higher in females and in running and other sports that emphasize leanness.

Identification of Risk Factors for Stress Fractures and Prevention

Prevention of stress fractures begins with the identification of risk factors. Risk factors can be divided into two categories: [1] extrinsic (i.e., related to the environment) and [2] intrinsic (i.e., internal to the individual). Suggested extrinsic risk factors include increased training volume or intensity, changes in terrain, smoking, and running in older shoes. Proposed intrinsic risk factors include previous history of stress fracture, female gender, menstrual dysfunction, lower body mass index (BMI), lower serum vitamin D, decreased calcium intake, foot type, leg length discrepancy, genu valgum, and increased Q angle [12, 18]. Few of these proposed risk factors have consistent evidence-based research to support their merit. A recent meta-analysis demonstrated that there are only two risk factors consistently supported in the literature: a history of previous stress fracture (OR 4.99) and female gender (OR 2.31) [19]. A history of previous stress fracture has been reported to account for a seven-fold increase in risk [20], and it is estimated that 18% of stress fractures are repeat injuries [17].

Comparable to athletes, military recruits continue to be at risk for stress injuries, and this risk has been closely studied. One investigator found that individuals who had participated in ball sports, mostly basketball, for 2 or more years prior to entering the military, had a decreased risk of stress fracture compared to those who had not been active [21]. Studies demonstrated a two to ten times higher risk in females in the military compared to male counterparts and a two to four times higher risk in those with amenorrhea versus eumenorrhea [22]. Stress fracture risk is also increased in military recruits who smoke or who wear running shoes more than 6 months old. [11, 22–24] As many military activities are completed in hard sole boots, the use of cushion insoles has been suggested as a way to decrease risk. However, studies have been inconsistent in showing a benefit, but overall, it is thought that cushioned footwear is protective [14, 23, 24].

Menstrual dysfunction is another significant risk factor for stress injuries and low bone density. Amenorrhea is one of the three components of the female athlete triad [25, 26]. The 2014 Female Athlete Triad Coalition Consensus Statement defines the female athlete as a triad of "low energy availability with or without disordered eating, menstrual dysfunction, and low bone mineral density." [25] An increasing number of triad risk factors are associated with an increased risk of stress fracture [27, 28]. Ackerman reported that female athletes with oligomenorrhea (defined as no menses for 3 months in the 6-month period prior to the study) had a 32% incidence of stress fracture compare to 5.9% in normal menstruating athletes and 0% in non-athletes. They noted that those with menstrual dysfunction did not see beneficial exercise-related gains in BMD [29]. Late menarche, defined as 15 years or older,

increased the risk of stress fracture, by as much as 30% per each year delay in one study [30] and four-fold in another [20]. Those with more severe injuries on MRI were more likely to have menstrual dysfunction [31]. The majority of studies report menstrual dysfunction as a risk factor for stress fracture in females [20, 29, 32, 33]. The consensus is that there is no increased or decreased risk of stress fracture associated with use of oral contraceptives [5, 19, 34].

The energy imbalance seen in the female athlete triad is a critical factor. Lower BMI is associated with an increased risk of stress fracture. While lower BMI is not a criterion of the female athlete triad, it is inherently connected as decreased energy availability will often, but not always, result in a lower BMI. A BMI less than 21 kg/m^2 had an increased risk of 15.3% (OR 2.4) of associated stress fracture in a prospective study of exercising females [27]. In a study of adolescent runners, having a BMI less than 19 increased the risk of a stress fracture three-fold and a history of eating disorder five-fold [20].

As the third component of the female athlete triad, low BMD is associated with an increased risk of a stress fracture. Having a Z-score ≤ -1 increased the risk of stress fracture 21% (OR 3.2) [27]. A review of stress fractures in runners noted that stress fracture in cancellous bone was associated with lower BMD [12]. In a prospective study of track-and-field athletes, an association between lower BMD and increased risk of stress fracture was found [34]. Personal low BMD is not only associated with an increased risk of stress fractures but also family history of osteoporosis or low BMD [30]. Lower BMD is associated with a longer time to recover from a stress fracture [31]. While the assertion that lower BMD is associated with increased risk of stress injury makes intuitive sense, it has not always been born out in the literature. Several investigators report no relationship between areal BMD and stress fracture occurrence [32, 33, 35]. This fact highlights the complexity of the pathophysiology of stress fractures, involving the relationships between training load, bone mineral strength, and geometry.

Certain sports are associated with increased stress fracture risk overall and at particular locations (Table 10.1). There is greater risk in sports that emphasize leanness, such as distance running, gymnastics, ballet, and figure skating [20, 28].

Table 10.1 Stress fracture associations with individual sports

Sport	Location of stress fracture
Baseball/softball (fast-pitch)	Ribs, proximal humerus
Basketball	5th metatarsal, sesamoids, calcaneus, tibia
Dance – Ballet	Metatarsals, tibia, fibula, femoral neck, pars interarticularis
Golf	Ribs
Gymnastics	Pars interarticularis, radius
Rowing	Ribs
Running	Metatarsals, sesamoids, navicular, tibia, fibula, femur
Soccer	Metatarsal, tibia

Based on data from Refs. [14, 16, 36, 45]

The highest rate of stress injuries occurred in girls' cross-country at 10.6 per 10,000 A-E, followed by girls' gymnastics at 7.4 per 10,000 A-E and boys' cross-country at 5.4 per 10,000 A-E [20]. Other investigators have reported higher incidence of stress fractures (15–20% of all injuries) in runners [8, 11, 14, 19]. The lowest rates were seen in boys swimming and diving at 0.2 per 10,000 A-E. Football had a low rate at 1.3 per 10,000 A-E but made up 16.5% of stress fractures given the large number of participants [17]. Girls who participated in dance or gymnastics were at increased risk of stress fracture, whereas boys had increased risk with additional seasons in running sports compared to their male peers who played basketball and had a lower rate [20]. This supports the recommendation by the authors that athletes should not do the same repetitive sport year-round.

For an adolescent, the amount of physical activity is as important as is the type. Several investigators have shown an association between high level of activity, specifically high-impact activity, and stress fractures. In a prospective study of exercising girls and women, the incidence of a bone stress injury, i.e. a stress fracture or stress reaction, was 14.7% in those participating in more than 11 h per week of exercise compared to 3.4% in those exercising <12 h per week (OR = 4.9, p = 0.005) [27]. Participating in more than 16 h per week of physical activity was associated with a 1.88 greater odds of developing a stress fracture [37]. Ninety percent of female adolescent athletes who developed a stress fracture were involved in high-impact activity, as defined as one or more hours per day of the following sports: tennis, cheerleading, volleyball, basketball, running, or soccer [38]. Using a prospective study design, every additional hour of high-impact activity per week (similar sports as noted above) in preadolescent and adolescent females was associated with an 8% increased risk of stress fracture [30].

Foot architecture has also been considered in previous studies. It has been theorized that pes cavus, or a high arch foot, would absorb less force during weight-bearing activity and transfer more force to the tibia leading to increased risk of tibial stress fracture. Pes planus, or a flat foot, would absorb more force, therefore increasing risk for metatarsal or other foot stress fractures. Literature reviews have been inconclusive regarding all stress fractures [22, 39]. A systematic review looking at relationship with tibial stress fracture found no consensus on the association of foot type and risk of stress fracture, in part due to differences in methodology. In the authors' experience, there is likely increased risk of stress fracture in running sports at extremes of foot types [11].

Prevention begins with identification of risks, but it is important to recognize that these injuries are multifactorial. Females examined for the effects of combined risk factors had a 29% increase (OR 5.1) of having a stress fracture if they participated in more than 12 h per week of athletic activity and had a low BMD. They had a 46.2% (OR 8.7) increase in stress fracture occurrence with the combination of participating in more than 12 h per week of athletics, involvement in a sport that values lean physique, and restrictive dietary behaviors [27]. There is little evidence for prevention strategies. Most evidence stems from studies in the military including the use of shock-absorbing insole as discussed above [24]. One randomized control

trial in female naval recruits found a 20% reduction in stress fractures over 8 weeks in recruits who received 2000 mg of calcium and 800 IU of vitamin D daily vs. placebo [40]. A study examining the use of osteopathic manipulative treatment to reduce stress fractures in collegiate cross-country runners found that it lead to a reduction in males (98.7% reduction, $p = 0.019$) but not in females (8.5% reduction, $p = 0.671$) [41]. It has been suggested that one preventative strategy could include childhood participation in ball sports as this participation has been shown to improve BMD and favorable bone geometry in military recruits and runners [42]. The American Academy of Pediatrics has published recommendations on the prevention of overuse injuries such as stress fracture, including rest days each week, off seasons, early diversification, and late specialization [43, 44]. In otherwise healthy children and adolescents, the authors recommend screening for risk factors at well-child exams, especially in higher-risk individuals such as active lean females. For those with a history of stress fracture, the treatment plan should include identifying and addressing risk factors with consideration of adolescent medicine or endocrine consultation if they have sustained multiple stress injuries.

Stress Fracture Diagnosis, Severity, and Location

General Clinical Diagnosis

Diagnosis is based on history and physical examination. Early diagnosis is important as it can prevent progression to worsened injury and avoid prolonged absence from activity [14, 17, 18].

Stress fractures tend to present with insidious onset of localized pain. In general, there is no history of acute injury. Initially the pain worsens with activity and improves with rest [12, 18]. If the athlete continues to exercise with pain, they will have pain earlier in their workout which will progressively continue for longer periods after exercise, until they reach a point where they have pain at rest [12, 14]. Pain is often described as dull or aching [16]. Onset is typically described as following a recent increase in intensity or volume of activity, although there is no predictable amount [12, 18]. Assess general health by asking about medications, including supplements such as ergogenic substances (e.g., glucocorticoids or hormonal therapies), and ask about previous surgeries and past medical history, specifically for conditions that could decrease their bone health. Examples of such disease processes include eating disorders, cancer, inflammatory bowel disease, chronic glucocorticoid use, or osteogenesis imperfecta [14, 16]. Assess the patient for the risk factors mentioned above: previous stress fracture, training regimen (hours per week, intensity, recent changes to regimen, etc.), nutrition, footwear, and menstrual history in females [12, 18].

On physical examination, the clinician should first inspect the area for swelling, asymmetry, and skin changes including erythema, which could suggest infection.

In the prolonged, untreated cases, there can be visible swelling. Stress fractures are bilateral in approximately 17% of cases; thus, it is important to examine the contralateral extremity as indicated [9, 14, 18]. If the bone is superficial, the patient will have a discrete area of bony tenderness. If the injured bone is not easily palpable, such as the femoral neck, it can be difficult to elicit point tenderness. To assess these difficult-to-reach areas, check for pain with range of motion testing or hopping [14]. For long bones, one can perform the fulcrum test. This maneuver consists of providing a bending force on either end of the bone to transmit force to any areas of weakness in the shaft. Pain with testing at the area of concern is a positive finding [14, 45]. Check the patient for possible predisposing factors, strength and flexibility imbalances, leg length discrepancy, and excessive pes planus or pes cavus, although evidence for these as predisposing factors is not well established, as discussed earlier [14]. Use of ultrasound or of a vibrating tuning fork to identify areas of maximal pain lacks the sensitivity and specificity to make them clinically useful [8]. The authors do not perform either of these tests.

There is a wide differential diagnosis for insidious bone pain including neoplasm, infection (osteomyelitis), periostitis, osteoid osteoma, nerve entrapment, and exertional compartment syndrome (ECS) [8, 14]. An important difference between stress fracture and ECS is that pain from the latter typically presents after a consistent intensity or amount of exercise and resolves relatively quickly with rest. It is often bilateral, and there is no pain with palpation on physical exam [18]. In addition, athletes with ECS may complain of tightness, in addition to paresthesia and rarely motor weakness with exercise [45].

Stress fractures are divided into two categories: low risk or high risk (Table 10.2). This distinction affects imaging choices and management. In general, low-risk fractures heal well with conservative management. High-risk fractures are at risk for delayed union, malunion, or nonunion among other complications [16, 18]. Imaging and management implications will be discussed below.

Table 10.2 High-risk vs. low-risk stress fractures

High risk	Low risk
1st metatarsal sesamoids	2nd–4th metatarsal shafts
Base of 2nd metatarsal	Cuboid, cuneiforms
5th metatarsal	Calcaneus
Tarsal navicular	Fibula
Neck of talus	Medial tibia
Medial malleolus	Femoral shaft, pubic ramus
Anterior tibia	Upper extremity, ribs
Patella	
Femoral neck	

Based on data from Ref. [16, 18]

Diagnosis of Common Stress Fractures by Location

Lower-extremity stress fractures make up the majority of stress fractures due to their weight-bearing nature, most sources citing 80–95%, whereas upper extremity stress fractures are rare [8, 15, 18, 19].

The tibia is the most common site for a stress fracture, making up about half of all stress fractures [8, 14, 18]. The most common location for tibial stress fractures is the posteromedial tibia. This is a low-risk stress fracture, and it can be difficult to differentiate from medial tibial stress syndrome (MTSS, more commonly known as shin splints). In general, a tibial stress fracture is diagnosed clinically as point tenderness with palpation of a discrete area of the tibia. MTSS is characterized by diffuse tenderness along the medial aspect of the tibia most commonly at the distal one-third with pain being worst at the soft tissue and can be bilateral [18]. The MRI literature suggests that MTSS is on a continuum with bone stress injuries [9]. Tibial stress fractures can also occur anteriorly and are high risk because they are on the tension side of the tibia putting them at risk for delayed or nonunion. When this complication occurs, the pathognomonic radiographic finding is known as the dreaded black line (Fig. 10.1 below) [14].

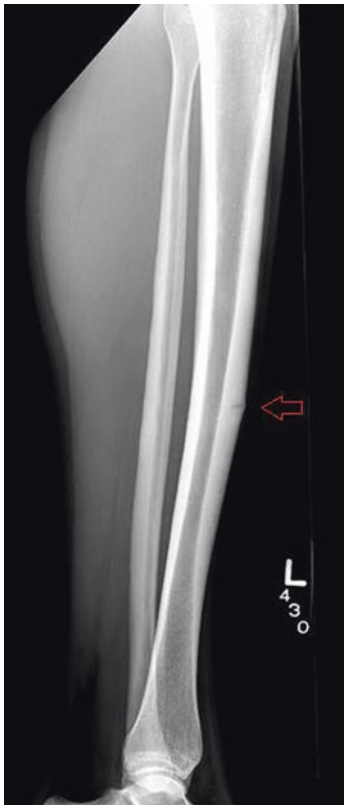

Fig. 10.1 Anterior tibial stress fracture with pathognomonic dreaded black line

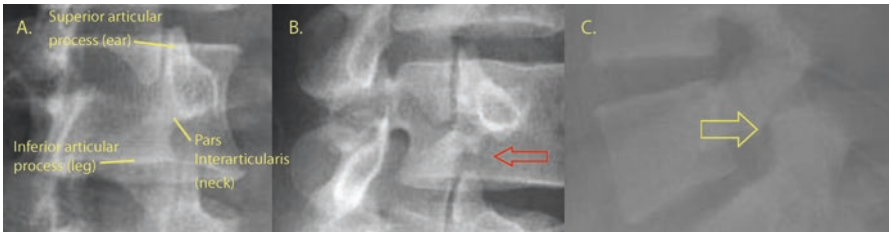

Fig. 10.2 Radiographs of pars interarticularis: (**a**) Normal oblique (**b**) Spondylosis on oblique (*red arrow*). (**c**) Spondylolysis on lateral (*yellow arrow*)

The metatarsals represent the second most common type of stress fracture, with the neck of the second metatarsal being the most common site. They were originally described in the military population, called "march fractures." These stress fractures are common in runners and dancers [18]. They are diagnosed by point tenderness on the bone where the patient complains of pain, most commonly occur in the shaft. Stress fractures of the 2nd to 4th metatarsal shaft are low risk, whereas stress fractures of the base of the second metatarsal and 5th metatarsal are high risk [16, 18].

The pars is the section of the vertebrae located between superior and inferior articular processes (Fig. 10.2). A stress fracture at this location is referred to as spondylolysis. If there are bilateral fractures, the vertebral body can slip forward, a condition known as spondylolisthesis. The prevalence is at least 6% and is considered the most common identifiable pathology of persistent low back pain in adolescents [46, 47]. Spondylolysis presents with insidious onset of pain that worsens with lumbar extension. Typically, it occurs in athletes whose sport requires repetitive lumbar extension loading such as dance and gymnastics but can occur in all sports. Patients are often tender to palpation at the midline and paraspinal muscles at the level of injury, most commonly at the L5 vertebrae [15, 46]. Active standing extension is painful. A single-leg hyperextension test can be performed (also known as the "stork test"). This consists of the patient standing on one leg and then actively extending their back, with a positive test being a pain with extension. It has been found that this test lacks the sensitivity and specificity to make it clinically useful [48]. In the authors' practice, the examiner also passively extends and then laterally flexes the back to each side with a positive test being pain with this motion. While none of these clinical tests can independently diagnose spondylolysis, the accumulation of positive tests supports the diagnosis and should prompt evaluation with imaging. Given the lack of reliability of the physical exam, imaging is required to make the diagnosis.

Imaging to Diagnose Stress Fractures

Radiographs and MRI are the primary imaging modalities used to identify stress injuries. Plain radiographs are typically negative initially following presentation and may remain normal for months. However, given the ease of access, low

radiation, and cost, they are still recommended as the initial imaging study and should be obtained during an evaluation for stress fracture [14, 18]. The sensitivity of radiographs is estimated to be 15% [9]. Possible findings consistent with stress fracture on x-ray include periosteal reaction, cortical thickening, or fracture line [12, 14]. If the x-ray is negative, but there is a high clinical suspicion and the site of concern is low risk, the practitioner may either treat empirically or proceed with further imaging. The authors will often treat based on clinical diagnosis as advanced imaging can be a financial burden. For high-level athletes or those who are not comfortable with the absence of a definitive diagnosis, additional imaging is recommended. If the x-ray is negative and there is concern for a high-risk stress fracture, then further imaging is also recommended.

MRI has become the gold standard as it provides early detection, lacks increased radiation exposure, and can give an indication of severity [9]. Nuclear bone scan was previously the gold standard, but given the large amount of radiation and lack of specificity, it has been replaced by MRI with perhaps the one exception being spondylolysis, as is discussed below [14]. Findings indicative of stress fracture on MRI include periosteal edema, bone marrow edema, and a fracture line [9]. When interpreting an MRI scan, it is important to note that bone marrow edema on MRI may be related to exercise alone [49]. CT is less sensitive and is not useful in early injury detection. It does have utility in certain stress fractures including navicular, pars, sacrum, and vertical tibial and can be used to distinguish an osteoid osteoma from a stress fracture [9].

Special consideration must be taken for spondylolysis. Imaging is needed to establish a diagnosis. Plain radiographs are the recommended initial study of choice. Traditionally four views are obtained, anterior-posterior (AP) and lateral and bilateral obliques, to get a view of the pars looking for the "Scotty dog" appearance of the fracture (Fig. 10.2). The oblique views do not increase sensitivity but increase radiation exposure. Thus, the recommendation is to obtain two views (AP and lateral) as the fracture can technically be seen on the lateral view [47, 50]. However, many clinicians are more comfortable with interpreting oblique views. Thus, this decision is clinician dependent. If the x-ray is negative, and there is a high clinical suspicion for spondylolysis, advanced imaging should be pursued. There is no consensus on which study is indicated next. The sensitivity for MRI to detect spondylolysis is estimated to be 81%, CT is 85%, and a nuclear medicine bone scan is considered the most sensitive. MRI and bone scan are capable of detecting lesions early [50]. Bone scan has significant associated radiation exposure with seven to nine times more exposure than a two-view radiograph [47]. Recent literature supports the use of MRI given the lack of radiation, but the sensitivity is lower especially if using adult protocols designed to look for disc disease [50]. CT is useful later in course, and a classification system has been developed to estimate the likelihood of bony union [51].

Two classification systems have been reported for MRI grading: Arendt and Fredericson. Both reported that higher-grade stress injuries took longer to recover [9, 14, 16, 18, 31, 52, 53]. Those with higher grade had prolonged recovery (31.7 weeks on average) compared to those with low-grade injuries (11.4 weeks). Thus, grading MRI may be helpful for counseling regarding recovery expectations [31].

The Evidence Regarding Treatment of Stress Fractures

General Principles

The initial treatment for a stress fracture targets the underlying condition or conditions that put an individual at risk. Further treatment is determined based on the location of the stress fracture itself, which identifies the injury as high or low risk.

As discussed above, stress fractures can be divided into high risk and low risk (Table 10.2) [16, 18]. High-risk stress fractures occur at sites with an increased risk for delayed healing, nonunion or fracture progression, and more aggressive intervention [54]. Non-operative management is often the first-line approach. However, a delay in diagnosis decreases the chance for successful recovery and makes surgical intervention more likely [55]. Low-risk stress fractures, on the other hand, respond well to conservative management. Symptoms are used to guide return to activity, which begins following an initial period of rest to achieve a pain-free state.

Rest is the mainstay of treatment for all stress fractures. Individuals with low-risk stress fractures should rest until their symptoms resolve [55]. Weight-bearing restrictions may also be implemented depending on the fracture location. Non-impact activities may be introduced early in a treatment regimen to maintain general conditioning if athletes remain pain-free [55]. For example, a ballerina may practice ballet technique while supine to maintain form and endurance. The challenge is attaining patient adherence especially among highly elite and competitive athletes who may be dependent on sport participation for their livelihood. Patients may not be adherent to activity modifications which could cause fracture progression and more time away from sport. Return to sport is completed in the following progression if an individual remains symptom-free: rest, non-impact, low-impact, and ultimately sport-specific activity [54, 55]. High-risk stress fractures generally require a longer duration of rest based on the risk of complications.

Evaluating limb biomechanics and identifying muscular imbalances are important components of stress fracture treatment. Although no consensus exists regarding risk based on foot type, extreme pes cavus or pes planus may predispose to stress fractures and should be considered during treatment [11]. Leg-length discrepancies should also be addressed. It is the authors' experience that clinically significant limb leg-length discrepancy as well as restricted or excessive motion at lower extremity joints increases the risk for stress fracture.

Footwear should be selected to accommodate each individual's foot type to minimize risk for injury. Cushioned shoes for those with a high arch versus a motion control shoe for those with low arches are recommended [18]. Orthotics may also be used to target excessive pronation. However, the authors suggest a trial of physical therapy be initiated first before orthotics are ordered, as the physical therapy may alter the need for or the mechanics requiring an orthotic. The exception to this is forefoot varus which will most likely require an orthotic regardless of progress made with physical therapy. Generally, shoes should be changed every 6 months or every 300–500 miles [23].

Evaluation for the female athlete triad should be considered with a stress fracture diagnosis. A dietary history may identify energy deficits predisposing athletes to stress fractures. One component of the female athlete triad is menstrual dysfunction, and adjusting an individual's training regimen in isolation may take months to years to see a return of regular menses [54]. The role of estrogen therapy for female athletes with amenorrhea is controversial [28]. A meta-analysis supported the conclusion that oral estrogen replacement is not associated with BMD improvement in women with anorexia nervosa; however, transdermal estrogen has shown promising results in improving BMD in women with this restrictive eating disorder [56]. Nutrition optimization to promote bone health will be discussed in more detail toward the end of this chapter.

Specific Treatment Based on Location

Treatment recommendations are based on the location of a stress fracture. Generally, low-risk stress fractures respond well to conservative therapy. High-risk stress fractures are more complex due to the risk for complications. Figure 10.3 provides a treatment algorithm for high-risk stress fractures, and Table 10.3 provides a quick reference for treatment [14].

Lower Extremity

Femoral Neck.

A stress fracture located on the superolateral, or tension side, of the femoral neck is susceptible to displacement and, therefore, classified as high risk [14, 57]. Surgical referral is recommended as first-line treatment due to limited success identified in the literature with conservative management [14, 58]. Stress fractures on the inferomedial, compression side, of the femoral neck respond well to non-operative treatment. They are classified as low risk because fracture displacement is rare [14]. The treatment consists of activity restriction with 4 to 6 weeks of non-weight bearing [14, 55]. If there is displacement of a femoral neck fracture, regardless of location, urgent surgical referral is necessary [55].

Patella

Patellar stress fractures are rare and high risk. Activity restriction and weight bearing as tolerated are acceptable if no fracture is identified on imaging [55, 59]. If an incomplete or nondisplaced fracture is seen on radiographs, the patient should be non-weight bearing with the knee immobilized in extension for 4 to 6 weeks [55]. A surgical referral is required if conservative treatment fails or if the patellar fracture is displaced at the time of diagnosis [55, 59]. If an early return to sport is required, an immediate surgical referral should be considered.

Tibia

The tibia is the most common location for stress fractures with the majority occurring in the posteromedial region [60]. The latter are considered low risk and respond

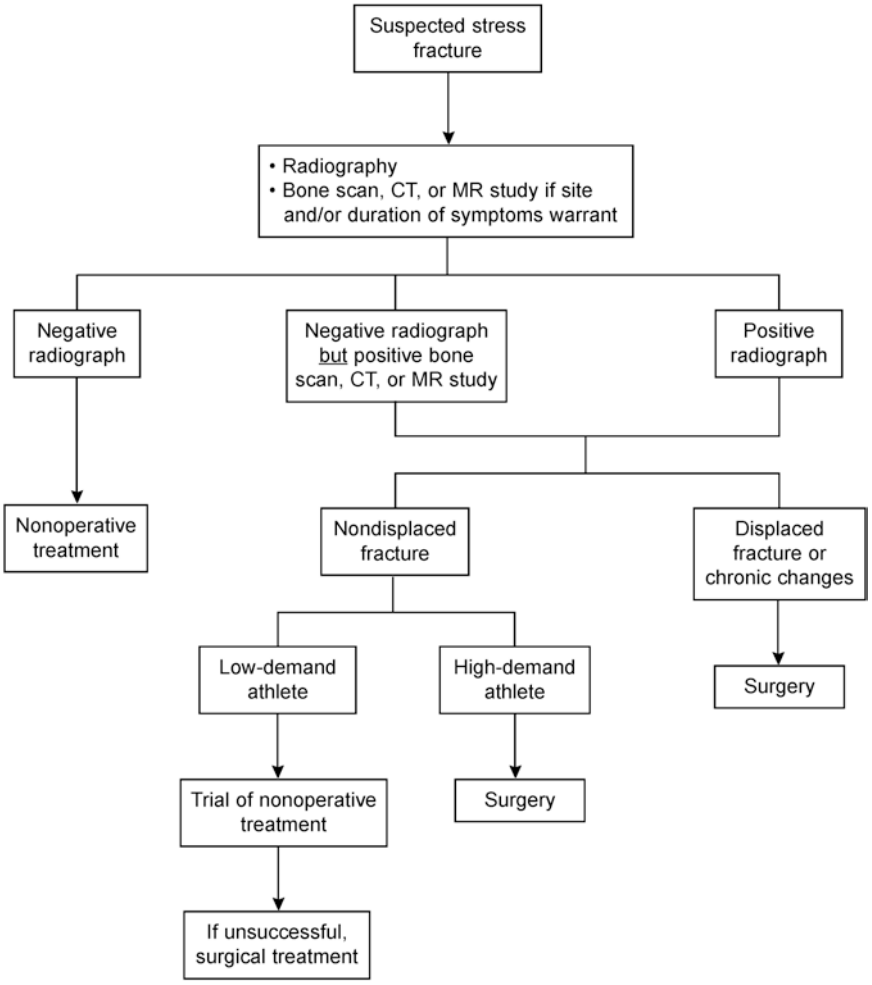

Fig. 10.3 Algorithm for evaluation and treatment of suspected high-risk stress fracture (Reprinted from Ref. [14]. With permission from Elsevier)

well to activity modification [54]. Most will heal within 4 to 8 weeks, and an athlete is able to return to low-impact activity once pain-free [54]. A gradual return to impact activity begins if the athlete remains symptom-free. Athletes often return to sport within 8 to 12 weeks from diagnosis [54]. Use of a pneumatic brace may expedite return to activity [61].

Stress fractures of the anterior tibia, on the other hand, have a high rate of nonunion and are high risk. The "dreaded black line" on radiographs (Fig. 10.1 below) is pathognomonic. Treatment recommendations vary in the literature with many athletes unable to return to their previous level of sport [62]. Initially an athlete

Table 10.3 Risk for complications and treatment for stress fractures by site

Site	Risk	Initial treatment[a]
Femoral neck	Tension side: High Compression side: Low	Tension side: Surgery Compression side: NWB[b] x 4–6 weeks Displaced: Surgery
Patella	High	Stress reaction: WB[c] as tolerated Fracture line: NWB[b] x 4–6 weeks Displaced: Surgery
Tibia	Anterior: High Posteromedial: Low	Anterior: NWB[b] x 6–8 weeks; surgery if poor healing at 3–6 months Posteromedial: WB[c] as tolerated 4–6 weeks +/− pneumatic brace
Medial malleolus	High	NWB[b] x 4–8 weeks Displaced: Surgery
Talus	High	NWB[b] x 6 weeks
Tarsal navicular	High	NWB[b] > 6 weeks Consider early surgical referral
Calcaneus	Low	WB[c] as tolerated 3–6 weeks
Fibula	Low	WB[c] as tolerated 3–6 weeks
Metatarsals	1st = high 2nd–4th = low 5th = high	1st: Variable; surgery if poor healing at 3–6 months 2nd–4th: WB[c] as tolerated 5th: NWB[b] x 6 weeks if *no* fracture line otherwise surgery
Pars interarticularis	Low	Rest
Humerus	Low	Rest
Ribs	Low	Rest

[a]Appropriate physical therapy
[b]Non-weight bearing (NWB)
[c]Weight bearing (WB)

should be non-weight bearing for 6 to 8 weeks [55]. If poor healing is identified at 3 to 6 months, surgical referral is recommended. Surgical intervention is suggested at the time of diagnosis if chronic changes are seen on imaging [14].

Medial Malleolus

A stress fracture of the medial malleolus is high risk due to susceptibility for non-union. Conservative treatment with non-weight-bearing cast immobilization for 4 to 8 weeks is often successful [14]. A surgical referral is recommended at the time of diagnosis for those with a fracture visualized on imaging, any fracture displacement, or an elite athlete wanting to minimize time away from sport [63, 64].

Talus

Most athletes will recover from talar stress fractures with conservative management. However, this remains high risk due to reports of delayed healing. The general treatment consensus is for 6 weeks of non-weight bearing, but cast immobilization is not required [14, 55]. Orthotics should be considered with return to activity to limit pronation [14, 55].

Tarsal Navicular

This is another high-risk stress fracture based on reports of fracture progression, delayed union, and nonunion. Most complications occur if conservative therapy occurs for less than 6 weeks [14, 65, 66]. Return to activity may take 5 months with conservative treatment; therefore, competitive athletes may benefit from surgical referral at the time of diagnosis to expedite return to sport [62, 67].

Calcaneus

This is a low-risk stress fracture with improvement following activity modification for 3 to 6 weeks [54]. Soft heel pads and stretching exercises to target the calf and plantar fascia may prevent recurrence [54].

Fibula

Stress fractures of the fibula often occur in the distal third and are low risk based on successful outcomes with conservative management. Symptom resolution typically follows 3 to 6 weeks of activity modification [54].

Metatarsals

1. 1st metatarsal sesamoids: Due to the risk of nonunion and recurrence, these are classified as high-risk stress fractures. Variability exists regarding first-line treatment ranging from non-weight-bearing cast immobilization for 6 weeks to a removable walking boot for 8 weeks to orthotics restricting forefoot dorsiflexion [55, 68]. Surgical referral is recommended if poor healing is identified at 3 to 6 months.
2. 2nd–4th metatarsal shafts: Stress fractures of the 2nd to 4th metatarsal shafts are low risk and heal within 4 weeks of activity modification [54]. Athletes should transition from a walking boot to a stiff soled shoe as symptoms resolve. Return to activity can begin once local tenderness has dissipated.
3. 5th metatarsal: Stress fractures of the 5th metatarsal are considered high risk. If no fracture line is seen on x-ray, treatment consists of non-weight bearing with cast immobilization for 6 weeks [14, 55]. On average athletes will return to sport after 14 weeks with conservative management [62]. Surgical treatment not only minimizes the risk of re-fracture or nonunion but also decreases the time away from sport [18, 62, 69]. Surgical referral is recommended if a fracture is identified on imaging or if a competitive athlete requires a faster recovery [55].

Spine

Pars interarticularis

Spondylolysis is a low-risk stress fracture. In an asymptomatic athlete, no treatment is recommended [54]. For those reporting symptoms, on the other hand, rest is the first-line approach. How long an athlete should rest remains controversial with literature suggesting between 6 weeks to 6 months. Regardless, an athlete should not return to sport until symptoms resolve. A TLSO brace may be used to decrease pain

by limiting extension. Pain-free physical therapy can be initiated early to emphasize spinal stabilization and core strengthening.

Upper Extremity

Humerus

Upper extremity stress fractures are rare and low risk. In adults, stress fractures are often seen in the humeral shaft, while skeletally immature athletes develop stress fractures of the proximal physis [70]. Rest is the mainstay of treatment with symptom resolution occurring in approximately 12 weeks [70]. A gradual return to activity begins following symptom resolution.

Ribs

Stress fractures of the ribs are low risk. Ribs 1 and 4 through 9 are most commonly affected [71], and healing occurs within 4 weeks of rest [54].

General Approach to Bone Health in Young Athletes

Twenty to 40% of peak bone mass is determined by an individual's lifestyle, the remainder being genetically determined [72] Physical activity and diet are the primary components of lifestyle in this regard [72]. The majority of bone mass develops by the end of the second decade of life, and Chap. 1 addresses optimization of bone health for healthy adolescents. Generally the same principles apply for athletes. It is recommended that adolescents complete at least 60 min of moderate to vigorous intensity exercise daily [6]. Sports participation is not required; however, a higher peak bone mineral density may be achieved if exercise is initiated during early puberty [73, 74]. A literature review of the effect of sport on bone health demonstrated increased bone mineral density with high-impact and odd-impact activity [74]. Improved bone mineral density and geometry are associated with increased physical stress [75].

Higher bone mineral density is achieved within the bones undergoing direct load; therefore, not all sport or physical activity promotes bone health equally, across the skeleton. Gymnasts, followed over 8 to 12 months, demonstrated improved bone mineral density related to high-impact activity [76]. Many authors have reported that high-impact activity results in increased bone strength [77]. This supports a role in injury prevention: having a baseline level of physical activity before starting into a new high-impact sport or exercise program is likely to be protective. There was a lower rate of stress fractures in runners who previously competed in a high-impact sport such as soccer [78].

Bone strength gains related to sport participation are not permanent as there is a decrease in BMD when high-impact activities are discontinued [79]. Despite this decrease, former athletes maintained a higher bone mineral density compared to nonathletes, further supporting the benefit of sports participation on long-term bone health [79]. Incorporating high-impact activity to promote improved bone strength

is well-documented; however, excessive exercise relative to calorie intake may cause menstrual irregularity and bone loss in female athletes [80, 81]. Female athletes with amenorrhea have lower bone mineral density [81] and an increased risk for stress fractures [82, 83]. The role of estrogen replacement to normalize menstrual dysfunction in this population remains controversial, but transdermal estrogen replacement may be appropriate for some female athletes with long-standing amenorrhea and low bone mass by DXA [84, 85]. The dietary contribution to bone health is well-recognized, and the broader nutritional concepts are discussed next.

Nutrition for Optimizing Bone Health in the Adolescent Athlete

The nutritional recommendations provided in previous chapters are appropriate for the general population. However, athletes – specifically those involved in weight control sports such as distance running, ballet, figure skating, and gymnastics – may have suboptimal energy intake, resulting in micronutrient deficiencies which can adversely affect bone development [86]. The risks of menstrual dysfunction, low bone mineral density, and stress fractures are increased by low energy availability. Energy availability is defined as the amount of energy remaining after exercise for all other metabolic processes each day [87]. Athletes looking to achieve optimal bone health should target an energy availability of ≥45 kcal/kg fat-free mass/day [88]. In the absence of having a fat-free mass measurement, the authors suggest estimating energy needs and multiplying by an activity factor of 1.3–1.5 (active or very active) and then following serially and adjusting as needed. In female athletes, adequate calcium intake may help to optimize the positive effects of exercise on bone [89], yet young female athletes often fail to meet calcium intake recommendations [90]. Among athletes, vitamin D is important for the prevention of bone injury, as identified by a study of male Finnish military recruits in whom fracture risk increased when their serum vitamin D concentration was less than 30 ng/ml [91]. As discussed above, a randomized controlled trial in female naval recruits showed a 20% reduced stress fracture incidence following supplementation with 800 IU vitamin D and 2000 mg calcium versus placebo [40]. The consensus opinion for the concentration of vitamin D for optimal bone health is a level above 30 ng/mL [92]. In a large prospective cohort study, vitamin D intake was associated with lower stress fracture risk among adolescent girls engaging in high-impact activity [30]. Athletes with a history of stress fracture, bone or joint injury, signs of overtraining, and muscle pain or weakness and those playing indoor sports may require a serum concentration 25-hydroxyvitamin D be measured [93].

The most recent Position Paper on Nutrition and Athletic Performance from the Academy of Nutrition and Dietetics and American College of Sports Medicine supports calcium intakes up to 1500 mg elemental calcium/day and 1500 to 2000 IU vitamin D/day to optimize bone health in athletes with either menstrual dysfunction or low energy availability [94]. An assessment of eating habits and practices allows an estimate of dietary calcium intake and will guide supplement recommendations.

Further recommendations on supplementation protocols can be found in Chap. 3. While a multivitamin/mineral supplement may be warranted in some cases, in healthy well-nourished athletes, supplementation will not provide ergogenic benefits.

In accordance with the aforementioned position paper, vitamin and mineral supplements are unnecessary for athletes who consume a diet providing high energy availability from a variety of nutrient-dense foods. Athletes presenting with restrictive eating habits and/or amenorrhea, marked calcium and vitamin D deficiencies, or a history of bone injuries should be referred to a sports dietitian as part of the treatment plan. Practitioners working with athletes, particularly females, should stress the importance of consuming adequate energy and a diet that is focused on food variety (rather than honing in too closely on individual nutrients) for optimal performance, bone integrity, and injury prevention.

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Bone Health in Adolescents with Chronic Disease

11

Erin H. Sieke and Rebecka Peebles

Introduction

Adolescence is a period of rapid bone formation, with skeletal mass approximately doubling between the onset of puberty and young adulthood. Appropriate accrual of bone mass during puberty is a major determinant of peak bone mass and thus has significant implications for bone health in adulthood. Adolescents with chronic disease are at unique risk for impaired bone health related to their underlying condition, treatment, and medical complications and comorbidities related to their illness. Hypogonadism, decreased physical activity, impaired linear growth, decreased lean body mass, chronic inflammation, and prolonged use of systemic glucocorticoids are common findings in pediatric patients with chronic disease and have significant impacts on bone mineral accrual and turnover. This chapter will focus on common chronic conditions that occur in adolescence and will review pathophysiology, presentation, evaluation, and management of bone disease in each condition. Published recommendations for the evaluation of bone health in common chronic diseases of adolescence are summarized in Table 11.1.

Marshall is a 16-year-old male who presents to your office with a chief complaint of bloody diarrhea. He reports intermittent diarrhea over the past 6 months but no prior episodes of blood in his stool. Review of systems is positive for fatigue. Marshall and his mother deny recent international travel, sick contacts, and exposure to animals. Upon review of Marshall's growth curves, you discover that he has lost 7 pounds since his last well-child

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Table 11.1 Dual-energy x-ray absorptiometry (DXA) and vitamin D screening guidelines in adolescents with chronic disease

Disease	DXA screening recommendations	DXA follow-up	Vitamin D screening
Cystic fibrosis	Children less than 8 years old should receive DXA screening if: • Significant risk factors for low BMD at clinician's discretion • Prior to prescribing specific treatments for low BMD Children >8 years of age should receive routine DXA screening if: • Weight less than 90% of median body weight • FEV1 less than 50% of predicted • Delayed puberty • High-dose glucocorticoid treatment for more than 90 days/year [1]	Based on initial DXA outcomes: • Every 5 years if the BMD Z-score is > -1 • Every 2 years if BMD Z-score between -1 and -2 SD • Every year if the BMD Z-score < -2 or if the child has experienced low trauma fractures	• Check 25-OH vitamin D levels yearly at the end of winter • Recheck after any treatment change [2]
Type 1 diabetes mellitus	Routine DXA screening is not recommended [3] Consider DXA screening if [3, 4]: • Low BMI • Increased daily insulin dose • Poor renal function • Fracture history • Diabetic complications (retinopathy, neuropathy, nephropathy) • Clinical features of bone disease (pain, kyphosis, decreased height)	Follow-up based on initial DXA outcomes [3]	• Check 25-OH vitamin D levels yearly at end of winter [4]
Celiac disease	Routine DXA screening is not recommended [3, 5] Consider DXA screening if [6, 7]: • Nonadherence to gluten-free diet • Low BMI • History of irregular menses • Anemia • Other risk factors for fracture	Follow-up based on initial DXA outcomes [3]	• Check 25-OH vitamin D levels at diagnosis and then yearly at the end of winter to assess for sufficiency [7]

(continued)

Table 11.1 (continued)

Disease	DXA screening recommendations	DXA follow-up	Vitamin D screening
Inflammatory bowel disease	Routine DXA screening [8]: • At time of diagnosis of IBD Consider obtaining a DXA at any point in children with IBD and any of the following risk factors [8]: • Suboptimal growth velocity, height Z-score < −2.0, or downward crossing height percentile curves • Weight or BMI Z-score < − 2.0 or downward crossing weight or BMI percentile curves • Primary or secondary amenorrhea • Delayed puberty • Severe inflammatory disease course, especially if albumin level < 3 g/dL • ≥6 months of systemic glucocorticoid use	Repeat DXA scans every 1 to 2 years in children and adolescents with IBD and BMD Z-score ≤ −1.0 at any point [8]	• Minimum level of sufficiency for children and adolescents with IBD is 32 ng/mL • Yearly monitoring at the end of winter, especially in populations with dark skin complexion [8]
Chronic kidney disease	No routine testing in the presence of CKD-mineral and bone disorder [9] Consider DXA [3]: • At time of fracture presentation	Follow-up based on initial DXA outcomes [3]	• Measure serum 25-hydroxyvitamin D concentrations at least yearly in patients with CKD stages 2–4 and elevated PTH [9] • Minimum level of sufficiency for children and adolescents with CKD is 30 ng/mL [9]
Cancer survivors	Baseline DXA screening at time of entry into long-term follow-up (usually 2 years after completion of treatment) [10] • If treated with any agent known to predispose to reduced BMD (glucocorticoids, cranial radiation, methotrexate, hematopoietic cell transplantation)	Follow-up as clinically indicated [10]	• No specific guidelines for frequency of vitamin D screening in cancer survivors • Calcium and vitamin D supplementation recommended if risk factors present

(continued)

Table 11.1 (continued)

Disease	DXA screening recommendations	DXA follow-up	Vitamin D screening
Hypogonadism	No specific guidelines for DXA screening in children and adolescents Consider underlying cause and screen according to clinical need	Follow-up based on initial DXA outcomes	• No specific guidelines for frequency of vitamin D screening

visit 7 months ago. His body mass index (BMI) percentile for age has dropped from the 55th percentile to the 15th percentile. In addition, Marshall's linear growth has slowed during this time. On physical exam, Marshall has diffuse abdominal tenderness without guarding or rigidity. Colonoscopy reveals ulceration and stenosis of the ileocecal valve, and biopsies are consistent with a diagnosis of Crohn disease. Oral glucocorticoid therapy is initiated.

What factors put Marshall at risk for impaired bone maturation, and what steps should be taken to evaluate his bone health?

Risk Factors for Impaired Bone Health in Adolescents with Chronic Disease

The mechanisms of bone disease are multifactorial and remain under investigation. Sex hormone suppression, decreased physical activity, impaired linear growth, decreased lean body mass, chronic inflammation, and prolonged glucocorticoid use are just some of the risk factors for impaired bone health that have been described in adolescents with chronic disease. In addition, significant interplay between these factors exists, with malnutrition leading to specific vitamin and mineral deficiencies that impact bone and contributing to impaired linear growth, decreased lean body mass, and delayed pubertal development, for example. A summary of these risk factors and their interplay can be found in Fig. 11.1.

Sex Hormone Suppression, Hypogonadism, and Menstrual Irregularity

Peak bone accrual occurs in adolescence in conjunction with the pubertal growth spurt [11]. Thus, adolescence represents a period of increased skeletal vulnerability, and alterations in pubertal development can have significant impacts in bone health not only during adolescence but extending across the lifespan [11]. Sex differences in hormonal regulation of the bone may explain variations in fracture risk, with some studies showing adolescent females with diseases impacting pubertal development at higher risk for fracture than males [12, 13]. Patients with hypogonadism, pubertal delay, or amenorrhea should be promptly referred for evaluation of bone health and nutritional status [8].

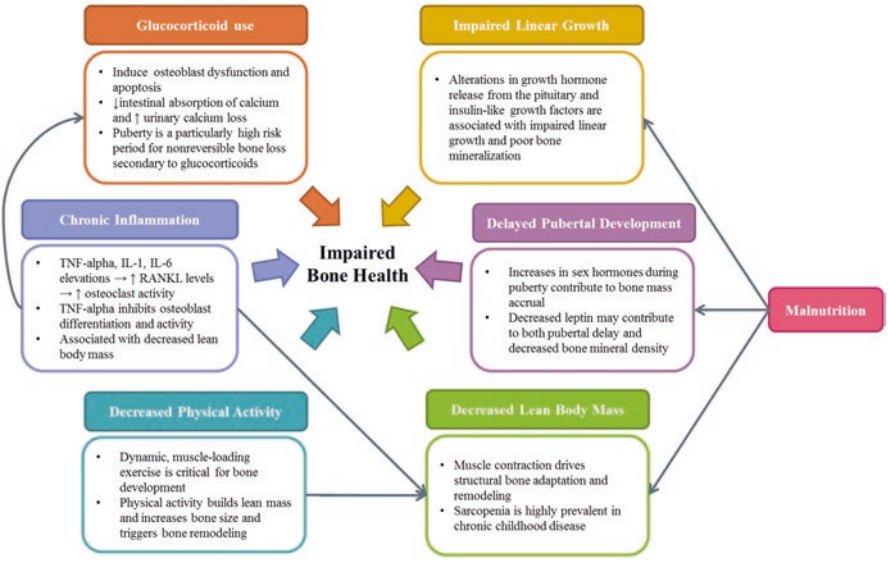

Fig. 11.1 Risk factors for impaired bone health in adolescents with chronic disease

In adolescent girls, amenorrhea is often the first sign of hypogonadism. A wealth of studies of other disease processes have demonstrated derangements in bone health associated with amenorrhea, including inflammatory bowel disease, celiac disease, cystic fibrosis, anorexia nervosa, relative energy deficiency in sport, and primary ovarian insufficiency [14–20]. Major contributors to this process are poor nutritional status, decreased body fat, and negative energy balance. Pubertal development is dependent on a well-balanced hypothalamic-pituitary-gonadal (HPG) axis, with leptin playing an important regulatory role in pubertal development [21]. In adolescents with decreased body fat, leptin is decreased and may contribute to both pubertal delay and decreased bone mineral density (BMD) later in life [22, 23]. Delayed onset of puberty leads to alterations in hormone levels. Sex hormones play an important role in bone mass accrual during adolescents, with a significant body of research focusing on the role of estrogen [24]. Estrogen leads to increased bone formation, decreased bone resorption, and decreased bone remodeling through effects on cytokine production and direct effects on bone cells, as depicted in Fig. 11.2. Although estrogen deficiency has been shown to lead to declines in both cortical and trabecular bone, trabecular bone mass is more severely affected [25].

Hypogonadism is also a common secondary cause of osteoporosis in males. The influence of testosterone on the male skeleton is partly exerted indirectly, as testosterone is aromatized to estrogen in many tissues, including the gonads, adipose tissue, skin, and bone [26]. Multiple studies have demonstrated that hypogonadal men treated with testosterone exhibit significant gains in BMD over relatively short periods of time, emphasizing the importance of sex hormone sufficiency [27, 28]. Androgens and estrogen both block interleukin-6 (IL-6), a cytokine that is

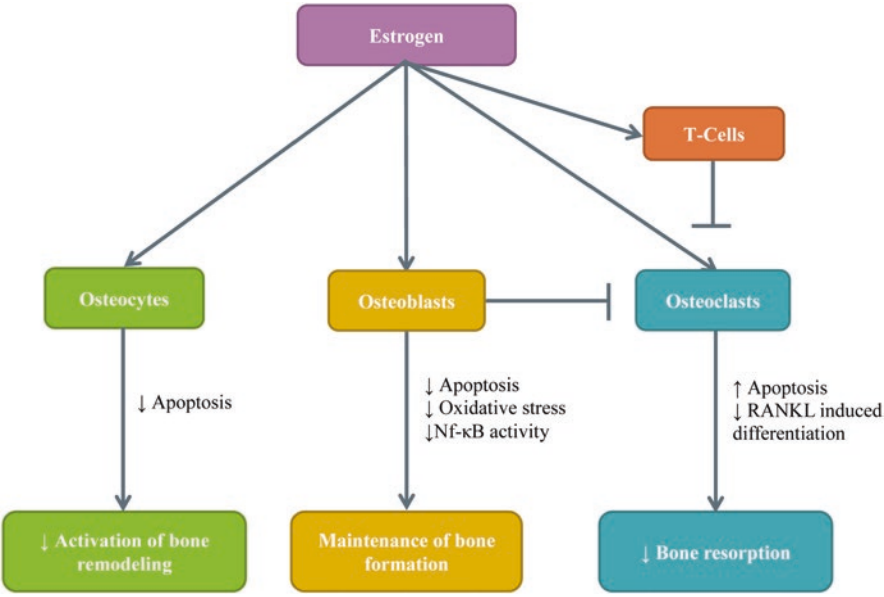

Fig. 11.2 Estrogen's impact on bone homeostasis

important in activating bone resorption. In addition, androgens promote osteoblast proliferation, differentiation, and lifespan with associated increases in periosteal bone formation [29].

Decreased Physical Activity

Adolescence is a period of significant bone modeling and remodeling during which periosteal surfaces are rapidly growing. Physical activity during this time period leads to increased bone mass on the periosteal bone surfaces, which is important for bone strength [30, 31]. Adolescents with chronic disease may be less physically active than their healthy peers for several reasons, including the burden of medical appointments and hospital stays, physical or mental symptoms related to the underlying disease, and physician recommendations regarding organized sports or other activities [32]. Multiple studies have demonstrated a positive association between physical activity and BMD in adolescents with common chronic diseases [31, 33–35]. Dynamic, impact-loading, and muscle-loading activities of a short duration have shown to be most effective at increasing bone size [30]. Regular weight-bearing exercise should be recommended to all adolescents with chronic disease unless clear contraindications, such as medical instability, exist [30, 36].

Impaired Linear Growth

There are multiple causes for impaired linear growth in adolescents with chronic disease, including poor nutritional status in malabsorptive gastrointestinal conditions such as inflammatory bowel disease, cystic fibrosis, and celiac disease, derangements in hormonal mediators, and adverse effects from medications [37–40]. The growth hormone/insulin-like growth factor (IGF) axis is a major determinant of linear growth, and multiple chronic diseases may interrupt these pathways [41, 42]. Insulin-like growth factors (IGF-1 and IGF-2), as well as changes in IGF-binding proteins (IGFBP), have been associated with impaired linear growth and poor bone mineralization [43]. BMD Z-scores measured by dual-energy x-ray absorptiometry (DXA) are underestimated in children with low height Z-scores, so results must be adjusted by size in order to evaluate bone health in children with growth stunting [32, 44–46].

Decreased Lean Body Mass

Lean body mass is essential for normal bone development. Muscle contraction drives structural bone adaptation and remodeling [47]. Sarcopenia, defined as decreased skeletal muscle mass, is highly prevalent in chronic childhood diseases [48, 49]. The causal relationship between lean mass deficits and derangements in BMD and bone microarchitecture is still under investigation, but multiple studies have demonstrated an association between the degree of lean mass deficit and bone deficits in children [37, 38, 50]. In a clinical setting, weight and body mass index (BMI) can be used as surrogate measures of lean mass, and low weight or BMI should prompt physicians to examine bone health in pediatric patients. Many studies have cemented this relationship, demonstrating higher BMD Z-scores in patients with higher BMI Z-scores and higher weight Z-scores [3, 4, 37, 51–53]. Measures of muscle mass or muscle size are often used as surrogates of forces acting on the bone, but studies have also demonstrated that pediatric chronic disease may be associated with abnormal muscle force relative to muscle size [54]. Impaired muscle force in children and adolescents with chronic disease may further contribute to impaired bone development [54].

Chronic Inflammation

Systemic inflammation is a hallmark of many chronic diseases in childhood. Elevated levels of inflammatory cytokines are seen in Crohn disease, cystic fibrosis, and celiac disease, among many others [55]. These inflammatory cytokines and other inflammatory mediators are known to have significant effects on several facets of bone health. In particular, cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) are commonly elevated in chronic disease and have well-delineated roles in bone metabolism [56]. TNF-α has been shown to prevent the differentiation of mesenchymal stem cells into osteoblasts,

promote the apoptosis of mature osteoblasts, and prevent osteoblasts from synthesizing collagen [57]. IL-1, IL-6, and TNF-α also act on signaling pathways, promoting osteoclast differentiation and activation while inhibiting osteoclast apoptosis [58]. In addition to these direct effects on bone formation and resorption, chronic inflammation also adversely affects muscle mass causing sarcopenia, another contributor to poor bone health in the growing skeleton [41].

Prolonged Use of Systemic Glucocorticoids

The use of systemic glucocorticoids is a cornerstone of treatment of a wide variety of chronic childhood illnesses. While they are beneficial in dampening the pro-inflammatory states associated with chronic disease, glucocorticoids also impair bone health through several mechanisms [6, 56]. Glucocorticoids induce dysfunction and apoptosis of osteoblasts, decrease intestinal absorption of calcium, and increase urinary calcium loss [56, 59, 60]. Although the minimum dose of glucocorticoids necessary to impact bone mineralization has not been delineated, several studies have demonstrated that puberty is a particularly high-risk period in which adolescents may suffer from nonreversible bone loss as a result of glucocorticoid exposure [61].

General Considerations in Pediatric Imaging Techniques in Chronic Disease

The skeleton is rapidly developing during adolescence, with changes to both cortical and trabecular components of the bone. Cortical bone is a dense, stiff bone found primarily in the shaft of long bones. Cortical bone forms the outer shell at the end of joints and the vertebrae. The high cortical bone content of long bones allows for a high resistance to torsional and bending forces. Gravitational forces and muscle-loading exercises are important moderators of cortical bone mass and density [62]. Trabecular bone, in contrast, is made up of trabeculae organized into a loose network and is found in the end of long bones, in vertebrae, and in flat bones like the pelvis. Trabecular bone is porous in nature, which allows for high resilience and shock absorption in the lumbar spine and epiphyseal regions of long bones.

Multiple imaging modalities have been developed to assess bone size, strength, and architecture, including DXA, peripheral quantitative computed tomography (pQCT), and high-resolution peripheral quantitative computed tomography (HR-pQCT). Although these methods are described in greater detail in Chap. 7, a brief description will be provided here, as they pertain to recommendations for screening and treatment.

DXA provides a two-dimensional assessment of body composition and bone mineral density and is unable to differentiate between cortical and trabecular bone. In contrast, pQCT allows for three-dimensional assessments of volumetric density and bone structure and can isolate specific deficits in trabecular and cortical bone

mass. HR-pQCT builds upon this technology, using precise measurements to assess trabecular and cortical bone microarchitecture in order to better predict fracture risk and determine bone strength. Currently, pQCT and HR-pQCT are primarily used for research, but a growing body of work highlights the potential utility of these tools in clinical assessments of bone health and fracture risk. It is important to note that DXA, pQCT, and HR-pQCT measurements are extremely dependent upon the technologist and there is a high degree of variability in both the skills of technologists performing the tests and of clinicians interpreting the results [63]. Patients should be referred to high-volume centers that have measures in place to assure quality control in acquisition, analysis, interpretation, and reporting of results, as poor quality results may result in inappropriate patient care decisions that can be costly and sometimes harmful to patients [63, 64].

Common Chronic Diseases That May Affect the Skeleton

Allison is a 10-year-old girl with cystic fibrosis who presents to your office for her annual well-child visit. Allison and her mother report that Allison eats a balanced diet with three to four servings of dairy per day and enjoys playing tennis after school. Allison's mom mentions that her daughter sometimes forgets to take her preventative medications on school days. Allison follows with a pulmonologist regularly for her cystic fibrosis, and her most recent forced expiratory volume in 1 second (FEV1) was 47% of predicted. Allison had a routine DXA screening after her 8th birthday that revealed a lumbar spine Z-score of −1.4 and a total hip Z-score of −1.7. You review the European Cystic Fibrosis Bone Mineralization Guidelines and order repeat DXA measurements since it has been 2 years since her last screening. Repeat DXA measurements demonstrate worsening bone health, with a lumbar spine Z-score of −1.8 and a total hip Z-score of −2.1. How should you counsel Allison and her mother?

Cystic Fibrosis

Cystic fibrosis (CF) is one of the most common autosomal recessive diseases in Caucasian populations, with prevalence rates estimated at 1 in 3000 births for Caucasians in the United States [65]. In addition, the prevalence of CF in nonwhite populations is rising with increasing use of newborn screening worldwide. In patients with CF, mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene lead to accumulated viscous secretions and multi-organ damage. With improvements in diagnosis and management of CF, more patients with CF are surviving into adulthood, with a median predicted survival of 41.6 years [66]. This extended lifespan has led to an increase in the prevalence of chronic medical complications of CF, including CF-related bone disease [6].

Pathophysiology of Bone Disease in CF

Multiple factors contribute to bone disease in CF, including poor nutrition, malabsorption, pancreatic insufficiency, delayed puberty, chronic lung infection and inflammation, decreased physical activity, impaired glucose metabolism, and immunosuppressive therapies including glucocorticoids and transplant-related

immunosuppression [67–69]. Poor growth and delayed maturation are well described in patients with CF [70]. Sarcopenia is also a common finding in patients with CF [71]. This deficit in lean mass leads to impaired loading of the skeleton during growth, resulting in smaller and more slender bones [72]. Growth stunting is an important confounder of DXA BMD results, and adjustments for short stature must be incorporated into the interpretation of DXA results in this population. The necessity of adjusting for stature was highlighted by a 2008 study examining DXA BMD results in children with CF which found that deficits in lumbar spine and total body BMD were attenuated after adjusting for height Z-score [38]. Malabsorption and pancreatic insufficiency lead to high rates (48–95%) of vitamin D deficiency in patients with CF, further contributing to bone disease in this population [68]. Vitamin D deficiency leads to decreased intestinal absorption of calcium and secondary hyperparathyroidism with resultant bone mineral resorption and bone fragility [67, 73]. In addition, the CFTR gene may exhibit a direct effect on osteoclast activation, leading to increased bone resorption [74].

Presentation of Bone Disease in CF

Low bone mass and BMD have been widely reported in adult patients with CF [69, 75]. Prevalence rates of osteopenia and osteoporosis in adults with CF are 23.5% and 38%, respectively. Bone microarchitecture is altered in young adults with CF, with impaired trabecular morphology and reduced connectivity between trabeculae [76]. In addition to low BMD, fracture risk is also increased in adult patients with CF. A meta-analysis from 2010 reported an overall prevalence of vertebral fractures of 14% [77], although prevalence rates of vertebral fractures in adults with CF have been reported to be as high as 30% in some series [6, 69]. Non-vertebral fractures are also common, with a pooled prevalence estimate of 19.7% in adults with CF [77]. To date, no long-term studies have evaluated the association between BMD and fracture risk in adults with cystic fibrosis.

Several studies have investigated BMD in children, adolescents, and young adults with CF. These studies have produced conflicting results, with some studies reporting normal BMD or low rates of decreased BMD in children with CF [78, 79], while other studies have reported low BMD in up to half of pediatric patients with CF [1, 67]. Risk factors for low BMD Z-scores in children include low BMI Z-scores, vitamin D deficiency, dysglycemia, glucocorticoid use, frequent exacerbations, worsened disease severity scores, frequency of antibiotic treatments, and lung function as measured by forced expiratory volume in 1 sec (FEV1) scores [1, 67–69]. Multiple studies have identified gender differences in CF-related bone disease; adolescent females with CF are at increased risk for decreased BMD compared to younger girls and boys of all ages [80]. Recent pQCT studies of children and adolescents with CF have identified deficits in trabecular and cortical bone parameters [81]. These deficits increased with age in adolescent females and were not fully explained by alterations in body composition [81]. In males, worsening pulmonary function was associated with greater deficits in bone parameters [81].

There are also conflicting data regarding the risk for fracture in pediatric patients with CF. One study examining rates of kyphosis in fracture in children, adolescents,

and young adults with CF found that the fracture rates for males and females with CF from birth to 5 years of age were comparable with healthy children [82]. However, female patients with CF between 6 and 16 years of age had increased rates of both fracture and kyphosis relative to children without CF, consistent with prior studies documenting increased risk for bone mineralization deficits in adolescent females [82]. One cross-sectional study of 43 CF patients, however, found a 9.2-fold increased fracture rate for CF patients compared to age-matched controls. Interestingly, prior studies have not found a relationship between DXA parameters and fracture risk, bringing into question the utility of DXA in identifying CF patients at risk for fracture [83, 84]. However, a recent study of children, adolescents, and young adults with CF reported that DXA and pQCT measures of BMD and BMC can identify a subgroup of CF patient at low risk for fracture [85]. Despite this encouraging finding, DXA and pQCT results had relatively low positive predictive values for fracture, which may be related to the multifactorial etiology of bone fractures and CF-related bone disease.

Evaluation

The European Cystic Fibrosis Bone Mineralization Guidelines have outlined recommendations for DXA screening and follow-up [1]. Routine DXA screening is recommended for children with CF greater than 8 years of age if they have risk factors for decreased bone mineralization, including weight less than 90% of median body weight for age and height; FEV1 less than 50% of predicted, delayed puberty; or use of high-dose glucocorticoid treatment for more than 90 days per year [1]. For adults greater than 18 years, routine DXA screening is recommended. In both pediatric and adult patients, DXA results should be adjusted for height and lean mass for height. Follow-up assessment of BMD should be based on initial DXA outcomes and repeated every 5 years if the BMD Z-score is > -1, every 2 years if the Z-score is between -1 and -2, and every year if the Z-score is <-2 or if the child has experienced low-trauma fractures. In children less than 8 years of age, DXA may be indicated in children with significant risk factors for low BMD or prior to prescribing specific treatments for low BMD [1]. As vitamin D deficiency has been identified as a contributor to decreased BMD in CF patients, 25-hydroxyvitamin D levels should be checked at least yearly, ideally at their seasonal nadir at the end of winter and after any treatment change [2].

Management

Patients with cystic fibrosis should be counseled to ensure they meet the recommended intake of calcium, phosphorus, vitamin K, and vitamin D in order to support bone health. Supplementation with vitamin D3 is preferred over vitamin D2 [2, 73]. Guidelines for replacement dosing are based on age and degree of vitamin D deficiency [2, 67]. Weight-bearing exercise should be encouraged. Use of bisphosphonates in adults with cystic fibrosis has shown benefits in BMD and fracture risk. However, bisphosphonate use has not been well studied in the pediatric population and has significant potential for adverse effects in the growing skeleton. Thus, bisphosphonate use should only be considered if there is prolonged glucocorticoid use, fracture history, or low BMD after transplant [1].

Type 1 Diabetes Mellitus

Type 1 Diabetes Mellitus (T1DM) is a chronic autoimmune disorder characterized by absolute insulin deficiency following autoimmune destruction of the insulin-producing beta cells of the pancreas. The age of presentation of T1DM has a bimodal distribution, with one peak at 4–6 years of age and a second peak in early puberty at 10–14 years of age. The incidence of T1DM is increasing worldwide, highlighting the need for screening for and management of complications related to T1DM.

Pathophysiology of Bone Disease in T1DM

Hyperglycemia, impaired function of growth factors, and decreased lean mass all contribute to impaired bone health in children and adolescents with T1DM. In contrast to other disorders highlighted here, bone disease in T1DM is primarily caused by decreased bone formation rather than increased bone resorption [86]. Osteoblast dedifferentiation, transdifferentiation, and death have all been described, with these findings most prominent at the time of onset of T1DM. These processes lead to a decrease in the number of mature and functioning osteoblasts and have been associated with a parallel increase in bone marrow adiposity [87]. Underlying microvasculopathy, decreased vitamin D levels, inflammation, and advanced glycation end products all contribute to impairments in bone health [6, 86, 88].

Hyperglycemia and glycosuria are common in patients with undiagnosed or inadequately treated T1DM and can lead to hypercalciuria and negative calcium balance [87]. In addition to hyperglycemia, insulin deficits may also contribute to skeletal fragility. Animal models have demonstrated that insulin has an anabolic effect on bone and that reductions in insulin production lead to a low bone turnover state with a decrease in osteoblast number and activity. This finding is supported by experimental data in humans demonstrating that insulin treatment can prevent the negative effects of T1DM on bone and even enhance bone formation [89, 90]. The effect of insulin on bone may be mediated by the insulin-like growth factor-1 (IGF-1) pathway; insulin inhibits IGF-binding protein 1 (IGFBP-1) expression in osteoblasts. Thus, in insulin deficiency, there is inadequate unbound IGF-1 to promote anabolic effects on bone [91]. Compared with matched healthy controls, adolescents with poorly controlled T1DM have elevated growth hormone secretion but low serum IGF-1 levels, highlighting the role of the growth hormone/IGF axis as a major mechanism for inadequate bone formation in adolescents with T1DM. Finally, it remains unclear whether the autoimmune process associated with T1DM may be directly involved in poor bone health. Increased levels of activated T cells are present in adolescents with T1DM and this area requires further investigation to delineate the impact of these immune processes on bone health in T1DM [92].

Presentation of Bone Disease in T1DM

Studies in adults with T1DM have documented normal to decreased BMD, with as many as 20% of patients over the age of 20 meeting diagnostic criteria for osteoporosis [88, 93]. Fracture burden has also been examined in adult patients with T1DM. Multiple studies of adults with T1DM and T2DM have demonstrated an increased risk of hip fracture [93, 94], with a meta-analysis reporting a relative risk

of hip fracture of 6.94 in adults with T1DM and 1.38 in adults with T2DM relative to healthy controls [95]. Diabetes complications, including diabetic retinopathy, nephropathy, and neuropathy, are also associated with a ten-fold increase in fracture risk in patients with T1DM [86]. Although BMD deficits likely contribute to fracture risk in adults with T1DM, a meta-analysis found that the increased fracture risk seen in T1DM cannot be solely explained by observed deficits in BMD alone. A multifactorial pathway to skeletal fragility in T1DM likely includes chronic hyperglycemia, impaired production of IGF-1, and the accumulation of advanced glycation end products in bone [95].

Multiple cross-sectional studies using DXA have reported that DXA measures of BMD and BMC were significantly lower in T1DM compared with healthy controls [96, 97]. Patients with a long duration of diabetes were more likely to have growth stunting and bone deficits [98]. These findings have been corroborated by altered bone geometry as measured by pQCT [97, 99], with a longitudinal pQCT study suggesting recovery of bone deficits following diagnosis and treatment [97]. In addition, one study found that early manifestation of T1DM in children is a risk factor for altered bone development, with impairments in cortical BMD and total, cortical, and muscle cross-sectional area [100]. The importance of glycemic control in T1DM is highlighted by multiple DXA studies reporting that poor metabolic control as measured by HbA1c is associated with worse BMD outcomes [96].

A recent population-based cohort study examined 30,394 children, adolescents, and adults with T1DM and found that type 1 diabetes was associated with an increased risk of incident fracture beginning in childhood [101]. Hazard ratios for incident fracture at all sites were 1.14 for males and 1.35 for females ages 0–19 years, while hazard ratios for incident hip fracture were 2.01 for males and 4.61 for females, suggesting a disproportionate risk of lower extremity fractures [101]. This was the first study to identify an increased fracture risk in children with T1DM and highlights the need for screening for skeletal fragility in children with T1DM and developing therapeutic interventions aimed at preventing and treating decreased bone mass accrual in children and adolescents.

Several small studies have investigated whether comorbid celiac disease and T1DM may lead to adverse bone outcomes relative to patients with T1DM alone. Prior studies have reported that T1DM patients with comorbid celiac have lower BMD compared with those with T1DM alone [88]. However, a recent population-based cohort study compared fracture risk in patients with both T1DM and celiac disease to those with only T1DM [102]. This study found that celiac disease did not influence the risk of incident fracture in patients with T1DM [102]. However, this result must be interpreted with care given the small absolute numbers of fractures ($n = 12$) in the T1DM and celiac disease group.

Evaluation

The most recent International Society for Clinical Densitometry (ISCD) guidelines published in 2013 do not recommend routine DXA or other imaging as a screening measure to assess bone health in pediatric patients with T1DM [3]. However, these recommendations were published prior to the landmark study by Weber et al. in 2015 demonstrating increased fracture risk in children and adolescents with T1DM

[101]. DXA screening may be warranted in patients with specific risk factors, including low BMI, increased daily insulin dose, poor renal function, and fracture history. However, it is important to recognize that fractures may occur even in the setting of normal BMD given the multifactorial etiology of skeletal fragility in T1DM [4, 101].

Zhukouskaya et al. published recommendations in 2015 for evaluation of bone health in patients with T1DM, starting with identification of risk factors [4]. These risk factors include clinical features of bone disease (e.g., back pain, kyphosis, decreased height), diabetic complications (e.g., retinopathy, nephropathy, neuropathy), high daily insulin requirements, low BMI, or reduced renal function. If risk factors are present, laboratory and DXA evaluation of bone health are recommended. If no risk factors are present, calcium intake and vitamin D status should be assessed routinely. Supplementation with calcium and vitamin D should be provided to meet target levels [4]. A summary of the 2011 Institute of Medicine recommendations for calcium and vitamin D intake is provided in Table 11.2.

Management

Current recommendations for the treatment of bone disease associated with T1DM focus on improving glycemic control and maintaining mineral homeostasis [4]. Intensive insulin treatment and improvement in glycemic control have been associated with improved bone outcomes [89, 90]. Calcium and vitamin D supplementation to maintain target levels may also promote improvements in bone metrics [104, 105]. Finally, physical activity has been demonstrated to have a positive effect on bone mineral acquisition in children with T1DM [34]. Weight-bearing sports including ball games, jumping activities, or gymnastics should be encouraged in children with adolescents with T1DM to optimize bone mineral acquisition during growth [106].

Celiac Disease

Celiac disease is an autoimmune-mediated disorder that occurs in genetically predisposed individuals who are exposed to gluten. Gliadin, a glycoprotein extract from gluten, has been shown to be toxic to enterocytes and incites a cell-mediated

Table 11.2 2011 Institute of Medicine recommendations for calcium and vitamin D intake

	Calcium (mg/day)		Vitamin D (IU/day)	
Age (y)	Recommended intake	Tolerable upper limit	Recommended intake	Tolerable upper limit
1–3	700	2500	600	2500
4–8	1000	2500	600	3000
9–18	1300	3000	600	4000
19–30	1000	2500	600	4000

Adapted from Ross et al. [103]

immune response [107]. Celiac disease is characterized by mucosal inflammation, villous atrophy, and crypt hyperplasia. These alterations in the small intestine cause malabsorption when gluten is ingested. Complications of unrecognized or untreated celiac disease include anemia, poor growth, and delayed puberty, all of which may contribute to bone disease in celiac patients.

Pathophysiology of Bone Disease in Celiac Disease

Bone disease in patients with celiac disease occurs secondary to malabsorption, malnutrition, hypogonadism, and inflammation. Bone disease has been described in celiac disease patients with and without gastrointestinal symptoms [108]. Malabsorption may increase the risk of vitamin D deficiency, although studies have reported conflicting findings regarding vitamin D status in children and adolescents with celiac disease [109, 110]. Vitamin D deficiency is associated with decreased BMD Z-scores in children and adolescents with celiac disease [111]. Untreated patients with celiac disease have been shown to have decreased lean body mass compared to healthy controls, which may lead to alterations in the functional bone muscle unit [112]. In addition, celiac disease may lead to poor bone health through an abnormal cytokine signaling pathway that favors bone resorption [5, 113].

Presentation of Bone Disease in Celiac Disease

In patients with celiac disease, low BMD is common at the time of diagnosis. A study of bone mineral content (BMC) revealed that 24% of patients had significantly low BMC for age (Z-score < -2) at the time of diagnosis of celiac disease [114]. Higher tissue transglutaminase antibody levels are associated with decreased BMD, although it remains unclear whether disease severity, as defined by either biopsy grade or self-reported symptoms, may contribute to bone mineralization deficits [113, 115]. One study suggested that low BMD may persist into adulthood in up to two-thirds of celiac disease patients; persistent bone disease may be a reflection of chronic subclinical disease in childhood prior to diagnosis with subsequent failure to achieve peak bone mass in adolescence and young adulthood [115]. In addition, a high-resolution pQCT (HR-pQCT) study of premenopausal women with celiac disease demonstrated deficits in microarchitecture of the trabecular and cortical compartments of peripheral bones that correlated with disease activity [116].

The fracture risk in children with celiac disease has not been well delineated. A cross-sectional population-based study in Sweden reported a 2.6-fold increased risk for hip fractures in pediatric patients with celiac disease relative to healthy controls [117]. However, this finding was based on small absolute numbers of hip fractures in both patients with celiac disease and controls, and other studies have reported no increase in fracture risk in patients with celiac disease [5]. A meta-analysis of eight studies reported a slightly increased fracture risk in patients with celiac disease (8.7%) when compared to healthy controls (6.1%), giving a pooled odds ratio of 1.43. No studies have investigated the association between BMD and fracture risk in children with celiac disease.

Evaluation

Routine DXA screening is not recommended for children with celiac disease at baseline or follow-up. However, screening may be clinically warranted in patients with severe growth retardation or malnutrition at diagnosis or in patients who do not have improvement in growth and symptoms despite strict adherence to a gluten-free diet. In these patients, DXA may provide helpful information on bone health and body composition that can inform clinical decision-making [3]. In addition, DXA assessment of BMD may be clinically warranted in patients who are not adherent to a gluten-free diet and have low BMI, history of irregular menses, anemia, or other risk factors for fracture [7]. Vitamin D screening is recommended at diagnosis and then yearly at the end of winter to assess for sufficiency.

Management

A gluten-free diet is associated with restitution of bone health in children with celiac disease, although the time needed to normalize BMD is not known [111, 113, 115]. Adolescents with celiac disease should receive at least the RDA for vitamin D and more as dictated by serum 25-hydroxyvitamin D concentrations. Patients with vitamin D deficiency should be repleted with repeat levels performed every 6–8 weeks while taking high-dose treatment [110].

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a term that comprises two major disorders: Crohn disease and ulcerative colitis. Crohn disease causes transmural inflammation that can affect any component of the gastrointestinal tract from the oral cavity to the anus, with the terminal ileum commonly afflicted. Ulcerative colitis affects the colon and is characterized by inflammation of the mucosal layer. The peak incidence of IBD occurs in patients between the ages of 15 and 30 years [118]. Children and adolescents with IBD often present with similar clinical features, but children and adolescents are at unique risk for growth failure and delayed puberty secondary to malnutrition. Both forms of IBD are associated with an adverse impact on bone modeling and the muscle-bone unit in developing children. However, descriptive studies of BMD in pediatric patients with IBD have demonstrated that BMD is lower in patients with Crohn disease compared to those with ulcerative colitis [119].

Pathophysiology of Bone Disease in IBD

Multiple factors contribute to suboptimal bone health in children and adolescents with IBD, including chronic inflammation, malnutrition leading to delayed linear growth and lean mass deficits, menstrual irregularities, delayed puberty, and use of glucocorticoid therapy [8, 52, 120]. As its name implies, IBD is an inflammatory process. Inflammation in IBD is primarily driven by the over-activation of T cells; these T cells increase the production of cytokines that stimulate bone resorption, promote osteoclast differentiation and activation, inhibit osteoclast apoptosis, and inhibit osteoblast differentiation [121, 122]. Decreased bone modeling, remodeling, and linear growth are observed in pediatric IBD, with growth stunting common at

presentation for treatment. In children with Crohn disease, many children go on to have permanent stunting, with decreased height Z-scores and lean body mass deficits often persisting despite treatment for IBD [41, 123]. The causal relationship between lean mass deficits and derangements in BMD and bone microarchitecture is still under investigation, but multiple studies have demonstrated an association between the degree of lean mass deficit and bone deficits in children with IBD, highlighting the importance of the functional bone muscle unit [49, 123].

In addition to IBD-related causes of poor bone health, glucocorticoid treatment for IBD also contributes to increased bone resorption. Glucocorticoid therapy is a mainstay of treatment of acute IBD flares. Several studies have investigated the role of glucocorticoids in bone deficits in IBD with conflicting results. Although some studies found an inverse relationship between cumulative glucocorticoid dose and BMD [49, 51], others showed no association [123–125]. A prospective study demonstrated decreased bone formation and resorption biomarkers during glucocorticoid therapy [126]. Bone formation and resorption biomarkers returned to normal values within 1 month after cessation of glucocorticoids, suggesting that alterations in bone turnover may be reversible [126].

Presentation of Bone Disease in Children with IBD

Bone deficits in pediatric patients with IBD are present at the time of diagnosis and typically do not fully recover with appropriate treatment [51, 124]. Multiple studies have demonstrated that adolescents with IBD have decreased BMD and impaired bone architecture at diagnosis, suggesting that untreated chronic inflammation contributes to poor bone health [123–125]. Although BMD Z-scores measured by DXA are underestimated in children with low height Z-scores, bone mineralization deficits persist even when adjusted for size [8, 41, 123]. Biomarkers of bone formation and bone resorption are observed to be 30–50% of normal in children with IBD compared to healthy controls [124]. This is consistent with findings of reduced trabecular bone turnover observed on trans-iliac bone biopsies of children presenting for initial evaluation of Crohn disease [127]. Recent pQCT studies of pediatric patients with Crohn disease have also demonstrated deficits in bone structure and geometry [123].

In a study of 733 children with Crohn disease, 488 children with ulcerative colitis, and 3287 age-, gender-, and geographic location-matched healthy controls, IBD was not associated with a higher risk of fracture at any site [128]. This is in contrast with an early case series reporting an increased risk of vertebral compression fractures in children with Crohn disease [129]. However, this case series was published prior to the use of biologic therapies for IBD, which may ameliorate fracture risk in this population. However, no studies to date have determined the impact of peak bone mass and lifetime fracture risk in a population of patients diagnosed with IBD during childhood.

Treatment of Crohn disease with anti-inflammatory therapy and improved nutrition is associated with improvement in bone biomarkers [124]. However, children with IBD continue to have decreased BMD and may even have worsening of mechanical properties of bone over time despite treatment [123, 124].

Evaluation

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) clinical practice guideline recommends BMD screening and monitoring in children with IBD [130]. A DXA evaluation is indicated in the presence of malnutrition, short stature, prolonged glucocorticoid therapy, severe disease with frequent relapses, or history of clinically significant fractures, with repeat scans annually in patients with BMD Z-scores more than one standard deviation below the mean [8, 130]. However, it remains unclear whether modest decreases in bone density predict fracture risk in children and adolescents with chronic illness [131]. Low BMI or weight Z-scores should also prompt evaluation of nutritional status and bone health, as BMI and weight Z-scores may indicate lean mass deficits. Many cross-sectional findings have cemented the relationship between BMI and bone mineralization in patients with IBD, demonstrating higher BMD Z-scores in patients with higher BMI Z-scores [37, 51, 124, 125].

Monitoring of serum concentrations of 25-hydroxyvitamin D is recommended at least annually [8, 14], with studies suggesting levels above 30–32 ng/mL are necessary for optimal small bowel calcium absorption and suppression of parathyroid hormone secretion [132].

Management

Treatment of Crohn disease with non-glucocorticoid-based treatments such as anti-TNF agents that work to decrease IBD-related inflammation has been shown to have beneficial effects on BMD and markers of bone metabolism [125, 133]. The REACH study examined the impact of infliximab induction and maintenance therapy in pediatric Crohn disease, finding that pediatric patients demonstrated significant increases in both bone formation and resorption during the induction period [134]. The observed increases in bone formation far surpassed those observed in adults treated with infliximab, suggesting that infliximab therapy may be particularly useful during adolescence when peak bone mass accrual is occurring [134].

A recent study of vitamin D supplementation in children and adolescents with IBD demonstrated that supplementation with 2000 IU of cholecalciferol was associated with increased trabecular BMD, cortical bone cross-sectional area, and maximal muscle power at 1 year follow-up. Current guidelines recommend a daily intake of 1000–1600 mg of elemental calcium in children greater than 4 years of age and adolescents with IBD [8]. A small randomized clinical trial of 13 adolescents with IBD compared zoledronic acid to placebo. A single IV dose of zoledronic acid was associated with increases in BMD Z-score at 6-month follow-up [135]. However, despite these encouraging results, treatment with bisphosphonates is not recommended for the treatment of decreased BMD without clinically significant fractures in children due to their long half-lives and the abnormal architecture of newly formed bone during treatment. Treatment of bone disease should incorporate intensive counseling to optimize nutrition, investigation of pubertal delay, and minimization of glucocorticoids [106].

Chronic Kidney Disease

Chronic kidney disease (CKD) in children is defined as a state of irreversible kidney damage or reduction in kidney function and is caused by a variety of congenital and acquired kidney disorders. Up to 60% of cases of CKD in children are caused by congenital etiologies, with congenital renal anomalies and glomerular diseases such as focal segmental glomerulosclerosis making up the majority of these cases. In children with chronic kidney disease (CKD), changes in bone and mineral homeostasis can lead to substantial complications including alterations in longitudinal growth, bone plasticity, and changes in body composition.

Pathophysiology of Bone Disease

Changes in mineral metabolism and bone structure occur in almost all pediatric patients with progressive CKD [136]. These changes occur as the result of abnormalities in the metabolism of calcium, phosphate, vitamin D, parathyroid hormone, and fibroblast growth factor 23 (FGF23) levels [137]. These biochemical changes result in mineral, skeletal, and vascular abnormalities now defined as CKD-mineral and bone disorder (CKD-MBD). Patients with CKD-MBD often have abnormalities in bone histology, longitudinal growth deficits, and extraosseous calcifications [138]. Parathyroid hormone has opposing effects on bone mineralization and has been shown to increase trabecular BMD while decreasing cortical bone mass [139]. In addition to hyperparathyroidism and abnormal mineral metabolism, CKD is also associated with delayed pubertal maturation, growth failure, abnormalities in the growth hormone axis, malnutrition, acidosis, and muscle deficits which all contribute to diminished bone health [48, 140]. In addition, treatment with glucocorticoids may further compromise bone health [137].

Presentation of Bone Disease in CKD

An increased risk for low BMD and fracture has been well described in adults with end-stage renal disease (ESRD) [141, 142]. These findings prompted investigation into bone disease in adults with mild to moderate CKD, with similar findings of decreased BMD and increased rates of fractures in these patients [143]. Multiple studies have demonstrated that femoral neck BMD predicts fracture in adults with chronic kidney disease [144, 145], with one prospective study of adults requiring hemodialysis reporting an association between both femoral neck and total hip BMD and incident fractures. In addition, a study of adult kidney transplant recipients found that both osteopenia and osteoporosis at the hip were independent risk factors for fractures [145].

Children and adolescents with CKD exhibit alterations in bone mineralization with opposing effects on the trabecular and cortical bone mass. pQCT studies of children and adolescents with mild-to-severe CKD have demonstrated increased trabecular bone mass and decreased cortical bone mass relative to healthy controls [48, 140]. These opposing effects have historically limited the use of DXA to detect bone mineralization abnormalities, as DXA is a two-dimensional technique that can only provide a summary of superimposed trabecular and cortical bone mass. A

study comparing DXA and pQCT results in children with advanced CKD and healthy controls found similar increases in trabecular BMD and decreases in cortical BMC as measured by both DXA and pQCT and highlighted the importance of adjusting DXA results for growth failure in CKD [146]. The mean total body BMC Z-score relative to age was −1.31, but after adjustments for height, Z-scores increased to −0.36 [146]. Multiple studies have identified an inverse relationship between lumbar spine BMD Z-scores and PTH levels [147].

Fracture burden among pediatric patients with CKD has been investigated in two recent prospective studies. The first of these examined 170 children and adolescents with CKD and ESRD and revealed that lower baseline cortical volumetric BMD predicted risk of subsequent fracture over an average follow-up of 1 year [137]. A subsequent investigation of fracture burden was conducted using the large prospective Chronic Kidney Disease in Children (CKiD) cohort: 537 children and adolescents with CKD were followed over 5 years in order to identify risk factors for subsequent incident fractures. The investigators found fracture rates that were two- to three-fold higher than published general population rates [148]. Advanced pubertal stage, greater height Z-score, difficulty walking, and higher parathyroid hormone level were independently associated with greater fracture risk, while phosphate binder treatment was associated with lower fracture risk [148].

Evaluation

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend ongoing monitoring of serum concentrations of calcium, phosphate, parathyroid hormone, and alkaline phosphatase. Recommended monitoring intervals based on CKD stage can be found in Table 11.3. In addition, serum 25-hydroxyvitamin D concentrations should be monitored at least yearly in patients with CKD stages 2–4 and elevated PTH [9].

Given the opposing effects of parathyroid hormone on the bone, DXA has limited utility in the screening and diagnosis of CKD-mineral and bone disorder. Bone density does not accurately predict the risk of fracture in patients with CKD, and no treatments have been shown to reduce fracture risk patients with CKD who have low BMD. Thus, routine DXA screening is not recommended, but DXA or pQCT may be indicated in patients presenting with fracture, with follow-up testing based on initial DXA outcomes [3].

Management

Control of bone and mineral homeostasis is an important concern in children and adolescents with CKD. The goals of therapy are to prevent phosphate retention, hypovitaminosis D, and hypocalcemia. Early detection and correction of these abnormalities are critical to improve bone health in pediatric patients with CKD. Serum phosphorus levels must be carefully monitored and kept in target ranges with diet and phosphate binders. Vitamin D supplements may be necessary to maintain 25-hydroxyvitamin D levels. Active vitamin D analogs, calcimimetic therapy, or parathyroid surgery may be necessary to control hyperparathyroidism.

Table 11.3 Kidney Disease Improving Global Outcomes (KDIGO) recommendations for monitoring of bone health parameters in children with chronic kidney disease

CKD stage (GFR mL/min/1.73 m^2)	Calcium and phosphorus	Parathyroid hormone (PTH)	Alkaline phosphatase	25-Hydroxyvitamin D
Stage 2 (66–93)	Every 12 months	Every 12 months	Every 12 months	Baseline value with repeat testing determined by baseline values and therapeutic interventions
Stage 3 (30–59)	Every 6–12 months	Baseline level with repeat testing determined by baseline level and CKD progression	Baseline level with repeat testing determined by baseline level and CKD progression	
Stage 4 (15–29)	Every 3–6 months	Every 3 months	Every 12 months or more frequently in the presence of elevated PTH	
Stage 5 (GFR <15 or dialysis)	Every 1–3 months	Every 3–6 months	Every 12 months or more frequently in the presence of elevated PTH	

Based on data from Ref. [9]

Cancer Survivors

Cancer in the adolescent and young adult population is a heterogeneous group of many disorders. The most common types of cancer occurring in this age group are lymphoma, melanoma, cancer of the male genital system, cancer involving the endocrine system, and cancer of the female genital tract [149]. Adolescents who have completed treatment for cancer often have ongoing physical and psychological comorbidities, with up to 70% of adolescent cancer survivors reporting at least one chronic health problem related to their disease [150].

Pathophysiology of Bone Disease in Cancer Survivors

The impact of cancer on bone health can be divided into direct effects of cancer and the impacts of cancer treatment. Childhood cancer can affect bone metabolism and growth through a variety of mechanisms, including detrimental effects on nutrition, physical activity, and pubertal progression during the critical periods of growth and bone accumulation during adolescence [151].

Cancer treatment can alter bone metabolism through local effects on bone, central nervous system, and endocrine effects from chemotherapy or radiation, and dietary modifications during and after cancer therapy [152]. Cancer treatments that can have direct, local effects on bone include antimetabolite chemotherapeutic agents such as methotrexate, glucocorticoids, and radiation therapy [152, 153]. In addition, chemotherapy and cranial radiation have both been observed to cause

pituitary dysfunction, including growth hormone deficiency and hypogonadism. The hypothalamus-pituitary-gonad and hypothalamus-pituitary-thyroid axes can also be impacted by peripheral effects of chemotherapy or radiation on the gonads or thyroid [152].

Presentation of Bone Disease in Cancer Survivors

The majority of bone density studies among children with cancer have been conducted in acute lymphoblastic leukemia (ALL) patients. Between 13% and 21% of children with ALL will have low BMD at the time of cancer diagnosis [154]. Treatment for ALL is associated with further decreases in BMD [154, 155]. pQCT studies have also demonstrated deficits in trabecular BMD after treatment for ALL [156]. The literature remains unclear regarding improvement in BMD following completion of treatment for ALL, with multiple studies showing conflicting results [154, 155]. Studies of other cancers in children and adolescents have also demonstrated impairment in bone health, with low BMD identified in as many as half of childhood cancer survivors [157].

Children and adolescents with cancer are also at increased risk of fracture [158, 159]. A study of 186 children with ALL examined fracture risk within 30 days of diagnosis and found that 16% of children had one or more vertebral compression fractures [158]. This study also found an association between BMD Z-score and fracture risk; for every one standard deviation reduction in BMD Z-score of the lumbar spine, the odds for fracture increased by 80% [158]. However, other studies have not found an association between low BMD and increased likelihood of fracture [154, 160].

In addition to decreased BMD and fractures, childhood cancer survivors are also at risk for other skeletal complications, including avascular necrosis, slipped capital femoral epiphysis (SCFE), and altered epiphyseal growth. Avascular necrosis disproportionately affects adolescents and is usually associated with high-dose glucocorticoids and bone marrow transplantation but has been described in association with other types of chemotherapy as well [161, 162]. A weak association exists between SCFE and common cancer treatments, with SCFE occurring most commonly after direct radiation to the hip [163].

Evaluation

The Children's Oncology Group has published guidelines for bone health screening in children and adolescents with cancer. They recommend that all patients treated with agents that predispose to reduced BMD (including glucocorticoids, cranial radiation, methotrexate, or hematopoietic cell transplantation) undergo screening of BMD using either DXA or pQCT at entry into long-term follow-up, which usually occurs 2 years after completion of cancer chemotherapy [10].

All patients should be carefully monitored for growth rates and pubertal progression both during and after cancer treatment. Endocrine evaluation including growth hormone, thyroid function, and gonadal function (luteinizing hormone and follicle stimulating hormone) should be considered if patients have signs of growth failure, deceleration in linear growth, or delayed progression of puberty [10]. To our

knowledge, no specific guidelines for vitamin D screening in cancer survivors have been released.

Management

Early identification and therapy of hormone derangements have the potential to preserve BMD. For example, patients with established hypogonadism should be treated with replacement gonadal steroids as appropriate to the patient's age, height, and pubertal status. Similarly, growth hormone therapy can augment BMD in patients with growth hormone deficiency secondary to cancer treatment. The Children's Oncology Group recommends that patients should meet recommended minimum daily intake of vitamin D for the general population for children [10].

Treatment for avascular necrosis depends on the severity of the lesion with the majority of cases treated initially with conservative therapy. Surgical intervention can be utilized if conservative therapy fails to improve symptoms [164].

Bisphosphonates are not recommended as a first-line treatment for deficits in BMD in children and adolescents because they have not been well studied during periods of active bone growth. In addition, the relationship between reduced BMD and fracture risk is not clearly delineated in children and adolescents, making it difficult to identify a subset of pediatric and adolescent patients who may benefit most from bisphosphonate treatment. Other therapies for cancer survivors with severe osteoporosis include calcitonin, selective estrogen receptor modulators, parathyroid hormone (teriparatide), and denosumab [165]. However, further longitudinal studies are necessary to elucidate the safety and efficacy of these drugs in children.

Hypogonadism

Hypogonadism is a syndrome characterized by deficiency of sex hormones. Hypogonadism can be broken down into hypogonadotropic hypogonadism, in which abnormalities in the pituitary gland or hypothalamus lead to inadequate secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which in turn suppress sex hormone secretion by the gonads, and hypergonadotropic hypogonadism, which occurs when the gonads are not producing sufficient testosterone in males or estrogen and progesterone in females [26, 166]. Sex hormone deficiency is associated with multiple medical comorbidities, including bone disease, metabolic syndrome in males, and increased central adiposity in women, among others.

Hypogonadotropic hypogonadism is the more common cause of depressed sex steroid levels in adolescents. While it is most commonly acquired, it can also occur as part of congenital syndromes such as Kallmann syndrome [166]. Although the etiology of hypogonadotropic hypogonadism is multifactorial, it frequently occurs secondary to disorders impacting nutrition, stress, or sleep [167]. In addition, central nervous system and pituitary tumors, head trauma, brain or pituitary radiation; medications such as GnRH agonists/antagonists, glucocorticoids, and chemotherapy; and illicit drug use can all impact GnRH secretion. Although some causes of

hypogonadotropic hypogonadism cause absent or decreased GnRH secretion, hypogonadotropic hypogonadism is more commonly caused by alterations in the pulsatility of GnRH secretion. The pulsatile nature of hypothalamic GnRH release is critical to the release of LH and FSH from the pituitary [168]. Circulating LH and FSH levels, as well as levels of the sex hormones testosterone, estrogen, and progesterone, decline when the frequency of GnRH pulses is too low or too frequent [166].

Primary ovarian insufficiency (POI) is a term used to describe a heterogeneous group of disorders that lead to hypergonadotropic hypogonadism, premature ovarian failure, and ovarian dysgenesis. POI occurs when women under the age of 40 experience oligomenorrhea or amenorrhea for 3 months or more with associated elevations of serum FSH. In many cases, ovarian function is still present but in an intermittent and unpredictable manner that can last for decades after diagnosis [169]. The mechanisms of POI are numerous and include genetic, autoimmune, toxic, and iatrogenic etiologies. Genetic causes of POI include Turner syndrome as well as mutations in fragile X mental retardation 1, galactose-1-phosphate uridyltransferase, bone morphogenetic protein 15, forkhead box L2, and the follicle-stimulating hormone receptor among others [169].

Turner syndrome is characterized by total or partial loss of the second X chromosome in phenotypic females, causing streak ovaries with depressed or absent estradiol production [170]. Girls with Turner syndrome typically have short stature, amenorrhea, infertility, and skeletal anomalies [171]. Although Turner syndrome often presents with primary amenorrhea in adolescence, patients with other causes of POI may experience normal pubertal development followed by secondary oligomenorrhea or amenorrhea during adolescence or adulthood [169]. For example, autoimmune oophoritis, smoking, and cancer treatments such as chemotherapy or radiation are common causes of POI that can lead to alterations in menstrual cycles and hormone levels before, during, or after pubertal development.

Pathophysiology of Bone Disease in Hypogonadism

Both hypogonadotropic hypogonadism and primary ovarian insufficiency lead to a lack of age-appropriate sex hormone levels. As previously described, estrogen plays an important role in bone growth, bone maturation, and bone turnover. During bone growth, estrogen is necessary for proper closure of epiphyseal growth plates during adolescence in both males and females [24]. At the onset of puberty, rising levels of estrogen stimulate an increase in growth hormone and IGF-1 secretion both of which exhibit anabolic effects on bone [47]. Thus, estrogen deficiency has numerous effects on the developing skeleton, including increased osteoclast formation and enhanced bone resorption, as demonstrated in Fig. 11.2. Estrogen inhibits bone catabolism by inhibiting differentiation of osteoclasts through a cytokine-mediated pathway; in the absence of estrogen, elevated numbers of osteoclasts are observed and lead to increased bone resorption [19, 21]. In males, testosterone has both direct and indirect anabolic effects on bone and is critical for the synthesis of estrogen via aromatization. Thus, both hypogonadotropic and hypergonadotropic causes of hypogonadism lead to impaired bone health and require careful screening and management of bone disease.

Turner syndrome is one cause of hypergonadotropic hypogonadism that has been shown to lead to significant impairments in bone maturation and strength. Skeletal abnormalities in Turner syndrome occur not only due to hypogonadism but also due to SHOX gene haploinsufficiency. SHOX is a gene on the X chromosome important for normal skeletal development [19]. Thus, in patients with Turner syndrome who are missing an X chromosome, bone health is further impaired.

Presentation of Bone Disease in Hypogonadism

A cross-sectional study examined 54 patients diagnosed with hypogonadotropic and hypergonadotropic hypogonadism with onset during adolescence, finding that females with hypogonadism had a significantly lower mean BMD at the lumbar spine and total hip than the female reference population [26]. In contrast, the average BMD of male patients was not significantly different from the control group [26]. This gender difference has been supported by other studies demonstrating that delayed puberty and male hypogonadism are not associated with an increased risk of decreased BMD or fractures [172].

A recent study compared BMD in 14 adolescent females with hypogonadotropic and 19 with hypergonadotropic hypogonadism [173]. The investigators found no statistically significant differences between the groups on measures of bone health, including BMD Z-scores and bone age. FSH levels were not an independent moderator of BMI Z-score, suggesting that sex steroid deficiency is a key factor in impaired bone health regardless of underlying cause [173].

Multiple studies have investigated bone health in hypogonadotropic hypogonadism secondary to malnutrition and negative energy balance in populations of patients with anorexia nervosa and relative energy deficiency in sport (RED-S). Studies of these populations have demonstrated significant reductions in BMD [50]. In addition, pQCT and HR-pQCT studies have demonstrated deficits in trabecular number, trabecular thickness, and cortical thickness, with a preferential loss of trabecular bone relative to cortical bone [174]. Bone health in eating disorders is discussed in more detail in Chap. 9, and bone health in athletes is reviewed in Chap. 10.

A study of young women with spontaneous POI revealed significantly lower BMD compared with controls despite no differences in BMI or age at menarche. Prior studies of adult females with POI have identified risk factors for low BMD including delay in diagnosis and treatment of estrogen deficiency, low vitamin D levels, estrogen replacement nonadherence, and lack of exercise [175]. In addition, minority women with POI were more likely to have BMD below the expected range for age when compared to Caucasians, possibly due to differences in modifiable risk factors such as exercise, disease management, and vitamin D levels [175].

pQCT studies of prepubertal females with Turner syndrome have identified wider bone diaphyses, lower cortical thickness, and normal trabecular density. However, BMD deficits have been described in adult women with Turner syndrome [176]. Delay in pubertal induction with sex hormone replacement is associated with decreased trabecular BMD and bone mass accrual [177]. Estrogen supplementation leads to improvement in pQCT bone metrics [178]. The fracture prevalence in female children and adolescents with Turner syndrome has not been well

characterized [3], but epidemiological studies in adults with Turner syndrome have demonstrated an increased rate of fractures [179].

Evaluation and Management

The first step in prevention and treatment of bone disease in hypogonadism is detection and management of the underlying cause of hypogonadism. For patients with hypogonadotropic hypogonadism, modifiable risk factors should be addressed, including nutritional status, psychological stress, and sleep hygiene. If the patient is on medication that may impact GnRH secretion, regimens should be adjusted if possible to allow for resumption of normal puberty. If the underlying cause of hypogonadotropic hypogonadism cannot be resolved, hormone replacement therapy may be necessary, such as in the case of brain or pituitary irradiation or congenital syndromes such as Kallmann syndrome [180]. In patients with anorexia nervosa or relative energy deficiency in sport, weight gain and appropriate intake of calcium and vitamin D are first-line treatments for both amenorrhea and bone deficits. However, in chronic, unremitting disease, hormone replacement has shown some success in increasing BMD in both patients with anorexia nervosa and amenorrheic athletes [181, 182].

Hormone replacement is generally indicated for hypergonadotropic hypogonadism, unless hormones are specifically contraindicated, for example, in the presence of a hormone-sensitive cancer. When hormone replacement is indicated, natural estrogen is preferred [180]. Oral and transdermal preparations are available, and preparation choice should be determined by patient preference and side effect profile in order to optimize adherence [180].

Estrogen replacement, when indicated, is associated with improvement in BMD and fracture risk [178, 183]. As delay in institution of estrogen replacement and nonadherence to hormone replacement increase the risk for low BMD, early diagnosis and early implementation of physiological estrogen and progestin replacement in young women are critical for promotion of bone health [18, 19].

A randomized controlled trial of hormone replacement in young women with spontaneous POI found that replacement of estradiol and progestin was associated with increases in bone mineral density, with no difference in BMD between POI patients treated with hormone replacement and control women at the end of the 3-year study period [18]. This study also examined the impact of testosterone on bone health and found that the addition of testosterone showed no further benefit [18]. Thus, long-term physiological estradiol and progesterone replacement should be considered in women with POI.

In Turner syndrome, estrogen can be used for pubertal induction with beneficial effects on bone. In addition to estrogen therapy, growth hormone therapy may be beneficial for adolescent females with Turner syndrome and significant short stature; in these patients, growth hormone therapy is associated with anabolic effects on bone and improved BMD [184]. In girls with Turner syndrome receiving growth hormone therapy, estrogen replacement can be started as early as 12 years of age with gradual increases to approximate physiologic levels of estrogen during

puberty, with close attention to absolute height and growth velocity while on estrogen replacement [19].

Other Childhood Conditions with Emerging Bone Literature

Obesity

Approximately one in five adolescents in the United States is obese, and childhood obesity has been a major focus of public health interventions over the past decade. Bone health is altered in obesity through multiple mechanisms, with both biological and behavioral characteristics associated with obesity contributing to alterations in bone mineral density and structure.

The impact of excess adiposity on acquisition of BMD is still under investigation, with studies producing conflicting results. While some studies report a positive association between adiposity and bone outcomes [185–187], others have reported an absent or negative association [188, 189]. More recent studies suggest that fat distribution may moderate the association between adiposity and bone outcomes [190, 191]. A recent pQCT study examined bone geometry and volumetric BMD in male and female children with obesity. This study found advanced skeletal maturation, greater calf muscle area, and greater muscle strength in obese participants compared to controls [192]. However, no significant differences in cortical or trabecular volumetric BMD were observed between the groups [192].

Several studies have also described an increased risk of fractures in children with obesity [193, 194]. It remains to be seen whether this increased fracture risk is associated with impaired bone development or other factors such as poor motor proficiency and inadequate compensation for the greater forces with falls. Futures studies are necessary to determine the interplay between bone mineralization, bone architecture, and fracture risk in children and adolescents with obesity. In addition, the impact of weight loss interventions on bone health in children and adolescents requires further study.

Human Immunodeficiency Virus

Low BMD is a described metabolic condition in human immunodeficiency virus-infected (HIV) patients. Children and adolescents with HIV have the greatest cumulative exposure to the negative effects of HIV infection and HIV treatments on bone. Epidemiological studies and clinical trials have suggested that the etiology of bone disease in HIV infection is multifactorial [195, 196]. Lifestyle factors such as smoking, alcohol, drugs, malnutrition, and low BMI may contribute to low BMD in some patients with HIV [196]. In addition, the virus itself likely has a more direct effect on bone demineralization through the effects of viral proteins, inflammation, and antiretroviral therapies [197–199].

A systematic review demonstrated an increased prevalence of low BMD in children and adolescents with HIV [200]. Initial studies have also suggested that suboptimal bone accrual may be persistent and result in reduced peak bone mass, bone quality, and fracture risk across the life course [201, 202]. Therapy with protease inhibitors and nadir CD4 T-cell count have been shown to negatively impact peak bone mass [203]. Every effort should be made to modify risk factors to prevent bone deficits in these patients, as they will require lifetime treatment for their infection.

Asthma

Asthma is a common chronic condition affecting adolescents that may lead to impaired bone health. Most studies of bone measures in asthma patients have focused on corticosteroid treatments for asthma. Systemic corticosteroid use increases the risk of fractures in asthma patients in a dose- and duration-dependent manner [204]. In addition, several studies have identified a dose-related association between inhaled corticosteroid and decreased BMD [205, 206]. In addition, asthma patients have been shown to have decreased serum 25-hydroxyvitamin D levels compared to healthy controls, which may contribute to impaired bone health [207, 208]. More recent studies have investigated asthma morbidity as a potential risk factor for bone loss, finding significantly reduced BMD in patients with asthma and airway hyperresponsiveness compared to healthy controls. Fracture risk has not been well delineated in children and adolescents with asthma.

Rheumatologic Conditions

A number of childhood-onset rheumatic diseases and their treatments can have significant impacts on bone maturation and skeletal health, including, but not limited to, juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), juvenile dermatomyositis, and scleroderma. Low BMD has been described in numerous rheumatologic conditions and is multifactorial. First and foremost, chronic inflammation has a significant effect on bone maturation and remodeling. The direct effects of chronic inflammation on bone turnover include increased osteoclastogenesis and accelerated bone resorption and are described in the risk factors section above. In addition, the treatment of inflammation commonly involves medications that have adverse effects on bone, including glucocorticoids. Other factors that contribute to poor bone health in adolescents with rheumatologic diseases include vitamin D deficiency and decreased participation in weight-bearing activities due to disease-related disability. Studies of adolescents with rheumatologic diseases have demonstrated that patients with autoimmune disorders were more likely to be vitamin D deficient than healthy controls [209].

Multiple rheumatologic diseases have been shown to lead to decreased BMD, including JIA, SLE, and juvenile dermatomyositis [210–212]. Glucocorticoid therapy is associated with a dose-dependent decline in BMD in pediatric patients

with rheumatologic conditions [211, 213, 214]. In addition, several studies have examined fracture risk in children with rheumatic disorders treated with systemic glucocorticoids. A prospective study revealed that 7% of children will have prevalent vertebral fractures in the first few weeks of glucocorticoid therapy, and 6% will have incident vertebral fractures within the first 12 months after glucocorticoid initiation [215, 216]. Risk factors for incident fractures included higher glucocorticoid doses and greater increases in BMI over the study period [215]. High disease activity is also a consistent predictor of bone morbidity [217].

Bone health assessment should be conducted in at-risk patients with rheumatic disease and should include a DXA-based BMD as well as a lateral thoracolumbar spine radiograph to assess for vertebral fracture [217]. A baseline spine radiograph should be obtained at the time of glucocorticoid initiation in any child anticipated to be on glucocorticoid therapy for 3 months or more, with follow-up at 12 months [217]. Routine screening of serum 25-hydroxyvitamin D levels should be performed for patients with autoimmune disorders [209].

Epidermolysis Bullosa

Epidermolysis bullosa (EB) is a family of rare genetic disorders characterized by blistering of the skin and mucous membranes in response to even minor mechanical trauma. Severe forms of EB can have numerous noncutaneous complications such as growth failure, anemia, esophageal strictures, cardiomyopathy, and renal insufficiency [218]. In addition, recent studies have shown that EB is associated with low BMD for age and pathological fractures [219]. The etiology of impaired bone development in EB is still being investigated, but reduced nutritional intake, high metabolic demand, decreased mobility, and chronic inflammation all likely contribute to decreased BMD [219].

Summary

Adolescents with chronic disease are at significant risk for poor bone health due to underlying disease mechanisms, comorbidities, and treatments with detrimental effects on bone. Alterations in bone mass accrual and bone remodeling result in decreased bone quality and strength. These changes have significant implications for fracture risk not only during adolescence but also extending across the lifespan. Treatment strategies for poor bone health associated with chronic disease in adolescents include optimizing of nutrition, maintaining vitamin and mineral homeostasis, encouraging weight-bearing exercise, minimizing use of glucocorticoids or other bone-impairing therapies, and treating the underlying disorder in order to prevent further bone impairment. Further research is needed to identify modifiable risk factors and novel targets for interventions to promote bone mass accrual in adolescents and decrease the lifelong incidence of fracture in patients with chronic disease.

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Bone Health in Immobile Adolescents

12

M. Zulf Mughal

Introduction

Adolescents with disorders associated with chronic immobilization such as moderate to severe cerebral palsy (CP) and Duchenne muscular dystrophy (DMD) are at increased risk of sustaining fractures, especially around the knee joint, following minimal trauma. These individuals, especially boys with DMD who are treated with high doses of glucocorticoids, are also at increased risk of sustaining vertebral fractures, without trauma. Vertebral fractures may be asymptomatic, or they can be associated with severe back pain. This chapter covers the mechanisms, prevalence and pathogenesis of fractures in adolescents with disorders associated with chronic immobility, especially CP, DMD, spinal muscular atrophy and spinal cord injury. Interventions and treatments that might improve low bone mineral content (BMC) and bone mineral density (BMD) in these individuals and which may help to reduce their fracture risk are also discussed.

Pathogenesis of Fractures in Adolescents with Immobility-Induced Osteoporosis

The process of skeletal development during childhood and adolescence is reviewed in Chaps. 1 and 2. Skeletal development begins in utero and continues throughout childhood and adolescence until skeletal maturity is reached. Bone is comprised primarily of a collagen matrix into which hydroxyapatite crystals, containing calcium and phosphate, are deposited. Growth is accompanied by increases in size (length, diameter and cortical thickness), the amount of bone mineral content

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contained within the periosteal envelope and strength of bones. The development of bone is dependent upon inherited genetic "template" that is modified by mechanical loading, nutritional and endocrine environments. Postnatal bone development is modulated by the mechanical forces to which the skeleton is subjected, which arise from muscle contractions, rather than from passive weight bearing [1]. Thus, muscle contraction generates forces that act on bones. According to Frost's mechanostat theory, bone responds to micro-strains (elastic deformation of bone), generated locally from mechanical loading activities, by adapting its growth, architecture (periosteal and endosteal bone dimensions), bone mass and bone strength, so as to prevent mechanical failure or fracture. In a healthy child, muscle mass increases during growth and puberty, leading to an increased mechanical loading of the skeleton. Thus, the skeleton of a healthy growing child continuously adapts to increasing mechanical loading from bigger and stronger muscles by increasing bone mass and appropriately altering the bone geometry [2]. Mechanical loading during growth is also an important stimulus for bone mass accrual [3].

In disorders associated with immobilization, such as CP, there is insufficient mechanical loading throughout childhood and adolescence. In neuromuscular conditions such as DMD and spinal muscular atrophy (SMA), there is progressive muscle weakness leading to reduction in mechanical loading, whereas adolescents with spinal cord injury (SCI) suffer abrupt immobilization of sub-lesional skeletal sites (e.g., the pelvis and lower extremities). Thus, in such clinical disorders associated with immobilization, insufficient mechanical loading results in inadequate periosteal bone apposition, reduced bone mass accrual, increased bone resorption and associated reduction in bone strength. Therefore, it is not surprising that radiographs of the bones of such individuals often show signs of slender long bones with thinning of cortices, prominent trabecular pattern due to osteopenia or the "washed-out appearance" (Fig. 12.1).

Besides immobilization, delayed or arrested puberty, undernutrition and low vitamin D status are associated with impaired bone growth, low bone mineral density and increased risk of fragility fractures. The timing of the puberty is critically important for skeletal development [4]. The onset of puberty may be delayed due to secondary hypogonadotropic hypogonadism in boys with DMD who are treated with chronic high doses of glucocorticoids [5]. Pubertal delay has also been reported in young adults and adolescents with CP [6]. A delay in the onset of puberty may lead to suboptimal skeletal development and increased risk of fractures [7, 8]. The peak bone mass, defined as the amount of bone mass accrued at the end of skeletal maturity, is largely achieved by the end of sexual and skeletal development [9, 10]; it is considered to be an important determinant of the risk of osteoporotic fractures that occur in later life [11]. In patients with CP, Henderson et al. showed that feeding difficulties and use of anticonvulsants and lower triceps skinfold Z-scores (used for the assessment of body fat) independently contributed to lower distal femoral areal bone mineral density (aBMD) [12]. Thus, in an immobilized adolescent, reduced mechanical loading, delayed or arrested puberty and other factors, such as undernutrition, may result in inadequate peak bone mass, which might increase his/her risk of developing osteoporosis in later life.

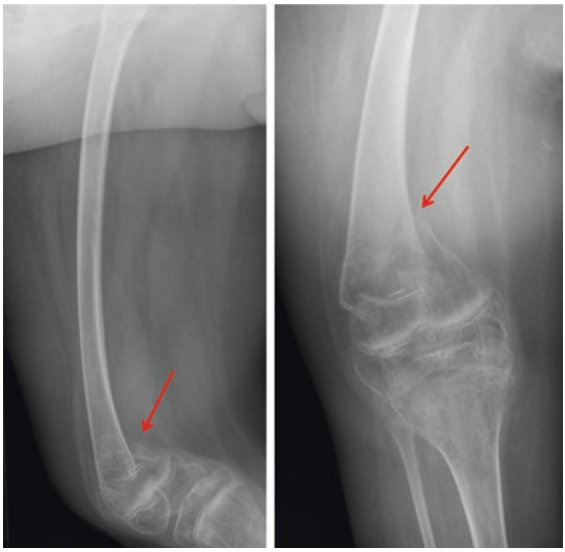

Fig. 12.1 Radiographs (Lateral and anteroposterior views) showing a right supracondylar femoral fracture in a 14-year-old non-ambulatory (GMFCS level V) boy with quadriplegic CP. The fracture came to light when he became distressed during transfer from the wheelchair to the bed. Parents noticed that the right knee was swollen. There was no history of trauma which was witnessed at any time. Note slender femoral diaphysis, thinning of cortices and osteopenia or the "washed-out appearance" of bones

Assessment of Bone Mineral Density in Children and Adolescents with Disabilities

Densitometric techniques used to assess bone health in children and adolescents are discussed in Chap. 7. Measurement of BMD and bone size parameters using dual energy x-ray absorptiometry (DXA), peripheral quantitative computed tomography (pQCT), quantitative computed tomography (QCT) and magnetic resonance imaging (MRI) may be used to assess bone health in immobilized children and adolescents. In severely disabled children and adolescents, whole body, hip or spine assessment of BMD by DXA can be challenging due to joint contractures, hip dysplasia, scoliosis or the presence of metal fixation devices. The femur is the most common site of fracture in disabled adolescents and young adults [13–18]. Harcke and colleagues have described the technique for measuring aBMD at the distal femoral region, the most common fracture site, in children and adolescents with disorders associated with immobilization [19, 20]. The lateral distal femur (LDF) scans are divided into three rectangular subregions, representing metaphyseal bone (LDF Region 1), the transition zone from the metaphysis to the diaphysis (LDF Region 2), and diaphyseal bone (LDF Region 3). Zemel et al. have published LDF reference data based on over 800 children and adolescents [21].

Chronically immobilized children and adolescents are also at increased risk for sustaining vertebral fractures, without trauma. In a cross-sectional study of 59 individuals with motor disabilities (e.g., CP, myelomeningocele, muscular dystrophy and syndromes causing motor disability; Gross Motor Function Classification System levels II–V), Kilpinen-Loisa et al. found compression vertebral fractures in 25% of subjects, on spinal radiographic screening [22]. Vertebral compression fractures have also been identified on spinal radiographic screening of boys with DMD [23, 24]. These vertebral fractures may be asymptomatic and can occur when lumbar spine areal BMD Z-score values are ≥ -2 [23, 24], a commonly used threshold value for subnormal BMD [25]. Therefore, the author recommends screening for vertebral fractures by yearly lateral thoracolumbar radiograph or by vertebral fracture assessment using DXA [26] in boys with DMD treated with high doses of glucocorticoids. Such radiographs could also be considered in other patient populations with low bone mineral density, who may be at increased risk for vertebral compression fractures.

Cerebral Palsy

CP is a term used to describe a group of nonprogressive disorders of movement and posture, resulting from an insult to the developing brain. It is one of the most common chronic disabling conditions, with a prevalence of 2.0–3.5 per 1000 live births [27]. The most common motor abnormality is spasticity, which may be categorized into diplegia, hemiplegia and quadriplegia. Other forms of CP include dystonia choreo-athetosis, ataxic or a mixture of these disorders. The Gross Motor Function Classification System (GMFCS) [28] is a widely used five-level clinical standardized system to classify the gross motor function of patients with cerebral palsy, with emphasis on function in sitting and walking. Children and adolescents with CP often have other disabilities, which may affect their quality of life and life expectancy. These include intellectual impairment, behavioural problems, hearing and visual problems, feeding difficulties, poor growth, recurrent respiratory infections and epilepsy. Secondary musculoskeletal problems include joint contractures, scoliosis and hip subluxation.

Fractures in Cerebral Palsy

Children and adolescents with CP are prone to low trauma fractures, which occur during normal activities such as dressing and transferring [29, 30] (Fig. 12.1). Such fractures are more common in non-ambulatory individuals, who are at the severe end of the spectrum of CP, defined as level IV or V according to the GMFCS [31]. Fractures not only cause pain, but they further limit the mobility of young people with CP, leading to muscle wasting through disuse, hospitalization and missed

schooling/collage. The cause of injury may not be clear in over 50% of cases, and delay in diagnosis is not uncommon [13]. In a recent study, there was lack of documented history of trauma in over 70% of cases of fractures [32]. In the medical literature, the term "spontaneous fracture" has been used to describe such fractures as they apparently occur without any known external cause [33]. Lack of a clear history of the injury causing the fracture, difficulties in communication, and delay in presentation sometimes leads to suspicion of child abuse [30, 33].

There have been a few large epidemiologic studies of fragility fractures in children and adolescents with CP. In a study of 763 children with CP, Leet and colleagues reported fracture prevalence of 12% [14]. In another large study of 1637 patients with CP, Presedo and colleagues reported fracture prevalence of 6% [13]. A systematic analysis by Mergler and colleagues reported a 4% annual incidence of fractures in non-ambulant children and adolescents with CP [31]. In a recent retrospective study from Sweden, Uddenfeldt Wort and colleagues [32] found that youngsters with CP with GMFCS levels I to III had a similar incidence and pattern for fractures as seen in healthy children and adolescents. However, those in GMFCS levels IV or V had a much higher incidence of atraumatic fractures.

Brunner and Doderlein [16] surveyed 37 patients with CP who had sustained 54 fractures with minimal trauma and found that the majority (74%) were in the femoral shaft and the supracondylar region. In a population-based study of 763 CP patients (1.3–18 years), Leet et al. found that over 70% of fractures occurred in lower limb bones [14]. In the study by Presedo et al., over 80% of fractures occurred in the lower limbs [13]. These investigators also found that over 10% of CP children and adolescents developed complications after a fracture, which included further fractures, malunion, non-union and infections, including pneumonia [13]. In summary, non-ambulant children and adolescents with CP are prone to fragility fractures. Such fractures predominantly occur in lower limb bones, particularly in the distal femur and proximal tibia. These fractures are associated with a high complication rate.

Besides non-ambulatory status, anticonvulsant use, undernutrition requiring gastrostomy feeding and low vitamin D status are associated with poor bone health in children and adolescents with CP [29, 31]. Uddenfeldt Wort and colleagues [32] found that CP youngsters with stunted growth, presumably from poor nutrition, had a four-fold increased risk for fractures in GMFCS levels IV–V. In this study, the use of anticonvulsants was associated with a two-fold increase in fracture risk in GMFCS levels IV–V. Previous fracture was also a predictor of subsequent fractures, presumably due to bone loss associated with immobilization [15, 31]. Immobilization of the hip in a spica cast following surgery was also associated with an increase in risk of fracture [34, 35]. Pre-existent contracture, stiff or dislocated joints, which restrict limb movements, also increases fracture risk [16]. In summary, pre-existing factors that limit limb movements and postfracture or postoperative immobilization are associated with increased risk of further fracture in children and adolescents with CP.

Bone Mineral Density in Cerebral Palsy

In a prospective longitudinal study of 69 subjects with moderate to severe spastic CP (ages 2 to 17.7 years; GMFCS levels III to V), Henderson et al. [36] noted that DXA measured lateral distal femoral (LDF) aBMD Z-scores decreased despite serial increases noted in aBMD. These results suggest that bone mass accrual in children and adolescents with CP was less than that expected in healthy individuals. Henderson and colleagues also studied the relation between LDF aBMD Z-scores and fracture history in a cross-sectional study of 619 individuals aged 6–18 years with muscular dystrophy ($n = 112$) or moderate to severe CP ($n = 507$), cared for at eight centres in the USA [37]. There was a strong correlation between fracture history and LDF aBMD Z-scores; 35–42% of those with aBMD Z-scores less than −5 had fractured compared with 13–15% of those with aBMD Z-scores greater than −1. Each 1.0 standard deviation decrease in LDF aBMD Z-scores increased the fracture risk by 6–15%. Using pQCT, Binkley and colleagues showed that subjects with CP had reduced distal tibial cortical bone area, periosteal and endosteal circumferences, thickness, bone mineral content and polar strength-strain index (a surrogate measure of bone strength derived from bone geometry and density), compared with controls [38]. Wren and colleagues found that mid-tibial cross-sectional area and cortical bone area, measured using QCT, were significantly lower in CP children with GMFCS levels III and IV in comparison to those with GMFCS levels I and II [39]. Using MRI, Modlesky et al. found underdeveloped trabecular bone microarchitecture in the metaphysis of the distal femur in children aged 8–14 years with CP becomes more pronounced with greater distance from the growth plate [40]. Taken together, results of these studies suggest that increased fragility of a long bone, such as the femur, in subjects with CP arises because of slower rate of bone mass accrual, smaller periosteal diameters, thinner cortices and underdeveloped trabecular bone microarchitecture in the metaphysis of long bones.

In summary, non-ambulant children and adolescents with CP have low BMD, which is associated with increased risk of fracture. Robust normative data are available for estimation of BMD at the LDF site. In children and adolescents with chronic immobilization, the 2013 Pediatric Official Positions of the International Society for Clinical Densitometry recommends assessment of BMD at the LDF site, which is the most common fracture site in children and adolescents with CP [41].

Duchenne Muscular Dystrophy

DMD is an X-linked recessive disorder due to mutations in the dystrophin gene, which affects 1 in 3600–6000 live male births [42]. It is caused by loss of function mutations in the dystrophin gene, which encodes for the dystrophin protein in muscle. Severe reduction or deficiency of dystrophin protein results in inflammation and necrosis of muscle fibres, which in turn results in progressive deterioration of skeletal and cardiac muscle function. This is accompanied by elevation of serum creatine phosphokinase levels and hypertrophy of calf muscles. Symptoms of DMD

usually come to light before 5 years of age. These include delayed onset of walking, abnormal gait (toe walking and/or a waddling gait), inability to run fast and difficulty in rising from the floor without assistance. Development of muscle contractures further affects ambulation. In these boys, scoliosis often becomes evident after loss of walking and progresses rapidly during the pubertal growth spurt. Scoliosis also contributes to progressive respiratory insufficiency. In the era before treatment with glucocorticoids, affected boys lost the ability to walk independently by early teenage years and died from respiratory insufficiency and cardiac dysfunction by their early 20s.

Currently, there is no cure for DMD, but the quality of life of patients can be improved by medical treatment and supportive care. Long-term treatment with oral glucocorticoids (GCS) helps to slow down deterioration of skeletal and muscle function. It also prolongs ambulation by 2–5 years [43]. Recent Cochrane review found moderate quality evidence from RCTs that GCS treatment improved muscle strength and function for about 12 months and strength for up to 2 years [44]. Oral GCS treatment also helps to maintain cardiac and pulmonary function [43] and reduced risk of development scoliosis [45]. Treatment with GCS along with better cardiorespiratory and orthopaedic supportive care led to improved survival of subjects with DMD. Current standard of care is to treat boys with DMD with either prednisone 0.75 mg/kg/day or deflazacort 0.9 mg/kg/day. However, long-term GCS treatment is associated with obesity, short stature, pubertal delay and increased risk of long bones and vertebral fractures.

Fractures in Duchenne Muscular Dystrophy

Results of a number of studies have shown that boys with DMD have increased risk of long bone and vertebral fracture [23, 24, 46–50]. In a large retrospective study, McDonald et al. found that approximately 20–25% of boys with DMD suffered long bone fractures. Lower limb fractures were common in independently mobile boys, while upper limb fracture were most common in males using knee–ankle–foot orthoses. Falling was the most common fracture mechanism in all mobility groups; lower limb fractures were often associated with permanent loss of ambulation [49]. King and colleagues found that long bone fractures were 2.6 times greater in GCS-treated DMD boys compared with those who were GCS naive or had received only a brief submaximal GCS dose [48]. In a recent retrospective longitudinal study of 30 boys with DMD <18 years, Ma et al. [24] found that 73% of the boys sustained at least one fracture and 23% sustained multiple fractures. Furthermore, 53% sustained at least one vertebral fracture, and 33% sustained at least one long bone fracture. Those who underwent periodic spinal radiographs starting around the time of GCS initiation were identified with vertebral fractures within 2 years following GCC initiation and at approximately 3 years earlier than boys who were not monitored with spinal radiographs. The majority of the boys with vertebral fractures identified through this screening programme were still ambulatory and over 50% were asymptomatic. In contrast, boys who were

diagnosed with vertebral fractures following presentation with back pain had more numerous and more severe vertebral fractures. In this cohort, there was no evidence of spontaneous vertebral body reshaping.

Three main factors contribute to reduction in BMD and increased risk of fracture in boys with DMD. First, progressive muscle weakness and immobilization adversely affect bone geometry and accrual of bone mineral content. Secondly, GCS can affect bone health resulting in low BMD and an increased propensity to fragility fractures via several mechanisms. GCS inhibit bone formation through reduction in osteoblast number and function [51]. There is an increase in the rate of bone resorption, through augmentation of receptor activator of nuclear factor kappa-B ligand (RANKL) and decreased expression of osteoprotegerin (OPG), which inhibits osteoclast differentiation. They also inhibit calcium absorption from the gastrointestinal tract and decrease the renal tubular reabsorption of calcium; the net effect of which is to increase osteoclastic activity through secondary hyperparathyroidism [52]. GCS also increase apoptosis of osteocytes, which are important for sensing mechanical loading as well as regulating bone remodelling. GCS-induced myopathy also contributes to bone loss through reduced mechanical loading of the skeleton [51]. Finally, long-term treatment of DMD boys with GCS results in secondary hypogonadotropic hypogonadism [5]. Resulting delayed or arrested puberty adversely affects bone health through inadequate muscle mass and bone mass accretion that occurs during normal puberty [4, 7]. Deficiency of testosterone, which acts on the periosteal surface leading larger bone size in bone, contributes to GCS-treated boys with DMD having slender long bones [5, 53].

Bone Density in Duchenne Muscular Dystrophy

Larson and Henderson [47] evaluated aBMD at the lumbar spine and proximal femur in 41 boys with DMD, while they were ambulatory, and again when they were no longer walking. During the ambulatory phase, the aBMD at the lumbar spine was only slightly decreased (Z-score −0.8), but with loss of ambulation, the aBMD fell to a mean Z-score −1.7. In contrast, aBMD at the proximal femur was reduced even when gait was minimally affected (Z-score −1.6) and then progressively fell to almost 4 SDs below the mean with non-ambulation. Forty-four percent sustained at least one fracture, and 66% of these involved the lower extremities. A subset of boys who were walking with aids and support at the time of fracture did not resume walking after the incident. In 39 DMD boys, Mayo et al. [54] noted that height adjusted lumbar spine (LS) aBMD Z-score remained stable within the first 2 years of starting deflazacort therapy but declined with loss of ambulation. In a study of 32 boys with DMD, Bianchi et al. [47] found that BMD Z-score was lower than normal in DMD boys, both at the spine and total body. The LS BMAD Z-score of boys treated with GCS taken daily was significantly lower ($p < 0.02$) than of those who were GCS naive; cumulative GCS dose correlated with decline in BMD ($p < 0.05$). Crabtree et al. [55] undertook longitudinal measurements of the projected bone area (BA), bone mineral content (BMC) and lean body mass (LBM), at

the lumbar spine and subcranial skeleton, in 25 prepubertal ambulant boys with DMD on an intermittent glucocorticoid (10 days on and 10 days off) regimen. At baseline the subcranial BA for height and subcranial BMC for LBM were significantly reduced, suggesting that reduced mechanical load from diminished muscle strength had resulted in narrow and light bones in their subcranial skeleton. After 30 months of GCS therapy, there was a significant increase in subcranial BA for height (wider bones) but a significant reduction of subcranial BMC for area (lighter bones). The authors suggested that periosteal bone envelopes had become bigger as an adaptive response to bone loss, secondary to disease progression and GCS therapy. At the lumbar spine, the baseline BMC was low for BA although appropriate for reduced LBM. At follow-up, there were no significant changes in BA, but small increases in BMC with respect to both BA and LBM, suggesting lack of detrimental effects on bone, at this site, after 30 months of GCS therapy.

In summary, progressive muscle weakness and long-term treatment with oral GCS put boys with DMD at increased risk of sustaining long bone and vertebral fractures. A long bone fracture is associated with permanent loss of independent ambulation. Vertebral fractures, which arise insidiously, may be asymptomatic or associated with severe back pain. Such fractures do not reshape spontaneously. Therefore, screening for vertebral fractures by routine spinal radiographic surveillance, starting at the time of GCS initiation, is important in assessment of bone health in boys with DMD. At the author's institution, a lateral thoracolumbar radiograph or vertebral fracture assessment (VFA) by DXA (Fig. 12.2) [26] is undertaken annually after initiation of GCS in boys with DMD.

Spinal Muscular Atrophy

SMA is a heterogeneous genetic disorder arising from degeneration of alpha motor neurons in the spinal cord, which results in progressive muscular atrophy and weakness. It is caused by homozygous mutations in the survival motor neuron 1 (SMN1) gene and a disease modifying gene, survival motor neuron 2 (SMN2). The estimated incidence of SMA is around 1 in 10,000 live births [56]. The disease is classified into three main types, based on the age at which the child presents with symptoms and the clinical severity. SMA type 1, also known as Werdnig–Hoffman disease, presents before 6 months of age with profound hypotonia, poor head control and difficulty in swallowing. These children rarely survive beyond the second birthday, without long-term mechanical ventilation. Infants with SMA type 2 present with delay in walking and attainment of motor milestones. With multidisciplinary care, nutritional support and nocturnal non-invasive ventilation, youngsters with SMA type 2 have survived into adulthood [57]. Individuals with SMA type 3, which is the mildest form of the disease, are able to walk and achieve normal motor milestone but lose ambulation around puberty as their disease progresses [57]. These adolescents have an increased tendency to fall before they become wheelchair users. Besides scoliosis, adolescents with SMA type 3 develop bone health issues related to immobilization.

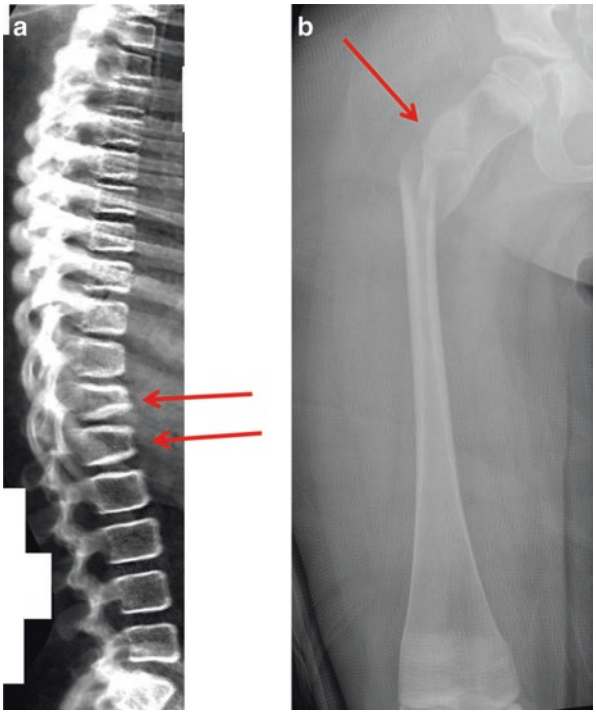

Fig. 12.2 A 10-year-old patient with Duchenne muscular dystrophy, who was treated with prednisone (0.75 mg/kg/day) since the age of 6 years, developed back pain. There was no history of trauma, and he was independently ambulant at the time. His lumbar spine (L1-L4) DXA measured bone mineral apparent (BMAD) Z-score was −1.6. Thoracolumbar radiographs of the spine showed compression fractures of T12 and L1 vertebral bodies. He was treated with 3-month intravenous pamidronate (total annual dose 12 mg/kg). His back pain resolved rapidly. Vertebral fracture assessment (VFA) by DXA (**a**) shows partial reshaping of fractured T12 and L1 vertebral bodies, 3 years after treatment with intravenous pamidronate. Note sclerosis of vertebral endplates as the result of pamidronate therapy. At the age of 14 years, when his mobility was declining, he slipped and fell on the bathroom floor, sustaining fracture of the proximal shaft of his right femur (**b**)

Long bone fractures have been reported in subjects with SMA [58–60]. Granata and colleagues reported that 9.3% of patients with SMA (types 1, 2 and 3) had suffered a fracture [61]. Fujak et al. found that 46% of SMA patients had a history of a fracture, with the majority in the supracondylar region of the femur [17]. Via et al. assessed biochemical markers of bone turnover, vitamin D status, LS BMAD and fractures in 1- to 14-year-olds with types 2 and 3 SMA [62]. Over 66% of these subjects had low body stores of vitamin D (serum 25OHD < 50 nmol/L) and 60% had plasma C-terminal telopeptide levels above the upper end of reference range, indicating an increased rate of bone resorption. Fifty percent of subjects had LS BMAD Z-score at ≤ −1.5 and over 23% had asymptomatic vertebral fractures identified on spinal radiographs. In a recent study, Wasserman et al. undertook the

natural history of bone health in patients with SMA types 1, 2 and 3, prior to bisphosphonate treatment [63]. In their study population, fractures occurred in 38% of patients, with the femur being the most common location. Eighty-five percent of patients had LDF aBMD Z-scores ≤ -2.0, and 13% fulfilled the 2013 the International Society for Clinical Densitometry (ISCD) criteria for the diagnosis of osteoporosis in children [25], i.e. vertebral compression fractures in the absence of high-energy trauma, or aBMD Z-score ≤ -2.0, two or more long bone fractures by 10 years of age, or three or more long bone fractures by 19 years of age.

In summary, children and adolescents with SMA have low bone mineral density at the LDF site and are at increased risk of suffering long bone fractures. As with other medical conditions associated with immobilization, supracondylar region of the femur is the most common fracture site. They are also at risk of sustaining vertebral compression fractures, without trauma.

Spinal Cord Injury

SCI can result from trauma to the spinal cord or myriad of other causes, such as spinal cord tumours, transverse myelitis, etc. SCI results in massive and precipitous bone loss in skeletal sites below the location of SCI (e.g. the pelvis and lower extremities). In adults, it has been shown that bone loss is more rapid in the metabolically active trabecular bone than in the cortical bone [64, 65]. In a cross-sectional study of 5–13 year old children with SCI, the DXA measured aBMD at the hip was approximately 40% lower, in comparison with healthy children [66]. Biggin et al. used pQCT to study volumetric trabecular BMD (vBMD) and calf muscle cross-sectional area (CSA) in 19 children with SCI (9 paraplegics and 10 tetraplegics) [67].They observed a significant loss of calf muscle CSA patients (Z-score −2.9), indicating sub-lesional muscle wasting. There was a significant reduction in tibial metaphyseal trabecular vBMD (Z-score of −3.9), diaphyseal cortical cross-sectional area ("slender bones"; Z-score of −2.9) and the polar strength-strain index (Z-score −2.7; a surrogate measure of bone strength derived from bone geometry and density). The mean tibial trabecular vBMD in 7 subjects who had sustained distal femoral or tibial fractures was lower when compared with those who did not sustain fractures ($n = 12$). Due to lack of loading from muscle contraction, the cross-sectional tibial geometry in SCI patients was transformed from the usual "teardrop appearance" to a more circular shape. This is in keeping with a lack of loading of bone as a result of muscle atrophy and prolonged immobility after SCI. Low bone mass puts patients with SCI at increased risk of sustaining fragility fractures. Over 30% of adults with SCI experience fragility fractures at the distal femur and proximal tibia [18].

Children and adolescents who are precipitously immobilized after SCI are at risk for developing hypercalcemia and hypercalciuria, due to uncoupling of bone turnover with reduced osteoblast-driven bone formation and increased osteoclast-mediated bone resorption [68].The hypercalcemia can affect around 23% of individuals with SCI, particularly adolescent males, possibly due to increased bone turnover

associated with rapid growth [69]. Symptoms of hypercalcemia include malaise, abdominal pain, polyuria, vomiting and dehydration. It is associated with increased risk of nephrocalcinosis, urolithiasis and renal failure. Treatment includes hydration, judicious use of furosemide (which will exacerbate the hypercalciuria) and intravenous bisphosphonates [70].

In summary, sub-lesional muscle atrophy and immobility following SCI reduces mechanical loading of bones, which results in low bone mass, slender bones and increased propensity to fragility fractures. Young patients with SCI are also prone to hypercalcemia and hypercalciuria.

Calcium and Vitamin D Supplements

Low body stores of vitamin D (as reflected by serum 25-hydroxyvitamin D [25(OH)D] concentration) have been reported in children and adolescents with CP [71]. In a study of institutionalized severely disabled Black South African children and adults with CP, Bischof et al. [72] found vitamin D status of subjects to be an important factor in the etiology of fractures. These investigators also reported an association between the number of fractures and use of anticonvulsants; older anticonvulsants, such as phenobarbital, are known to increase catabolism of vitamin D. The systematic review by Fehlings et al., which was updated by Ozel et al., concluded that [73, 74] vitamin D and calcium were possibly effective in improving BMD, but data were inadequate to make recommendations on their effectiveness to prevent fragility fractures. In a prospective study, Bianchi et al. [75] observed that treatment with calcifediol (25(OH)D) and calcium-rich diet resulted in decreased bone resorption and increased lumbar spine and whole body BMC and BMD.

In summary, there is a paucity of high-quality RCTs on the role of vitamin D treatment and adequate dietary calcium intake in reducing the risk of fragility fractures in an immobilized adolescent. Nevertheless, in these youngsters the provision of vitamin D supplements to maintain serum 25(OH)D concentrations >50 nmol/L (20 ng/mL), along with recommended dietary reference intake for calcium for age and gender, is important for maintenance of bone health.

Bisphosphonate Therapy

Bisphosphonates are synthetic analogues of inorganic pyrophosphate which act at mineralized bone surfaces to inactivate bone-resorbing osteoclasts. In children and adolescents treated with bisphosphonates, bone resorption is inhibited, but bone growth continues resulting in increase in aBMD and bone strength through a combination of increased cortical thickness and trabecular number. In children with moderate to severe osteogenesis imperfecta, cyclical intravenous pamidronate disodium pentahydrate (pamidronate) therapy was associated with improvements in vertebral aBMD and inreduction in both bone pain and fracture rate [76]. Systemically administered bisphosphonates (intravenous pamidronate or zoledronic

acid) are increasingly being used to treat children and adolescents with symptomatic fragility fractures on compassionate grounds.

Systematic reviews of cross-sectional studies and small placebo-controlled randomized controlled trials of treatment of non-ambulant children and adolescents with CP with bisphosphonates led to improvement in vertebral and femoral aBMD [73, 74]. Howe et al. observed that intravenous pamidronate therapy improved bone mineral density, reduced pain and pain-related sleep disturbance in children and adolescents with chronic neurological conditions [77]. In 32 children and adolescents with CP (age 2.9–19.6 years; GMFCS levels III to V), treated with intravenous pamidronate, Sees and colleagues [78] observed decrease in pretreatment rate of 2.4 fractures per year to posttreatment rate of 0.10 fractures per year ($p < 0.001$). However, some CP patients experienced fractures upon stopping cyclical pamidronate treatment; approximately 60% percent of fractures were located adjacent to the margin of a "pamidronate bands", which act as "stress risers" [79].

In deflazacort-treated DMD boys, treatment with oral alendronate for 2 years had a positive effect on whole body and lumbar spine BMD Z-scores [80]. Treatment of 7 DMD boys who had symptomatic vertebral fractures with intravenous pamidronate or zoledronic acid led to improvements in back pain and stabilization or partial reshaping of previously fractured vertebral bodies [23]. However, bisphosphonate therapy did not prevent the development of new vertebral fractures. Prophylactic treatment with oral risedronate in 52 DMD patients resulted in stabilization of spinal BMD and fewer vertebral fractures compared to 15 bisphosphonate naïve controls [81].

Treatment with intravenous zoledronic acid for 18 months in a 12-year-old boy with non-traumatic SCI resulted in improvement in DXA measured total body lumbar spine areal BMC and BMD and pQCT measured trabecular vBMD and BMC in both tibia and radius [82]. As mentioned previously, intravenous bisphosphonates are useful for treatment of hypercalcemia in immobilized adolescents [70].

In summary, intravenous bisphosphonate therapy in children and adolescents with disorders associated with immobilization results in increase in BMD and results in reduction of long bone fractures. Intravenous bisphosphonate therapy also results in reduction in pain associated with vertebral fractures. However, the cyclic method of delivering the intravenous bisphosphonates is prone to creating "stress risers" in the growing patient, which are associated with fractures. At present time there are no data from RCTs to inform decisions about the choice of bisphosphonate, the administration route, the dose and the duration of therapy.

The Role of Physical Therapy Interventions

Systematic review of a variety of weight bearing physical therapy trails in children and adolescents with CP [73, 74] concluded that there was insufficient evidence that these interventions increase BMD. Whole-body vibration therapy (WBVT) can be used as part of the rehabilitation programme to improving muscle strength, coordination and BMD [83, 84]. In adolescents and young adults with mild to

moderate CP (GMFCS levels II–III), Gusso et al. found that [85] 20 weeks of WBVT was associated with increases in pQCT and DXA measured muscle mass, BMC and BMD in the axial and appendicular skeletal sites. A significant improvement in mobility, assessed by the 6-min walk, was also observed after WBVT. Further studies are needed to confirm these findings in youngsters with disorders associated with immobilization.

Summary and Recommendations

1. Non-ambulant adolescents with CP are prone to fragility fractures, which predominantly occur at the distal femur and proximal tibial sites. Long bone fractures, which often occur after minor falls, are also common in individuals with disorders associated with progressive muscle weakness. In boys with DMD, long bone fracture is associated with permanent loss of independent ambulation:
   (i) *Caregivers should be aware of this risk and appropriate precautions should be undertaken to avoid accidents, for example, during transfer of the adolescent from the wheelchair to bed.*
   (ii) *Measures to avoid falls, particularly when mobility is declining in boys with DMD, should be put in place.*
   (iii) *The duration of postoperative immobilization, which is associated with increased risk of further fractures in adolescents with CP, should be kept to as short as possible.*
2. A clinically significant history of fracture in combination with low bone densitometry findings is necessary for a diagnosis of osteoporosis in adolescents. The 2013 Pediatric Official Positions of the International Society for Clinical Densitometry [25] states that DXA measurement is part of a comprehensive skeletal health assessment. In adolescents with disorders associated with chronic immobilization, assessment of the lateral distal femoral areal BMD should be considered as it is the most common site of long bone fractures:
   (i) *Clinician should consider measuring lateral distal femoral aBMD in patients with a significant long bone fracture history (≥ 2 long bone fractures by the age of 10 years OR ≥ 3 long bone fractures at any age up to age 19 years), especially when treatment with intravenous bisphosphonates is being considered.*
3. The finding of one or more vertebral compression (crush) fractures is indicative of osteoporosis, in the absence of local disease or high-energy trauma (The 2013 Pediatric Official Positions of the ISCD) [25]. Up to 25% of chronically immobilized youngsters have been found to have vertebral compression fractures. Such fractures, which are more common in boys with DMD treated with long-term high dose oral GCS, may be asymptomatic and can occur when lumbar spine areal BMD Z-score values are ≥ −2.0:
   (i) *Currently, there is no consensus regarding screening for vertebral fractures in children and adolescents with disabilities. However, in boys with DMD treated with long-term high doses of GCS, screening for vertebral fractures*

by annual lateral thoracolumbar radiograph, or by vertebral fracture assessment using DXA, is justified.

4. Adequate body stores of vitamin D and dietary calcium may improve BMD in patients with CP; however, the evidence for prevention of fragility fractures is lacking [73, 74]. Nevertheless, for maintenance of bone health:
   (i) *Vitamin D deficiency should be identified and corrected to maintain serum 25(OH)D concentrations > 50 nmol/L (20 ng/mL), at least.*
   (ii) *Inadequate intake of calcium should be corrected by providing dietary reference intake for calcium, for age and gender.*
5. Pubertal delay, which is common in boys with DMD on long-term high dose oral GCS, has also been reported adolescents with CP. Delayed or arrested puberty adversely affects bone growth and bone mass accretion. While there is currently no evidence from RCTs that timely induction of puberty in boys with DMD treated with long-term high dose oral GCS will improve bone mass and reduce future risk of fragility fractures, author's recommendations are:
   (i) *Pubertal assessment should be undertaken from the age of 10–12 years of age.*
   (ii) *Delayed puberty is defined as that not occurring by 14 years in boys and 13 years in girls.*
   (iii) *Treatment of delayed puberty with sex steroids, for example, testosterone or oxandrolone (a non-aromatizable anabolic steroid with a weak androgenic effects, which does not promote excessive skeletal maturation) in boys with DMD treated with high dose of GCS, for up to 6 months, may be used for induction of puberty.*
   (iv) *Occasionally, induction of puberty may not be successful in boys with DMD. Such individuals with arrested puberty require testosterone replacement therapy, which in a growing adolescent, may lead to early closure of epiphysis and worsening of GCS-induced short stature.*
6. Bisphosphonate therapy has been shown to improve BMD and reduce the risk of fragility fractures in children and adolescents with CP and other neuromuscular disorders. Treatment of DMD boys with symptomatic vertebral fractures with intravenous bisphosphonates was associated with improvement in back pain and stabilization of fractured vertebrae:
   (i) *Treatment with intravenous bisphosphonates should be considered on compassionate grounds in youngsters with a significant fracture history (see bullet point number 2) and aBMD Z-score ≤ −2.*
   (ii) *Intravenous bisphosphonate therapy should be considered in patients with symptomatic vertebral fractures, with or without low lumbar spine BMD.*
   (iii) *There are no clear guideline on treatment of asymptomatic vertebral fractures identified through routine screening (see bullet point number 3). The treatment of such fractures should be based on clinical judgement made on case by case basis.*
   (iv) *Currently there are no guideline to inform decisions about the dose of bisphosphonate and the duration of treatment.*

Clinical Vignettes

Anne is a 14-year-old girl with CP arising from perinatal hypoxic-ischemic encephalopathy. She is severely disabled (GMFCS level V), blind and deaf and suffers from epilepsy. At the age of 12 years, Anne suffered a fracture of her right distal femur during a tonic-clonic epileptic seizure. Thirteen months later, her caregivers noticed that she appeared to experience pain when her left leg was moved. Her left knee was noted to be swollen and radiographs revealed fracture of her left distal femur. There was no history of trauma. Both fractures healed after appropriate immobilization. She is due to undergo elective surgery on her right dislocated hip, and her parents would like to know (1) if hip surgery will increase Anne's risk of suffering further fragility fractures and (2) if there are any strategies that might help to reduce her risk of suffering further fractures.

Question
Is Anne's risk of suffering further fragility fractures?

Answers
Yes, Anne is at increased risk of suffering further fractures as:

(i) Previous fracture is a predictor of subsequent fractures.
(ii) Immobilization of the hip in a spica cast following surgery is known to be associated with increased in risk of fracture.

Question
What assessments would you undertake?

Answers
(i) Assess Anne's dietary calcium intake.
(ii) Check her vitamin D status by measuring her serum 25(OH)D level.
(iii) Measure her lateral distal femoral aBMD.
(iv) Screen for vertebral fractures by either lateral thoracolumbar radiograph or by vertebral fracture assessment using DXA.

Question
What strategies would you recommend to reduce Anne's risk of suffering further fractures?

Answers
(i) Ensure that Anne is getting the recommended nutrient intake for calcium.
(ii) Ensure that her serum 25(OH)D is > 50 nmol/L (20 ng/mL).
(iii) Anne has suffered two fragility fractures of her long bones. If her lateral distal femoral aBMD Z-score is significantly reduced (≤ −2), then treatment with intravenous bisphosphonates for up to 2 years may increase her BMD and reduce risk of fragility fractures.
(iv) Ensure that the period of postoperative immobilization after hip reconstruction surgery is kept to minimum.
(v) Ensure that all Anne's caregivers are aware that she is at higher risk of suffering fragility fractures of her long bone after her surgery.

Joel is a 15-year-old with DMD, who was treated with deflazacort 0.9 mg/kg/day, administered daily by mouth, since the age of 5 years. His mobility started to decline from the age of 12 years. He has been having annual bone mineral density measurements by DXA since the age of 6 years. His lumbar spine (L1 –L4) BMAD Z-score declined from +0.8 at the age of 6 years to −1.6 at the age of 14 years. At the age of 13½ years, Joel tripped and fell sustaining a fracture of his right femoral shaft, which was treated by insertion of an intramedullary rod. Since then he has been a wheelchair user. Over the past 6 weeks, Joel has been complaining of back pain which has affected the quality of his sleep, and he has not been able to sit in his wheelchair for more than 2 h. His back pain is only partially alleviated with oral acetaminophen and ibuprofen, which he has been taking on an as-needed basis.

Question
How would to you assess and manage Joel's back pain?

Answers
Further investigations and management of Joel's back pain:

(i) Even though Joel's LS BMAD is not significantly reduced (Z-score ≤ −2), he should have a lateral thoracolumbar radiograph or vertebral fracture assessment by DXA. This revealed that Joel has anterior compression fractures of T8, T9 and T 10 vertebral bodies.
(ii) Treatment of Joel's symptomatic vertebral fractures with intravenous bisphosphonate therapy, e.g. with pamidronate or zoledronic acid, may help to improve his back pain and help to stabilize/partially reshape the fractured vertebral bodies.

Question
What further assessments and investigations would you undertake before commencing specific treatment?

Answers

(i) Ensure that Joel's serum 25(OH)D is > 50 nmol/L (20 ng/mL), so as to reduce the risk of him becoming hypocalcemic after pamidronate or zoledronic acid infusion.
(ii) Ensure that Joel is getting the recommended nutrient intake for calcium.
(iii) Undertake pubertal assessment, as treatment of his DMD with deflazacort puts him at risk of delayed or arrested puberty. Such delay may have contributed to his risk of long bone and vertebral fractures, and it adversely affects bone health through inadequate muscle mass and bone mass accretion that occurs during normal puberty. Delayed puberty should be treated with testosterone or oxandrolone for 6 months.
(iv) While Bisphosphonate-associated osteonecrosis of the jaw (BROJN) has not been reported in children and adolescents, Joel should have a thorough dental assessment prior treatment with intravenous pamidronate or zoledronic acid. In adults, dental examination with preventive dentistry measures are recommended prior to treatment with oral or intravenous bisphosphonates, especially

in patients with pre-existing dental disease or other risk factors, such as treatment with glucocorticoids [86]. There is evidence that in adult patients who were screened and received preventive dental care before initiating bisphosphonate therapy had a lower incidence of BROJN [87].

Three months ago, Malcolm a previously well 13½-year-old boy suffered severe hypoxic ischaemic acquired brain injury, secondary to drowning. In spite of resuscitation and full paediatric intensive care support for 32 days, Malcolm has survived with severe spastic quadriparesis. Since discharge from the paediatric intensive care unit, he has been bed bound and totally dependent for all activities of living including washing, dressing, feeding and toileting. He is unable to communicate verbally. Over the past 24 h, Malcolm has been passing large volumes of urine (>2 ml/kg/h) and was noted to be clinically dehydrated (~ 5% loss of body weight), and his plasma biochemistry was as follows:

Na 145 mmo/L (135–145)
K 3.5 mmol/L (3.5–5.3)
BUN 9 mmol/L (2.5–6.5)
Creatinine 111 μmol/L (50–90)
Corrected Ca 3.45 mmol/L (2.2–2.7 mmol/L)
Inorganic P 1.2 mmol/L (1.1–1.4)
Alkaline phosphatase activity 98 i.u/L (150–500)
PTH 1.2 pmol/L (1.1–6.9)
25(OH)D 63 nmol/L

Question
What is the diagnosis and your interpretation of Malcolm's laboratory investigations?

Answer
Malcolm has developed hypercalcemia secondary to precipitous immobilization, following his acquired brain injury. In adolescents, who have increased bone turnover, immobilization results in increased osteoclastic activity and release of calcium from skeletal stores, resulting in hypercalcemia. The hypercalcemia leads to a nephrogenic diabetes insipidus-like state causing excessive body water excretion, resulting in dehydration. This explains his raised serum BUN and creatinine. Hypercalcemia results in suppression of plasma parathyroid hormone level (PTH). Malcolm's low serum alkaline phosphatase activity reflects reduced osteoblastic activity.

Question
What further assessments and investigations would you undertake?

Answer
Check for hypercalciuria and organize an ultrasound scan of kidneys to look for nephrocalcinosis and/or nephrolithiasis.

Question
How would you manage Malcolm's current problem?

Answer

Initial management should involve correction of dehydration with normal (0.9%) saline. Loop diuretics can exacerbate the hypercalciuria and so should be used judiciously. Intravenous pamidronate or zoledronic acid inhibit osteoclastic activity and help to decrease serum calcium concentration. These drugs should be used with caution in patients with impaired renal function.

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Treatment of Adolescent Osteoporosis

13

Monica Grover and Laura K. Bachrach

Introduction

The diagnosis and management of osteoporosis in childhood and adolescence require the expertise of pediatric providers. Extrapolating from the approach used to label adults with osteoporosis can be misleading and even harmful. The criteria for the diagnosis of "osteoporosis" in pediatrics include a history of low trauma fractures and cannot be based upon low bone mineral density (BMD) alone. Several of the disorders linked to bone fragility in older patients also cause osteoporosis in children and teens. However, the skeletal fragility in younger patients typically results from a failure to achieve the expected *gains* in bone strength without or with the increased bone *loss* seen in adults. Unlike adults, growing patients who recover from the underlying illness have the potential for spontaneous improvements in bone strength. These differences in the pathophysiology and natural history of bone fragility in pediatrics influence the approach to treatment. None of the drugs used to treat osteoporosis in older adults have been approved by the Food and Drug Administration (FDA) for pediatric use. Nonetheless, these agents are prescribed on a compassionate-use basis for younger patients with fragility fractures.

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This chapter will focus on the definition of pediatric osteoporosis, the distinction between primary and secondary causes, and the indications for pharmacologic treatment in adolescents with bone fragility. Addressing early threats to bone health is key to reducing the risk of fractures throughout adult life [1, 2]. The discussion outlines the controversies about when and how to employ drugs that persist because of inadequate pediatric data. Oversight of osteoporosis drug therapy in adolescents requires guidance from specialists experienced in pediatric skeletal disorders. The primary care provider plays an essential role by recognizing teens at risk for fracture, encouraging general bone health measures, addressing early threats, and involving bone experts in the care. This overview of drug therapy for osteoporosis can prepare primary care physicians to provide general information to families on the current state of the art of pharmacologic therapy for teens with bone fragility.

The Definition of Pediatric Osteoporosis

Vignette 1

Mother brings Kelly, her 14-year-old daughter, to your office with concerns for her bone health. Mother, who is 49 and perimenopausal, has just been diagnosed with osteoporosis based on a BMD T-score of −2.6. Kelly's mother and grandparents have no history of fractures or other chronic health problems. Nonetheless, Mother worries that Kelly may also have "osteoporosis" because she has been complaining of lower back pain for a month. A lateral spine x-ray from urgent care clinic last week did not show any fractures. Kelly's only broken bone was a radius fracture at age 8 after she fell while running on pavement. She consumes only 8 ounces of milk daily so Mother is now giving her daughter a calcium supplement. Kelly has had regular menses since menarche at age 12. On examination, she is a well-appearing teenager with BMI at the 50th percentile. She has paraspinal muscle stiffness but no spine tenderness or deformity. Mother then shows you Kelly's DXA scan that her gynecologist ordered as a favor. The report states that Kelly has "osteopenia" based upon spine and hip T-scores of −2.1.

This case underscores some of the potential pitfalls in defining osteoporosis in a child or adolescent. Firstly, DXA scans should be performed in centers experienced with pediatric patients. As discussed in previous chapters, BMD results should be reported as Z-scores, which are standard deviations from the mean for healthy youth of similar age, sex, height, and ethnicity [3, 4]. T-scores are not appropriate for patients younger than 30 since they compare the BMD results to healthy adults who have attained peak bone mass. When recalculated using pediatric reference data [5], Kelly's BMD Z-scores are −1.7, within the low end of the normal range. Z-scores below −2 are considered "low BMD for age"; the term "osteopenia" should not be used in pediatric patients to describe Z-scores between −1 and −2.

The diagnosis of osteoporosis in a child or adolescent cannot be made based upon BMD findings alone [6, 7]. In 2013, a panel of pediatric bone experts from the

International Society of Clinical Densitometry (ISCD) revised the criteria for the diagnosis of pediatric osteoporosis to include:

- The presence of one or more vertebral compression fractures (VF) occurring without major trauma or local disease
- The presence of low bone mineral content (BMC) or BMD for age (Z-score < −2.0) *plus* a clinically significant fracture history of long bone fractures (≥ two fractures by age 10 years OR ≥ three by age 19 years)

These criteria reflect the limitations of bone densitometry as a surrogate measure of bone strength in children and teens. There is no established "fracture threshold" based upon BMD Z-scores that reliably predicts bone fragility in youth. This is in contrast to older adults in whom a BMD T-score of < −2.5 has been used to diagnose osteoporosis [8]. Furthermore, pediatric Z-score values vary depending upon the reference database used to calculate them [9]. In addition, fragility fractures can occur in patients with normal BMD especially during glucocorticoid (GC) therapy when bone quality may decline faster than bone mineral [10]. A vertebral compression fracture that occurs without trauma or local disease is a reliable clinical indicator of inadequate bone strength that can be used to diagnose pediatric osteoporosis. These fractures may go unrecognized since an estimated 40% are asymptomatic. For this reason, routine lateral spine surveillance is recommended in high-risk patients [11].

Kelly's mother should be reassured her daughter has neither osteoporosis nor low BMD for age. Her history of one forearm fracture is non-concerning since it occurred with trauma at the most common skeletal site for pediatric injury. The family history is negative for clinical bone fragility. Given mother's concerns, it is reasonable to explore if there are any skeletal risk factors (e.g., a history suggestive of celiac disease) and to encourage bone health through diet and activity. Kelly does not warrant therapy with an osteoporosis drug.

Primary Versus Secondary Osteoporosis

Vignette 2

Maria is an 11-year-old female who sustained a left femur fracture 6 weeks ago after slipping on the wet kitchen floor. An orthopedic surgeon treated the fracture and recommended follow-up with her primary care provider. Maria's medical history is negative apart from a tibia fracture at age 4 and a radius fracture at age 6 sustained during pillow fights with her siblings. Her examination is unremarkable including teeth and eyes. She has a normal chemistry panel, complete blood count, thyroid function, and a negative celiac screen. Her 25-hydroxyvitamin D [25(OH)D] is 16 ng/mL, which you treat with 6 weeks of supplementation with 50,000 IU once weekly. Her repeat 25(OH)D is 28 ng/mL. Mother brings Maria to the office to ask if any further evaluation is needed.

Table 13.1 Causes of primary osteoporosis

Osteogenesis imperfecta
Syndromes:
Bruck syndrome
Marfan syndrome
Ehler-Danlos syndrome
Osteoporosis-pseudoglioma syndrome
Paget's disease
Metabolic:
Wilson's disease
Homocystinuria
Menkes' kinky hair syndrome
Galactosemia
Idiopathic juvenile osteoporosis

Vignette 3

Eleanor is a 12-year-old diagnosed with a mixed connective tissue disease 8 months earlier after developing weight loss, myalgia, and occasional fevers. Her symptoms have improved markedly on 15 milligrams of prednisone daily, and she has regained the weight lost. Mother brings Eleanor to the office today because she has been complaining of back pain for 3 weeks that does not lessen with heat or massage. She denies any recent falls or other trauma. A lateral spine x-ray shows "vertebral deformities in the thoracic spine at T12 and lumbar spine at L4 and L5."

These cases represent examples of primary (section "Vignette 2", Maria's story) and secondary (section "Vignette 3", Eleanor's story) osteoporosis listed in Tables 13.1 and 13.2, respectively. Primary osteoporosis in childhood or adolescence results from mutations altering the biosynthesis or turnover of bone or cartilage [12]. Osteogenesis imperfecta (OI), the most common of the heritable disorders, usually results from alterations in the structure of type I collagen, the bone matrix protein. Several new mutations have been identified that affect posttranslational processing of type I collagen or other biosynthetic abnormalities [13]. The Sillence classification of OI describes the extensive variability in clinical presentation ranging from a severe, perinatal lethal form (OI type II) to milder forms that may be diagnosed only in late adulthood [14]. Extraskeletal findings found in some patients include blue sclera, joint hyperextensibility, skin laxity, hearing loss, and dentinogenesis imperfecta. Long bone fractures may result in pain, deformities, and reduced mobility. Vertebral compression fractures or scoliosis compromises respiratory capacity and leads to death in the most severe forms. The timing of fractures in patients with OI parallels the pattern seen in the general population, with peaks during the toddler and adolescent years [14]. Genetic testing for OI should be considered in patients with possible extraskeletal findings and those with an excess of low trauma fractures especially in the absence of other apparent risk factors. These

Table 13.2 Causes of secondary osteoporosis

Chronic inflammatory disorders
Inflammatory bowel disease
Juvenile idiopathic arthritis
Celiac disease
Cystic fibrosis
Immobilization
Cerebral palsy
Myopathic disease (e.g., Duchenne muscular dystrophy)
Epidermolysis bullosa
Endocrine disturbance
Turner syndrome
Anorexia nervosa
Type 1 diabetes
Cancer and therapies with adverse effects on bone health
Acute lymphoblastic leukemia
Post chemotherapy for childhood cancer
Posttransplantation (non-renal)
Hematologic disorders
Thalassemia
Sickle cell disease
Drug induced
Glucocorticoids
Immunosuppressants
Antiepileptics
Medroxyprogesterone

investigations can be performed in commercial laboratories using blood samples. One study found that genetic mutations could be identified in 98% of patients with clinical diagnosis of OI [15].

Maria's history of bone fractures in section "Vignette 2" is concerning. The most common site of childhood fracture is the distal forearm [16]. Her femur fracture occurring without major trauma is a very unusual injury, suggestive of bone fragility. Maria's history of earlier long bone fractures during low trauma play at home also raises suspicions for abnormal bone strength. Any patient with low trauma fractures warrants a thorough history, physical and laboratory exam as outlined in Chaps. 5, 6, 8, 11, and 12. Maria has no history of chronic illness or medications that would cause secondary osteoporosis, and her mild vitamin D deficiency is unlikely a sufficient explanation for the fractures. Despite the absence of blue sclera, abnormal dentition, or hyperextensibility, Maria warrants further work-up. This would include a lateral thoracolumbar spine x-ray (T4 to L4) even though she denies back pain. The x-ray reveals several "vertebral deformities" which represent

vertebral fractures. Genetic studies confirm Maria has a mutation in her type 1A collagen consistent with OI, and she is referred to a pediatric bone expert for pharmacologic therapy.

Secondary osteoporosis develops as a consequence of chronic disease and the medications used to treat them (Table 13.2). Inflammatory bowel disease, rheumatologic disorders, malignancy, transplantation, cerebral palsy, Duchenne muscular dystrophy (DMD), cystic fibrosis, and anorexia nervosa are among the more common causes of acquired bone fragility [17–19]. These diverse disorders share one or more common skeletal risk factors including nutritional deficits, reduced mobility, increased inflammatory cytokines, sex steroid or growth hormone deficiency, and exposure to osteotoxic drugs. The net result is reduced bone formation, which may be compounded by increased bone resorption. These disorders are discussed in more detail in Chap. 11.

Patients with inflammatory bowel disease, rheumatologic disorders, and acute lymphoblastic leukemia (ALL) can present with low bone mass and fractures at the time of diagnosis due to chronic inflammation or malnutrition [20–22]. The risk of fragility fracture, especially at the spine, increases within months of initiating therapy with GC for these conditions [11, 23–25].

Eleanor's case is illustrative of the rapidity with which vertebral fractures can develop during GC therapy. The "vertebral deformities" reported on her spine x-ray likely represent fractures that are painful in this case. These films should be reviewed by a radiologist familiar with the standardized scoring system described by Genant that can distinguish between normal variants and true fracture [26–28]. Eleanor warrants referral to a bone expert to consider pharmacologic therapy for osteoporosis.

Not All Bone Fragility Is Osteoporosis

Vignette 4

Adam, a 12-year-old non-ambulatory, African American boy with severe developmental delay, is referred as a new patient. He is an ex-25-week premature infant who is dependent on formula feeds via *gastric tube four times a day. He has a history of tibia and radius fractures that occurred while his mother gently bathed and dressed him. Mother tells you that the physician who evaluated him in the emergency department after his last fracture suggested he might need osteoporosis drug therapy. On exam, his height, weight, and BMI are all at the third percentile. He is nonverbal, cannot sit without support, and has a cast on his right lower leg. His exam is otherwise unremarkable without bruises or rachitic features. Blood tests from the emergency room showed a normal CBC, ESR, calcium, and creatinine with an elevated alkaline phosphatase which the doctors attributed to his recent fracture. His 25(OH)D and serum phosphorus levels were low at 18 ng/mL and 2.1, respectively.*

Adam's history of severe developmental delay and multiple fractures during routine care raises concerns for underlying bone fragility without or with possible non-accidental trauma (NAT). Certain fractures are typical for abuse and should be

carefully evaluated by an experienced radiologist [29]. There was no suspicion for NAT in this case, and a full medical work-up was performed.

It is important to distinguish between osteoporosis and osteomalacia as both can cause bone fragility but require a very different therapeutic approach. Osteomalacia or rickets is characterized by an increase in the amount of unmineralized bone matrix, whereas osteoporosis reflects a reduction in the quantity or quality of normally mineralized bone. Common causes of osteomalacia include deficiencies of vitamin D, calcium, or phosphorus and chronic liver or kidney disease [30]. Genetic causes include hypophosphatasia and hereditary hypophosphatemic rickets [31]. Laboratory studies that can help differentiate osteomalacia from osteoporosis include renal and liver function, alkaline phosphatase, 25(OH)D, parathyroid hormone, calcium, phosphorus, and magnesium (the latter two of which are not included in a standard chemistry panel). Genetic testing for other causes of osteomalacia is appropriate once the more common nutritional, renal, or hepatic causes are excluded. Mutations in the tissue-nonspecific alkaline phosphatase (*TNSALP*) gene cause hypophosphatasia [32] by impairing function of alkaline phosphatase. This results in accumulation of inorganic pyrophosphate (PPi) and pyridoxal-5′-phosphate; PPi inhibits bone mineralization. Hypophosphatasia presents with varying degrees of clinical severity from early tooth loss alone to severe craniosynostosis, fractures, failure to thrive, seizures, and respiratory failure.

Adam's laboratory work-up revealed low serum 25(OH)D as well as low serum and urine phosphorus, suggestive of nutritional osteomalacia as a cause for his fractures. After supplementing his formula with additional vitamin D3 and phosphorus, Adam's alkaline phosphatase and 25(OH)D were normalized, and he has had no further fractures. He remains at risk for bone fragility from immobilization but is not currently an appropriate candidate for osteoporosis drug therapy.

Pharmacologic Therapy: Indications for Therapy

Vignette 3: Eleanor's Case Revisited: Questions About Osteoporosis Drug Therapy

Eleanor and her mother return to the office with questions about how to treat her daughter's bone fragility. Mother is concerned about Eleanor's persistent back pain and the newly diagnosed vertebral fractures; she worries her daughter might fracture more bones in the future. Mother has heard about pills used to treat osteoporosis in older women; she wonders if these agents would be safe and helpful for Eleanor.

The first step in the management of pediatric osteoporosis is to address *all modifiable risk factors* as outlined in detail in Chaps. 6, 8, 9, 11, and 12. Ensuring adequate caloric, calcium, protein, and vitamin D intake, optimizing physical activity, as tolerated, and treating endocrine deficiencies are essential before starting pharmacologic therapy. Primary care providers play an important role in fostering nutrition and physical activity because subspecialists who may focus on only one

organ system can overlook these general measures. Control of inflammation is key because elevated cytokines impair bone formation and accelerate bone loss in a pattern similar to GC excess [33]. GCs should be titrated to the lowest effective dose that controls the underlying disease. In some conditions, biologic agents can replace GCs as a means to reduce inflammatory disease, resulting in improved bone health. For example, anti-TNF-α therapy resulted in an increase in both trabecular BMD and cortical area in young patients with Crohn's disease [34]. In another study, spine BMD Z-scores increased in juvenile idiopathic arthritis (JIA) during treatment with an anti-TNF α agent [35]. The effects of anti-TNF-α therapy on fracture incidence are not available at this time.

Once fragility fractures of the spine or long bone have occurred, discussion of pharmacologic agents is reasonable. Therapy with osteoporosis drugs requires consultation with experts familiar with the complexities of this treatment in pediatric patients. Nonetheless, the primary care physician should have a general background on their efficacy and side effects for younger patients.

Controversies persist over the optimal drug, dose, and duration of therapy for primary and secondary osteoporosis in pediatrics. Since bone fragility in pediatrics results at least in part from inadequate gains in bone size, mineral, and microarchitecture, the ideal therapeutic agent would be an *anabolic drug*. These agents stimulate bone growth, reshaping, and mineral accrual. The most widely used anabolic agent (e.g., teriparatide, trademark Forteo) carries a black box warning against use in young patients because of a concern for osteosarcoma [36].

An alternative class of osteoporosis agents are bisphosphonates (BPs) that act as *anti-catabolic* agents reducing bone resorption [37]. BPs adhere to the surface of the bone where they are ingested by osteoclasts and then act to impair cell function and cause cell apoptosis. In younger patients, reduced bone loss during BP therapy combined with ongoing growth can result in net gains in the trabecular and cortical bone [38].

Several oral and parenteral BPs have proven efficacy to reduce fractures in postmenopausal women, elderly men, and adults with steroid-induced osteoporosis. None of them have FDA approval for use in pediatrics because of inadequate randomized controlled trials [37]. Nonetheless, BPs are widely used on a compassionate basis to treat low trauma vertebral or long bone fractures in children and teens.

Candidates for BP therapy include those with moderate to severe OI and secondary osteoporosis due to chronic illnesses [37]. For younger patients with curable disorders such as ALL, it may be reasonable to observe without BP treatment because these youth may recover bone strength spontaneously after completing chemotherapy [39]. Considering BP treatment sooner is appropriate for patients facing persistent threats to bone health such as those with DMD or OI and older patients with less time to grow and reshape bone [37]. The presence of a VF, even if mild or asymptomatic, increases the likelihood of additional spine fractures in the future, a phenomenon known as the "VF cascade." Hence, early treatment of mild asymptomatic vertebral fractures in these chronic patients may be justifiable [11, 22, 25].

Controversies persist about the optimal agent and dose of BP to choose because of inadequate data from treatment trials in pediatrics [37]. Cochrane reviews [17, 40] and other reports provide excellent summaries of current knowledge about drug efficacy, adverse effects, and the limitations of study design [37, 41–45]. There are few randomized, controlled trials, and most have been short term using BMD as the outcome measure rather than important clinical endpoints such as mobility, pain, and fractures.

Oral BPs such are alendronate and risedronate are poorly absorbed from the gastrointestinal tract and must be taken on a completely empty stomach with 6 ounces of tap water only. Patients must remain upright and not consume anything for at least 30 min to prevent esophageal irritation. These regimens make compliance challenging in adults and perhaps even more so in teens. The most widely used of the parenteral agents is intravenous pamidronate prescribed in doses ranging from 4 to 9 mg/kg/year divided every 2–4 months for initial therapy. The newer, more potent BP, zoledronic acid (ZA) can be infused more rapidly and less frequently than pamidronate [46]. The pediatric dose of ZA is typically 0.05–0.1 mg/kg/year divided every 3–6 months [47].

There are few data comparing the efficacy of the different BPs to increase BMD and reduce bone pain and fractures in pediatric patients. A randomized, controlled trial in patients with OI found oral alendronate to be no more effective than placebo in reducing bone pain and fractures [48]. Other studies using oral BPs have shown variable efficacy at reducing non-vertebral fractures [50]. Overall, the literature suggests that intravenous agents are more effective than oral agents to reduce vertebral fractures [49].

Given the severity of Eleanor's vertebral fractures, she was offered BP therapy. Blood work was obtained prior to her first infusion to ensure she had normal renal function, adequate vitamin D and minerals, and a normal CBC. She received pamidronate therapy for 2 years, and subsequent spine radiographs showed marked improvement in her vertebral fractures as shown in Fig. 13.1.

Pharmacologic Therapy: Adverse Effects and Monitoring

A brief acute-phase reaction (myalgia, bone pain, fever, nausea, vomiting) is common after the first exposure to BP. Onset is typically at 18–24 h after an intravenous infusion. Symptoms are usually mild and respond to treatment with antipyretics and antiemetics. Transient hypocalcemia, hypophosphatemia, and hypomagnesemia are less common events occurring 3–5 days after BP administration. Serum calcium, phosphorus, and magnesium should be checked a few days following the first exposure to BPs. Electrolyte abnormalities occur more frequently after high-dose pamidronate or ZA [46]. Optimizing calcium intake and 25(OH)D level before and after the infusions reduces the risk of hypocalcemia. Uncommon side effects include nephrotoxicity, anterior uveitis, and atrial fibrillation (never reported in children and

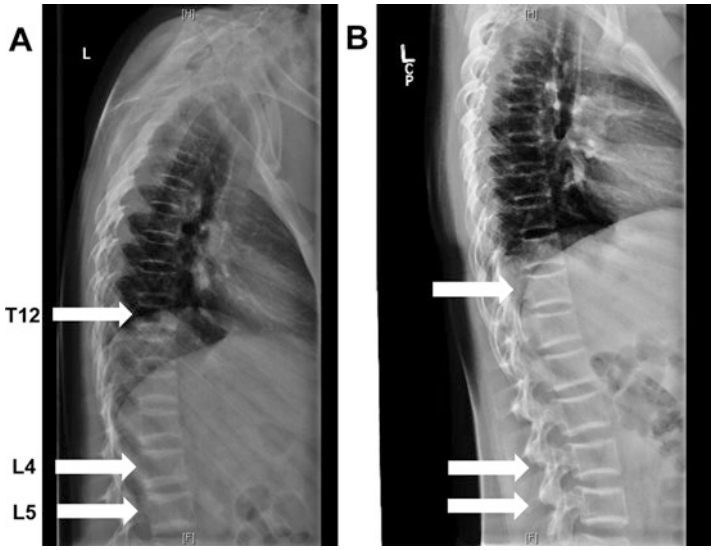

Fig. 13.1 Vertebral body reshaping during bisphosphonate therapy in a 12-year-old girl with mixed connective tissue disease. Panel A shows diffuse osteopenia of the vertebral bodies with prominence of the endplates. Superior endplate compression deformity is noted of T12 as well as L4 and L5. Panel B shows reshaping of vertebral bodies after a year of bisphosphonate therapy

adolescents). Renal insufficiency should be ruled out before starting BP therapy, and renal function should be monitored carefully during treatment. In patients with immobilization disorders or muscle wasting from inflammatory causes, serum creatinine may not accurately reflect renal function; cystatin C has been proposed as an alternative marker.

Long-term safety concerns include the potential for teratogenicity. The half-life of BPs is in years. Over time, the BPs are released from bone and can cross the placenta to a developing fetus. To date, studies of infants born to mothers treated before or during pregnancy suggest minimal risk [50]. Nonetheless, some experts have suggested that BPs be discontinued 6 months prior to a planned pregnancy.

Though spontaneous healing of fractures does not appear to be impaired, patients who have been treated with BPs have a greater risk of delayed healing after rod insertion surgery [51]. Some have recommended that BP therapy be discontinued for 4 months after an osteotomy procedure or until healing is evident [52].

Over-suppression of bone turnover with BP therapy remains the most controversial concern. The more serious manifestations of over-suppression seen in adults treated with BPs appear to be uncommon in children and teens. There are no reported cases of avascular necrosis of the jaw and only rare reports of atypical femur fractures (AFF) [53–55]. One retrospective study concluded that the risk of AFF was related to severity of OI and not to exposure to BPs [56].

Pharmacologic Therapy: How Long to Treat

Vignette 5: More Questions

James has been receiving pamidronate infusions for 2 years, and he has had no fractures during this time. His grandmother who is on treatment for osteoporosis tells James' dad that he should be having a "drug holiday" to avoid serious complications from his bone medicine. Dad asks if it is time to stop this treatment since James is now fracture-free.

The optimal duration of BP therapy varies depending upon the indication for treatment. The greatest gains in bone mineral and geometry occur during the first 2–4 years of BP therapy [57]. BPs can be discontinued before that time in patients whose underlying disease or risk factors have resolved, and they are clinically stable for 6–12 months. Criteria for clinical stability include reshaping of VF (as shown in Fig. 13.1), absence of new vertebral and long bone fractures, absence of bone pain, and improvement in mobility and BMD Z-score [58]. For children with persistent skeletal risk factors such as immobilization disorders and OI, long-term therapy is recommended. Younger patients who have stopped BP before they have completed growth have sustained long bone fractures where there is a "density differential" [60, 61]. These occur at the junction of proximal bone, which has been strengthened by BP therapy and the distal, newly formed "untreated" bone (as shown in Fig. 13.2).

As discussed above, evidence of over-suppression of bone turnover is uncommon in pediatric patients receiving BPs. To reduce the risk of overtreatment, the BP dose is generally reduced by 50% after the initial 2–3 years of therapy and continued as maintenance until final height is reached [59]. Iatrogenic osteopetrosis was reported in one child who received four times the usual high dose of pamidronate for 3 years [60]. Some centers use urine or blood markers of bone turnover to monitor for over-suppression of bone turnover during pharmacologic therapy [61, 62]. The most commonly measured parameters are procollagen type I N-terminal propeptide (PINP; a marker of bone formation) and serum collagen type I cross-linked C-telopeptide (CTx; a marker of bone resorption) [63].

Primary Prevention: BP Therapy Before a First Fracture

Pharmacologic therapy for pediatric osteoporosis is generally reserved for patients who have already sustained one or more fragility fractures. If physicians could accurately identify those most likely to fracture soon, it would be reasonable to conduct trials to assess the safety and efficacy of primary prevention (treatment before the first fracture).

Valuable insights into the factors predictive of incident vertebral fractures have come from longitudinal observational studies of pediatric patients receiving GCs for ALL or rheumatologic disorders [11, 25]. Risk factors correlated with an increased risk of future fracture include VFs at baseline, higher doses of GCs (average daily and cumulative), greater disease severity, high BMI Z-scores, low BMD Z-scores,

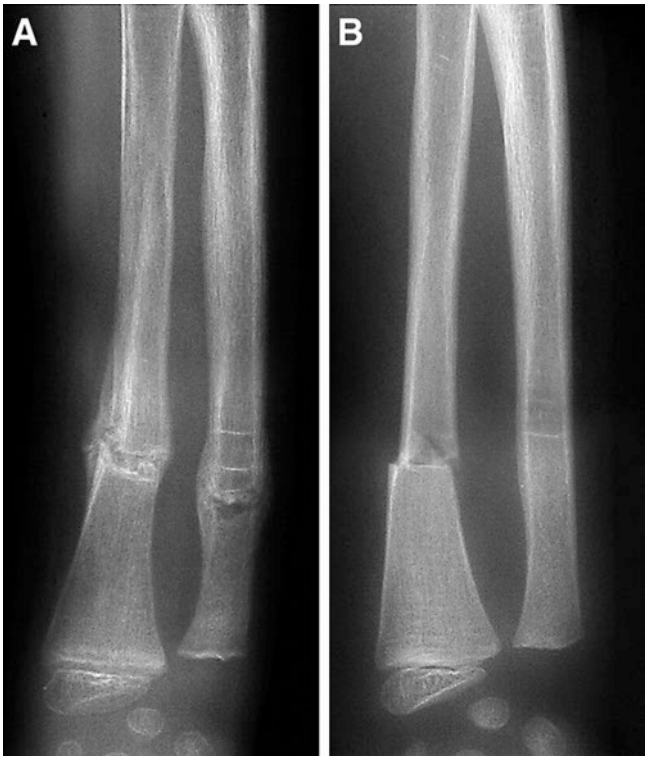

Fig. 13.2 Distal forearm radiographs of a boy with OI type IV. He had received pamidronate from 3 months to 2.2 years of age. About 3 years after treatment discontinuation, he fell on the outstretched right arm and fractured both radius and ulna close to the transverse line that was formed during the last pamidronate infusion (**a**). Four months later, a similar accident led to the fracture of the left radius at a corresponding location (**b**) (Reprinted from Rauch et al. [75]. With permission from Elsevier)

and back pain. Since VFs are often asymptomatic, the true incidence of VFs may be underestimated without routine annual lateral thoracolumbar spine x-rays.

The characteristics of patients with DMD most likely to fracture have also been refined. An estimated 25–50% of boys with DMD sustain long bone or symptomatic VF with additional patients experiencing asymptomatic VFs [64–67]. A retrospective study found that routine screening for VF from the onset of GC in DMD patients allowed detection and treatment of VF at earlier stages [45]. Correlates of future fracture in DMD include deficits in lateral distal femur BMD, a history of long bone fracture, and GC therapy for longer than 1 year [66, 67].

Primary prevention trials using BPs have been limited. One non-randomized study offered oral risedronate to boys with DMD at the time they began GC therapy. During a mean follow-up period of 3.6 years, the BP treatment appeared to be of benefit; 8% of treated subjects ($N = 36$) had vertebral fractures as compared to 35% of untreated controls [68].

Pharmacologic Agents on the Horizon

Denosumab, a monoclonal antibody to RANK ligand, has proven effective as an alternative anti-resorptive agent in adults [69]. The medication offers the advantages of subcutaneous administration and a shorter half-life than BPs. Avoiding prolonged suppression of bone turnover would be particularly valuable in younger patients facing only transient threats to bone health (such as those treated for ALL). The experience with denosumab in pediatric patients is limited to case reports. A 2-year treatment trial in OI type VI found the therapy to be associated with increased BMD, vertebral reshaping, increased mobility, and reduced fractures [70, 71]. The potential benefits must be weighed against risks associated with this drug. There have been reports of exaggerated bone resorption as the effects of denosumab wane. Marked hypercalcemia (from rapid bone turnover) has been reported in a pediatric patient [75]; an increase in vertebral fractures has been observed in postmenopausal women following discontinuation of denosumab [72, 73]. Denosumab and other novel agents like the sclerostin antibody and anti-Tgf-ß antibody remain experimental for pediatric patients [74].

Conclusions

The challenges of recognizing and treating pediatric osteoporosis are myriad. Early bone fragility can develop during the course of several genetic or acquired diseases that compromise the expected gains in bone mineral, geometry, and microarchitecture. The diagnosis of osteoporosis in teens cannot be made based on low BMD alone. Current criteria include a history of a low trauma vertebral fracture or multiple long bone fractures in combination with low BMD. Since as many as 40% of vertebral fractures are asymptomatic, it is important to consider surveillance lateral thoracolumbar spine radiographs in some high-risk patients even in the absence of back pain.

Management includes identifying and addressing all modifiable risk factors. Primary care providers (PCPs) can play a vital role in helping to identify youth with bone fragility. Clinical warning signs include frequent long bone fractures and any low trauma vertebral or femoral fracture since these are very atypical sites for fracture in children and teens. PCPs can also help to reinforce the importance of adequate nutrition and activity to foster bone health in all teens but especially those with chronic illness.

Treatment with pharmacologic agents may be appropriate for teens who meet the pediatric criteria for osteoporosis, especially if they face ongoing disease with limited potential for spontaneous recovery. Controversies surrounding the optimal drug, dose, and duration of therapy persist despite the increased use of osteoporosis drugs in pediatrics. Because of these complexities, specialists with expertise in treating younger patients should direct drug therapy. Nonetheless, primary providers can help to educate families about the ways that management for osteoporosis in

teens may differ from that in the elderly. With ongoing research, the goals are to refine drug treatment for pediatric osteoporosis and ultimately to prevent a first fracture in teens at greatest risk.

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Conclusion: A Clinical Bone Perspective

14

Sarah Pitts and Catherine M. Gordon

Vignette 1

Meghan is a healthy 13-year-old who presents for her annual physical examination. She has had normal growth and development, no chronic illnesses or hospitalizations, takes no medications, and has never sustained a fracture. Her only concern today is some acne on her forehead, for which she seeks treatment. Menarche was 4 months ago, and she has had 3 menstrual periods that were not overly heavy or prolonged. Her body mass index (BMI) is at the 60th percentile. She plays softball, exercising 4–5 days per week. She denies safety concerns or engaging in any high-risk behaviors. When asked about her diet, she says she eats a "regular" diet. Mom says Meghan is a good eater, getting a fruit or vegetable at each meal, and not eating too much "junk." When asked about dairy consumption, Meghan reports having milk with her breakfast cereal (although she does not drink what is left in the bowl), a yogurt at lunch, occasional cheese on her sandwich a few times per week, and occasional ice cream for dessert. She does not take any supplements. Her physical exam is normal.

Meghan is a healthy adolescent who would not necessarily warrant referral to a nutritionist, although some would argue that every teen would benefit from such a consultation when feasible. It is likely up to the primary care clinician to identify the dietary calcium and vitamin D deficiencies at this critical juncture for Meghan. As noted in Chap. 3, the RDA for calcium is 1300 mg/day and 600 IU/day of vitamin

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D. If a typical 8 oz. glass of milk contains 300 mg of elemental calcium and 100 IU of vitamin D, then a teen would need to drink four glasses over the day to approach his/her goal for calcium, while still being deficient in vitamin D. Many adolescents do not like milk, and some avoid dairy products all together. While there are other sources of both calcium and vitamin D, many patients, parents, and clinicians overestimate their intake of calcium and vitamin D when relying on leafy greens, nuts, or soy. Teen friendly websites such as http://youngwomenshealth.org/2013/10/17/calcium/ or http://youngmenshealthsite.org/guides/vitamin-d/ are helpful references for patients, parents, and clinicians to review the dietary content of calcium and vitamin D in various foods. Taking a minute to emphasize how important adequate calcium and vitamin D intake is for adolescents is critical, via diet or supplements.

Vignette 2

Connor is a 15-year-old football player who presents to your office with his third fracture in 3 years. At the age of 12, he broke his 5th metatarsal in a snowboarding accident. At the age of 13, he broke his "ankle" in a mountain bike accident. Today, he presents with a proximal humeral fracture after a particularly tough tackle during a game. His fractures have all healed appropriately, but his mother thinks something must be wrong with his bones given the number of fractures he has sustained.

Fractures in active adolescents with moderate to severe mechanisms of injury are common, but could his mom be right? As noted in Chap. 5, all encounters start with a good history and physical examination. Make sure the mechanism of injury resulting in fracture is clearly described. Connor's injuries were likely associated with significant force. Had he been hit by a soccer ball and broken his tibia, concern for an underlying bone quality deficit or primary connective tissue disorder would be higher. Assessing Connor's growth and pubertal trajectory gives a view into how healthy the hormonal milieu has been for his developing skeleton, as well as reflecting his nutritional status. As noted above, a dietary history is essential. What has his past medical history entailed? A history of poorly controlled asthma, necessitating frequent courses of oral glucocorticoids, would raise concern. Ask about his dental health, another marker of bone health. A full review of systems will shed light on the likelihood of an emerging concurrent chronic illness contributing to weak bones, such as celiac disease or Crohn disease. Is there a family history of multiple fractures suggesting the potential for a genetic connective tissue disorder?

Assuming his story is as basic as Meghan's, in vignette 1, you turn to his physical examination. Normal vital signs, musculature, nutritional status, and gait; white sclerae; age-appropriate Tanner staging; the absence of thyromegaly, scoliosis, pectus excavatum, and café au lait macules; and a Beighton score less than 5 are reassuring findings.

Laboratory assessments may or may not be necessary in this situation. Should he describe inadequate calcium and vitamin D intake, obtaining a serum calcium, phosphorus, parathyroid hormone, and 25-hydroxyvitamin D [25(OH)D] may be appropriate to inform treatment recommendations should he be found to have vitamin D

deficiency. Calcium and vitamin D intake are always important, but especially so as fractures are healing. Assessing for vitamin D deficiency is not recommended routinely for healthy adolescents, but for adolescents in whom you have concerns regarding bone health, such an assessment is warranted.

Vignette 3

Nicole is a 16-year-old with anorexia nervosa resulting in secondary amenorrhea, bradycardia, constipation, and cold intolerance. She was first diagnosed at the age of 14 years and has been followed by an interdisciplinary care team subsequent to a medical admission, a 2-week stay in a residential treatment program, and a 6-week intensive outpatient treatment program. At medical admission she was 74% of her goal BMI; she is now 82% of her goal. She continues to struggle with eating-disordered thoughts and behaviors. She has never fractured a bone and takes calcium and vitamin D supplements per her dietician's recommendations. Menarche was at age 13, and she had two lifetime periods before cessation of menses. Review of her growth charts show that she has not grown in height since age 13.5. On physical examination, she is thin with lanugo on her back, and her fingers are cold, but her examination is otherwise normal. Prior laboratory evaluation did not suggest any medical causes for malnutrition. Her most recent 25(OH)D level was 36 ng/mL, during the winter season. She identifies as female and would be attracted to males; never having been sexually intimate. She has been exercise limited given her low weight status, although she eagerly wants to get back to cross country, and her mother suspects she is exercising in her room regularly. Dual-energy x-ray absorptiometry (DXA) scans obtained at the age of 15 were analyzed and adjusted for a delayed bone age of 13.5 years and revealed a BMD Z-score of −1.2 at the total body less head and a Z-score of −1.7 at the spine. There is a family history of low bone density in Nicole's mother and in the maternal grandmother. Nicole's mother asks you if a repeat DXA is warranted and whether starting birth control pills would protect Nicole's bone health.

Nicole's story is far too common, and her mother's concern about Nicole's bone health is appropriate, as is described in Chaps. 3, 9, and 11. At age 15, her bone density was below normal for her age, and another year of amenorrhea and nutritional deficiency is only going to impair her bone health further. Repeating a bone age and DXA measurements to look at change over time would inform the discussion you have with Nicole and her mother about her bone health. As was reviewed in Chap. 9, combined oral contraceptive pills are not an appropriate therapeutic intervention for Nicole's bone health and would only be considered if she were to need a contraceptive agent. Should her bone density decline at this critical time when she is supposed to be gaining bone mass, transdermal estrogen with cyclic progesterone could be considered and discussed with Nicole and her mother. The critical piece to support Nicole's bone health remains weight restoration.

Given Nicole's slow weight gain and prolonged amenorrhea, exercise restriction remains in place. Frequently, parents and patients ask why such restrictions are enforced when exercise has other physiologic and psychological benefits. Patients promise they will eat more if they are allowed to reengage in the sports they love. As discussed in Chaps. 3, 9, and 10, individuals do not reap the physical benefits of exercise while malnourished, and there are higher risks for injury in amenorrheic

athletes. While it is very difficult to keep adolescents from the social and athletic activities they enjoy, as medical providers, it is our job not to collude with eating-disordered thinking. Clinicians must make their best recommendations based on the evidence at hand. There is no one weight that Nicole must be to allow her to re-engage in sports. The decision is made by her treatment team based on her history, mental health state, and ability to demonstrate that she can increase her dietary intake. Nicole must know that the only way her team can understand her nutritional and metabolic needs is if she is honest about the exercise in which she is engaging behind closed doors. The ability to return to sports is ultimately in her hands.

Vignette 4

Thomas is a 12-year-old with eosinophilic esophagitis, severe persistent asthma, seasonal allergies, and multiple food allergies including milk, soy, and tree nuts. He has been treated with high-dose chronic-inhaled glucocorticoids since he was 2 years old and has received too numerous to count courses of oral prednisone; his last 3-month course ended 1 week ago. He has failure to thrive with his weight and height curves plateauing since the age of 10 years. He is prepubertal. His 25(OH)D was 18 ng/mL most recently. He does not like to take the supplements that have been prescribed to him. He lives at home with his parents and is in the 7th grade, getting Bs and Cs. He is bullied at school by peers for his small size and he started seeing a therapist for associated anxiety. He does not engage in sports, and outdoor activities are curtailed by his asthma and allergies. He has never sustained a fracture.

Despite the lack of fracture, Thomas should be evaluated by a clinician with expertise in bone health. As reviewed in Chaps. 11 and 12, adolescents with chronic illness are at high risk for bone health complications, including asymptomatic vertebral compression fracture. Thomas has numerous bone health risk factors which put him at risk for fracture and future osteoporosis. While it may not be possible to stop, or even reduce, his chronic glucocorticoid therapy, other aspects of his care need to be addressed to optimize his bone density, including his malnutrition, vitamin D deficiency, dietary calcium deficiency, and delayed puberty. A baseline height age and bone age adjusted DXA would be warranted given these risk factors to guide future care and to follow over time to measure the success of interventions. Should his medical conditions improve, along with his growth and nutritional status, then it is possible that a repeat DXA may not be necessary in the future, but only time will tell.

Vignette 5

Felicia is a cognitively impaired, non-ambulatory 15-year-old presenting for her annual physical. Her history is significant for an hypoxic-ischemic event at birth, resulting in significant neurocognitive deficits. Her parents and nurse take excellent care of her. She sees a dietician and receives enteral feeds through a G-tube. Menarche was at age 13, and she has manageable, monthly periods. She has a seizure disorder that is well-controlled on

lamictal. Her 25(OH)D last winter was 45 ng/mL. She has baseline constipation that is well managed with twice-daily Miralax. She used to spend 30 minutes per day in a stander, but 2 months ago she sustained a femur fracture. The physical therapist reports that Felicia's leg was awkwardly trapped between the bed and her chair during a transfer. Felicia's mother worries that Felicia was abused, although she has never had concerns with that physical therapist before. DXA scans have not been obtained to date.

While non-accidental trauma should be considered in all pediatric fractures, fragility fractures are not uncommon in non-ambulatory adolescents such as Felicia (as outlined in Chap. 12). It is also not unheard of for a patient such as Felicia to not have undergone DXA until there are sequelae from bone fragility, as DXA measures obtained prior to this fracture may not have changed clinical care. At this point in time, Felicia should be referred to someone with expertise in the use of bisphosphonate, and DXA scans should be obtained.

Because of her femur orthopaedic hardware and bone fragility, the site(s) to scan must be considered. If she can be safely lifted to the scanning table, a spine scan, hip scan (contralateral to hardware), distal femur scan, and/or forearm scan could be considered. If positioning allows, the spine and contralateral hip would be ideal given robust comparative normative data with which to generate a Z-score.

The choice to initiate bisphosphonate therapy depends on clinician practice, the DXA results, and the family's interest in initiating a medication with potential adverse side effects. Some clinicians would prefer to wait until a second fracture to initiate therapy, as it is possible that such a fracture will not occur at all or for several years. However, some families are so traumatized by the experience of a fragility fracture that they opt to initiate any therapy that may offset the chances of a second occurrence. Common side effects with first infusion include low-grade fever, myalgias, and irritability typical of an acute-phase reaction. Nausea and vomiting are also possible. Such symptoms are not typically seen with subsequent infusions. Electrolyte abnormalities, including hypocalcemia and hypophosphatemia, can occur with each infusion and can be severe. Adequate intake of calcium, phosphorus, and vitamin D is essential.

Researchers continue to seek the best ways to optimize the bone health of adolescents at risk for low bone density and fracture, given the significant morbidity associated with adult osteoporosis. As outlined in this text, anabolic therapies such as teriparatide demonstrate large gains in bone mass, but risk for osteosarcoma mitigates use in younger populations. Further research in safe anabolic therapies for adolescents are warranted.

Similarly, management of the adolescent athlete with recurrent stress injuries remains a true hurdle for otherwise healthy teens. The solution may best lie in advocacy by clinicians with schools and coaches. Later school start times and opportunities to complete school work during school hours may afford teens the opportunity to obtain more sleep. An emphasis on adequate nutrition, days of rest, stretching, and cross training by coaches and health educators would support a clinician's and family's efforts to keep athletes healthy and in the game.

In this text, the science of adolescent bone health has been reviewed from a clinical perspective. More research is needed, especially in areas not elaborated on in

this compendium, including the bone health of transgender adolescents receiving cross-sex hormone therapy and/or after pubertal blockade, and in adolescents with polycystic ovary syndrome. Despite evolving evidence, there remains a great deal of "art" in the day-to-day management of each adolescent's unique bone health needs, as they sit in the greater context of their complex lives. Certain practices, such as provision of the recommend daily allowance (RDA) for calcium and vitamin D, are standard. However, which supplements to take, how to treat vitamin D deficiency for a given individual, what goal weight to achieve, how to provide hormone replacement therapy, and when to initiate bisphosphonate therapy are nuanced. Experts in the fields of endocrinology, adolescent medicine, rheumatology, nephrology, sports medicine, and orthopedics, all fields which include a focus on bone and mineral metabolism, can serve as important resources and as potential referrals.

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