Bone Health in Adolescents with Chronic Disease

11

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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].

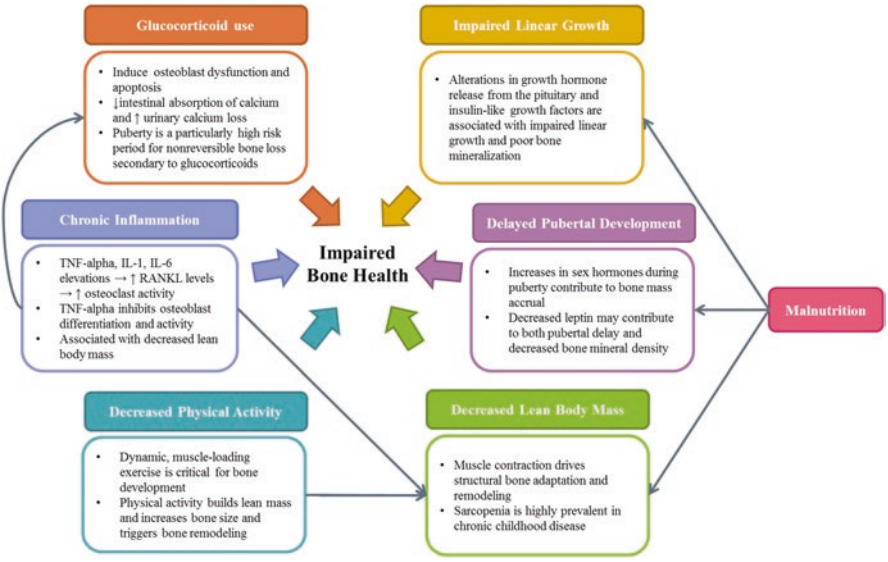

Fig. 11.1 Risk factors for impaired bone health in adolescents with chronic disease

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

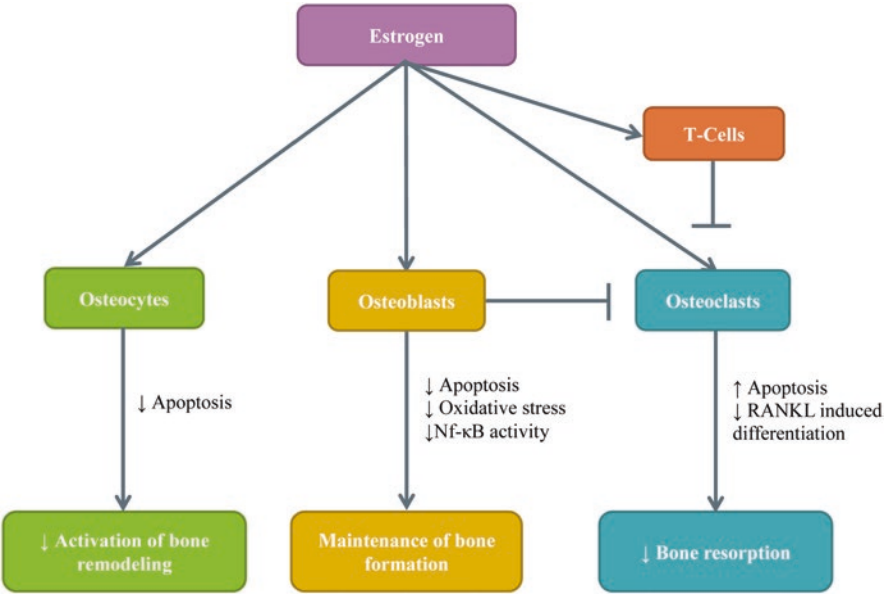

Fig. 11.2 Estrogen's impact on bone homeostasis

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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