HHS Public Access

Author manuscript

Endocrinol Metab Clin North Am. Author manuscript; available in PMC 2017 January 30.

Published in final edited form as:

Endocrinol Metab Clin North Am. 2016 June ; 45(2): 433–441. doi:10.1016/j.ecl.2016.01.009.

Update on Bone Health in Pediatric Chronic Disease

Kristen M. Williams, MD

Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY 10029, USA, Kristen.williams@mountsinai.org

Keywords

Pediatric; Chronic disease; Osteoporosis; Bone mineral density; DXA

INTRODUCTION

In recent years, there has been greater focus on both short-term and long term consequences of childhood chronic disease on bone health. Pediatric disorders, along with their associated comorbidities and treatment modalities, are known to have a multifactorial effect on bone development. Bone strength, the product of bone quality and mineralization, is largely determined by the maximum bone mass achieved during childhood and adolescence.[1] There are a multitude of hormones and other intrinsic factors involved in bone modeling and remodeling, and adequate growth relies on optimal vitamin D levels, nutritional status, and exercise. Inadequate nutrition and physical activity along with chronic inflammation and illness can lead to compromised peak bone mass and accelerated bone loss and ultimately result in an increased risk for osteoporosis and fracture.[2] In the past, low bone mineral density (BMD) was a condition primarily seen in adults. With increased prevalence and detection of decreased bone mineralization in children and adolescents, it is thought that adult bone disease may originate in these earlier years. Furthermore, there is a lack of prospective data evaluating the relationship between bone density and fracture incidence in children with chronic illness[2] that may persist into adulthood, causing significant impairment in quality of life.

There are many pediatric diseases that are complicated by impaired bone health. The focus of this report is to highlight bone health assessment and management, focusing on 3 common pediatric disorders frequently evaluated by pediatricians and pediatric endocrinologists: Cystic Fibrosis (CF), Celiac Disease (CD), Type 1 diabetes mellitus (T1DM).

OVERVIEW OF BONE HEALTH

Skeletal development starts in the developing fetus with condensation of mesenchyme into cartilage that is eventually replaced with bone.[3] Bone modeling, or the formation that occurs

The author has nothing to disclose.

during childhood and adolescence,[4] is affected not only by genetics but also by gender, hormonal factors, nutritional and vitamin D status, and weight-bearing exercise. Remodeling, as defined by osteoclast-mediated resorption of old bone and osteoblast-mediated formation, occurs in young adulthood and beyond. This is further regulated by the interaction of the receptor activator of nuclear factor κB (RANK)–RANK ligand (RANKL)–osteoprotegerin (OPG) system (pathway involved in maintaining the balance of RANKL and osteoclast-mediated bone resorption and OPG and osteoblast-mediated bone formation). Modeling and remodeling are also under the influence of other hormones and cytokines, such as parathyroid hormone and tumor necrosis factor (TNF)-α.[5] Overall, increased bone density occurs when formation exceeds resorption. Peak bone mass is achieved by the early 20s and, if compromised, can increase the risk of osteoporosis and fracture in adulthood.[4]

CHRONIC DISEASE AND BONE HEALTH

Chronic diseases, their treatments, and resulting comorbidities are all associated with diminished bone mineral accrual and possible bone loss.[3,4] There are many pediatric disorders that are associated with impaired bone health (Table 1).[4] Children who are affected by these disorders are at risk of low BMD and possible fracture due to malabsorption, pancreatic insufficiency, reduced weight-bearing physical activity, delayed puberty, hypogonadism, and chronic inflammation. Low vitamin D levels, the result of decreased body mass index (BMI), malabsorption, and side effects of medications, can result in nutritional rickets and low bone mineralization.[1] The functional bone-muscle unit is also affected by disease. Muscle mass and strength increase during growth and puberty, leading to an increased mechanical load on the bone. This results in a positive change in both dimension and strength of bone. The ability of bone to respond to such change is greatest during childhood.[6] In patients in whom lean muscle mass is negatively affected, either due to poor mobility, delay in puberty, or steroid exposure, bone growth is further impacted.[2] Prolonged inflammation exacerbates bone loss. Inflammatory markers, such as TNF-α, interleukin (IL)-1, and IL-6, alter bone modeling and remodeling by inhibition of osteoblast differentiation, impaired collagen synthesis, and promotion of osteoclastogenesis,[5,7] leading to an imbalance favoring resorption. Glucocorticoid use is also associated with decreased BMD[8] and increased fracture risk occurs in those children receiving more than 4 courses or more than 90 days of steroid treatment in a year.[5] Inflammation that is present in diseases that require steroid treatments may be a confounder in determining the risk of bone impairment. Nevertheless, studies show that glucocorticoid use itself leads to increased bone resorption via augmentation of the effects of RANKL, decreased OPG function, inhibition of osteoclast apoptosis, and reduced osteoblast number and function.[7] Glucocorticoids can also affect muscle breakdown, the growth hormone–insulinlike growth factor (IGF)-1 axis, and gonadotropin levels,[7] having a cumulative effect of bone resorption.

MEASUREMENT OF BONE DENSITY

Although there are different modalities to assess bone mineralization in children, the ultimate goal is to identify patients who may be at risk for fracture. Despite the availability and safety of some of these imaging modalities, it has become apparent that interpretation of bone mineralization in the growing child or adolescent can be challenging.[2] DXA is used to

assess bone mineral content (BMC) and areal BMD. It is the most common imaging method used due to its availability, cost-effectiveness, speed, and safety.[2] In pediatric patients, evaluation of the spine and total body minus head are preferred sites to the hip because change in geometry can have an impact on DXA interpretation. Low BMD in children is defined by a DXA outcome *z* score of less than − 2.0 SDs after adjusting for age, gender, and body size.[2] Osteoporosis is defined in children or adolescents as low BMD along with clinically significant fracture (ie, long bone, vertebral compression, or 2 or more upper extremity long bone fractures).[9] Underestimation of BMD and inconsistent results are common, particularly in those children with chronic illness.[4] Recently expanded reference data for pediatric DXA outcomes in evaluation of BMD of children may not be applicable to those with chronic illness.[10] Children with chronic illness can have low bone area for height (narrow bones), short stature, growth delay, and decreased lean muscle mass,[5,6,11] which may confound BMC and BMD measurements. Many studies do not address or adjust DXA results for height, particularly when evaluating the lumbar spine, and as a result may overestimate the prevalence of low BMD in certain disorders. When assessing children with or without chronic illness, DXA results should be adjusted for age, gender, height, pubertal status or bone age, and weight when possible. DXA outcome measures may be more accurate in determining true bone deficits after adjusting for lean mass as well, because reduced bone mass may represent a compensatory response to reduced muscle mass.[6]

Fracture risk assessment as related to DXA is generally performed in patients that are otherwise healthy.[2] The use of DXA to predict fracture is limited in pediatric patients[4,9,12] and fragility fractures have occurred in the presence[2] and absence of low BMD.[9,11] Nevertheless, there are studies demonstrating an inverse relationship between DXA BMD and fracture history supporting use of DXA screening in certain pediatric disorders.[11]

Other imaging modalities available for the evaluation of bone include CT and ultrasound. Quantitative CT is used to assess volumetric bone density. Although this method is less affected by bone size and overlying adipose tissue to estimate bone strength, its use is prohibited not only by higher radiation doses but increased costs compared with DXA. Quantitative ultrasound is also becoming more available and readily studied[4] because it is radiation free and noninvasive. Both lack sufficient reference data for children and adolescence and, therefore, are used primarily for research.

PEDIATRIC BONE HEALTH: CYSTIC FIBROSIS

CF is an autosomal recessive disorder involving mutations of the CF transmembrane conductance regulator (CFTR) gene, leading to accumulated viscous secretions and multiorgan damage.[13] Because the median age of survival in patients with CF is now closer to 40 years,[13,14] there has been an increase in prevalence of multiple comorbidities, including CF-related bone disease (CFBD). Known risk factors for CFBD include poor nutrition, chronic lung infection and inflammation, pancreatic insufficiency, delayed puberty, decreased physical activity, and medications, including glucocorticoids and transplant-related therapies.[15,16] The presence of impaired glucose metabolism in CF-related diabetes and possible direct effect of the CFTR on osteoclast activation[12,13] may also be responsible for the bone disease reported in both children and adults.

Low bone mass is reported in up to 38% of adult patients with CF and is associated with severity of systemic and lung disease as well as a history of malnutrition.[14–16] To date, there are no long-term studies evaluating fracture risk as related to BMD, and reports on overall BMD outcomes in children and adolescents with CF are conflicting. BMD *z* scores in adolescents are associated with low BMI and vitamin D levels, worsened disease severity scores,[14,17] and frequency of antibiotic treatments.[10] Much of the variance in BMD outcomes may be further explained by the change in forced expiratory volume in one second (FEV_1) scores.[14,16] Sands and colleagues[17] also reported on BMD scores as normal in 51% of children, moderately low in 32% of children, and low (as defined by a *z* score < −2.02) in 17% of children. These results are supported by similar studies with 9% to 27% of children having low BMD; however, other reports have demonstrated normal mineralization when BMD was corrected for body size.[17] BMD as evaluated by DXA has also not improved in the last decade, despite reduction in disease severity and advancements in other modifiable bone risk factors.[15]

Vitamin D deficiency, another known risk factor in CFBD, leads to decreased intestinal absorption of calcium and secondary hyperparathyroidism,[18] worsening the risk for increased resorption and bone fragility. Despite conflicting data on the optimal cutoff level for vitamin D,[10] low vitamin D levels are found in 48% to 95% of patients,[14,17] and daily treatment may depend on severity of disease and level of pancreatic insufficiency.

Prevalence of vertebral fractures has been reported as high as 30% in adults with CF.[12,13,18] There are few data with respect to the risk of fracture and DXA outcomes in children despite the associated comorbidities accompanying these fractures. Incidence of fracture is much less in children compared with adults[19]; however, there is still a significant increase compared with healthy controls.[16] Vertebral fractures, in particular, may worsen lung volumes, have an impact on chest physiotherapy, and can be a contraindication to transplantation.[16,17]

Routine screening DXA (with correction of height and lean mass for height[19]) is recommended in adults greater than 18 years and in children greater than 8 years if ideal body weight is less than the 90th percentile, FEV_1 is less than 50% predicted, if the patient has delayed puberty or has received high-dose glucocorticoid treatment for more than 90 days per year.[16] Follow-up assessment should be based on initial DXA outcomes, including repeat evaluation every 5 years if BMD *z* scores are greater than −1, every 2 years if *z* scores are between −2 and −1, or yearly if *z* scores are less than −2.0.[10] There are no specific guidelines to routinely check bone turnover markers; however, 25-hydroxyvitamin D levels should be checked yearly, preferably at the end of winter and after any treatment change.[20]

PEDIATRIC BONE HEALTH: CELIAC DISEASE

CD is an autoimmune-mediated disorder in genetically predisposed individuals who are exposed to gluten,[21] leading to malabsorption. Complications of unrecognized or untreated CD include anemia, poor growth and delayed puberty.[22–24] Bone disease, including pain, osteoporosis, and fractures, is also seen in patients with untreated CD.[21,25] Low BMD is the result of malabsorption, hypogonadism, and inflammation.[23,24] An abnormal RANKL/OPG

ratio, favoring bone resorption, has also been described in adult patients with CD.[23–25] Low BMD has been described at diagnosis[21,25] and may persist in up to two-thirds of patients into adulthood.[26] In 1 study, 22% of children with CD had BMD *z* scores between −2 and −1 and up to 13% had BMD *z* scores less than −2.[23] Jatla and colleagues[27] reported low BMC for both spine and whole body in children evaluated within 1 month of CD diagnosis compared with healthy controls. A significant difference between both groups persisted only in whole-body assessment after adjusting for height. Mora and colleagues[22] found significantly lower BMC in whole body but also lower BMD in CD children at both spine and whole body after adjusting for body size.

Lower BMD has been associated with higher tissue transglutaminase antibody levels.[26] There is concern that persistent bone disease may reflect chronic subclinical disease in childhood and subsequent failure to achieve peak bone mass.[26] It is unclear if disease severity, as defined by biopsy grade or reported symptoms, may be related to BMD outcomes.[23] Maintaining a gluten-free diet is the mainstay of treatment of CD and although Hartman and colleagues[21] found no significant difference in DXA outcome data comparing children who were and were not compliant with the diet, quantitative ultrasound results at the tibia demonstrated worsening *z* scores in the latter group. Fracture risk in patients with CD is variable. Some studies report no increased fracture rates.[24] Jatla and colleagues[27] reported hazard ratios in adult patients ranging from 1.3 (overall fracture) to 1.9 for the hip. Fracture, particularly of the hip, is extremely rare in children.

Currently, there are no consistent guidelines regarding when or with what frequency to assess BMD via DXA with newly diagnosed CD or in those with subclinical disease.[24,26,28,29] Frouda and colleagues[24] as well as the International Society for Clinical Densitometry (ISCD)[11] recommend not evaluating BMD if children are compliant with the diet because data support full recovery. Guidelines from the United Kingdom, however, recommend testing in all patients at time of diagnosis[29] whereas others restrict assessment to those who are not adherent to the diet or have lower BMI, history of irregular menses, anemia, or other risk factors for fracture.[30]

When DXA is used, the ISCD recommends evaluating both spine and whole body to assess BMC. Jatla and colleagues[27] have recommended assessing BMC instead of BMD because altered growth and body composition may have an impact on results. Furthermore, whole-body DXA assessment is recommended to avoid missing affected children during screening.

PEDIATRIC BONE HEALTH: TYPE 1 DIABETES MELLITUS

T1DM is an autoimmune condition of absolute insulin deficiency with increasing prevalence worldwide. There are multiple known complications associated with T1DM, with a recent focus on evaluation and management of bone disease. Patients with T1DM have reduced bone mineralization, smaller bone size, and increased fracture rates.[31] Hyperglycemia; impaired function of growth factors, including insulin, growth hormone, and IGF-1; younger age at onset; decreased lean muscle mass; and poor glycemic control are known risk factors for bone disease in diabetes.[31] Compared with the disorders discussed previously, decreased bone formation contributes to impaired bone health more than increased bone resorption.[32]

Decreased levels of osteocalcin, a product of osteoblasts and marker of bone formation, are found in patients with diabetes. With improvement in hemoglobin A_{1c}, these levels may normalize.[33] Insulin binds to its receptor on osteoblasts, inhibiting the production of OPG and promoting resorption.[11] In the absence of insulin, there are increased levels of OPG and decreased RANKL.[32–35] Underlying microvasculopathy, decreased vitamin D levels, inflammation, and increased levels of advanced glycation end products further contribute to impaired bone health.[28,32]

Adults with T1DM have normal to decreased BMD,[4,28,36] with up to 20% of patients over the age of 20 reported as having osteoporosis.[28] Decreased BMD has been reported at the hip and lower BMD in the spine compared with controls.[33] It is unclear how early these changes may be occurring because there are conflicting data in adolescents with respect to BMD[4,33,36] and there are no long-term studies assessing change in BMD over time.[33] In adolescents, BMD outcome scores have been associated with IGF-1 levels and degree of glycemic control.[28] It is known that adults have significantly increased fracture risk[35,37] that is associated with disease duration.[38] Khan and Fraser[33] found a relative risk of hip fracture of 6.94, with other reports ranging from 3.7 to 12 times the risk compared with healthy controls.[28,32,39] Diabetes-related comorbidities, including retinopathy and nephropathy, are also associated with a 10-times increased risk of fracture in patients with T1DM.[33] Although there have been no reports of increased fracture in children with T1DM,[11] prolonged poor metabolic control and potential for metabolic bone disease in those patients with coexisting CD warrants continued monitoring and preventative measures to reduce fracture risk in the future.

At this time, the ISCD does not recommend routine DXA or other imaging as a screening measure in pediatric patients with T1DM.[11] In those patients with specific risk factors, including but not limited to low BMI, increased daily insulin dose, poor renal function, and fracture history, evaluation with DXA may be considered. Nevertheless in patients with T1DM, fractures may be seen even if the setting of normal BMD.[31]

TREATMENT OF PEDIATRIC BONE DISEASE

The primary goals of managing pediatric bone disease associated with chronic disease focus on preventative strategies to support sufficient bone mineral accrual and limit factors that promote increased resorption. Treating the underlying disorder can help normalize bone mineralization early on in diagnosis. In CD, adhering to a gluten-free diet has been associated with complete recovery of decreased BMD within the first 12 months of treatment.[21,23,25–27] Although there are few long-term studies to evaluate BMD in those on a gluten-free diet,[22] normalization of BMD as many as 8 years postdiagnosis has been described.[25] The question remains as to why 30% of adult patients with CD have osteoporosis[40] or fail to recover lower BMD after diagnosis and change in diet.[24] Optimizing insulin doses in patients with T1DM to improve glycemic control and limit microvascular and inflammatory disease is also expected to at least partially reverse any bone deficits. All patients should be encouraged to participate in regular weight-bearing exercise because there is a known positive correlation between BMD and lean muscle mass.[19] Nutrition should be optimized, including vitamin K intake in patients with CF.

Supplementation with vitamin D to replete to a goal of 30 ng/mL is recommended for all patients at risk for bone impairment. Those patients with malabsorption may need 2 to 3 times the recommended dosing for age. In CF, vitamin D_3 is preferred exclusively over vitamin D_2,[16,18,20] and guidelines for a replacement dosing schedule exist for age and degree of vitamin D deficiency.[17,20] Finally, use of bisphosphonate therapy has been studied in adult patients with T1DM, CF, or CD. There is some evidence for potential benefit in patients with CF and antiresorptive agents may be recommended if there is prolonged glucocorticoid use, fracture history, or low BMD after transplant.[10] In CD, antiresorptive therapy has been reserved for postmenopausal adults. Finally, there is concern that these agents may have limited benefit in patients with T1DM, because there may already be a significant lack of bone resorption. Overall, prevention, early recognition, and treatment are required to help minimize adverse outcomes of poor bone health in chronic illness.

SUMMARY

Children with chronic disease are at risk early on for poor bone health, particularly in the conditions discussed previously. Alterations in bone remodeling as influenced by specific complications of each disorder result in decreased bone quality and strength and possible increased fracture risk. Future research in this area is needed to further identify modifiable risk factors and treatment options to allow for optimization of bone mineral accrual and decrease lifelong incidence of fracture.

REFERENCES

1. Saggese G, Vierucci F, Boot AM, et al. Vitamin D in childhood and adolescence: an expert position statement. Eur J Pediatr. 2015; 174(5):565–576. [PubMed: 25833762]
2. Crabtree NJ, Arabi A, Bachrach LK, et al. Dual-energy X-ray absorptiometry interpretation and reporting in children and adolescents: the revised 2013 ISCD Pediatric Official Positions. J Clin Densitom. 2014; 17(2):225–242. [PubMed: 24690232]
3. Gilbert, SF. Developmental biology. 6th. Sunderland (MA): Sinauer Associates; 2000. Osteogenesis: the development of bones. Available at: http://www.ncbi.nlm.nih.gov/books/NBK10056/
4. Langman CB. Osteoporosis in children and adolescents. Osteoporosis Clinical Updates. 2010 [Accessed January 14, 2016] Available at: http://nof.org.
5. Leonard MB. Glucocorticoid-induced osteoporosis in children: impact of the underlying disease. Pediatrics. 2007; 119(Suppl 2):S166–S174. [PubMed: 17332238]
6. Lee DY, Wetzsteon RJ, Zemel BS, et al. Muscle torque relative to cross-sectional area and the functional muscle-bone unit in children and adolescents with chronic disease. J Bone Miner Res. 2015; 30(3):575–583. [PubMed: 25264231]
7. von Scheven E, Corbin KJ, Stagi S, et al. Glucocorticoid-associated osteoporosis in chronic inflammatory diseases: epidemiology, mechanisms, diagnosis, and treatment. Curr Osteoporos Rep. 2014; 12(3):289–299. [PubMed: 25001898]
8. Acott PD, Wong JA, Lang BA, et al. Pamidronate treatment of pediatric fracture patients on chronic steroid therapy. Pediatr Nephrol. 2005; 20(3):368–373. [PubMed: 15690187]
9. Bishop N, Arundel P, Clark E, et al. Fracture prediction and the definition of osteoporosis in children and adolescents: the ISCD 2013 Pediatric Official Positions. J Clin Densitom. 2014; 17(2): 275–280. [PubMed: 24631254]
10. Sermet-Gaudelus I, Bianchi ML, Garabédian M, et al. European cystic fibrosis bone mineralisation guidelines. J Cyst Fibros. 2011; 10(Suppl 2):S16–S23. [PubMed: 21658635]

11. Bianchi ML, Leonard MB, Bechtold S, et al. Bone health in children and adolescents with chronic diseases that may affect the skeleton: the 2013 ISCD Pediatric Official Positions. J Clin Densitom. 2014; 17(2):281–294. [PubMed: 24656723]
12. Putman MS, Milliren CE, Derrico N, et al. Compromised bone microarchitecture and estimated bone strength in young adults with cystic fibrosis. J Clin Endocrinol Metab. 2014; 99(9):3399–3407. [PubMed: 24926955]
13. Siwamogsatham O, Alvarez JA, Tangpricha V. Diagnosis and treatment of endocrine comorbidities in patients with cystic fibrosis. Curr Opin Endocrinol Diabetes Obes. 2014; 21(5):422–429. [PubMed: 25105995]
14. Sheikh S, Gemma S, Patel A. Factors associated with low bone mineral density in patients with cystic fibrosis. J Bone Miner Metab. 2015; 33(2):180–185. [PubMed: 24633535]
15. Putman MS, Baker JF, Uluer A, et al. Trends in bone mineral density in young adults with cystic fibrosis over a 15 year period. J Cyst Fibros. 2015; 14(4):526–532. [PubMed: 25698451]
16. Aris RM, Merkel PA, Bachrach LK, et al. Guide to bone health and disease in cystic fibrosis. J Clin Endocrinol Metab. 2005; 90(3):1888–1896. [PubMed: 15613415]
17. Sands D, Mielus M, Umławska W, et al. Evaluation of factors related to bone disease in Polish children and adolescents with cystic fibrosis. Adv Med Sci. 2015; 60(2):315–320. [PubMed: 26183540]
18. Simoneau T, Sawicki GS, Milliren CE, et al. A randomized controlled trial of vitamin D replacement strategies in pediatric CF patients. J Cyst Fibros. 2015 [Epub ahead of print].
19. Brookes DS, Briody JN, Munns CF, et al. Cystic fibrosis-related bone disease explored using a four step algorithm. J Cyst Fibros. 2015; 14(1):127–134. [PubMed: 25169790]
20. Tangpricha V, Kelly A, Stephenson A, et al. An update on the screening, diagnosis, management, and treatment of vitamin D deficiency in individuals with cystic fibrosis: evidence based recommendations from the cystic fibrosis foundation. J Clin Endocrinol Metab. 2012; 97(4):1082–1093. [PubMed: 22399505]
21. Hartman C, Hino B, Lerner A, et al. Bone quantitative ultrasound and bone mineral density in children with celiac disease. J Pediatr Gastroenterol Nutr. 2004; 39(5):504–510. [PubMed: 15572890]
22. Mora S, Barera G, Beccio S, et al. A prospective, longitudinal study of the long-term effect of treatment on bone density in children with celiac disease. J Pediatr. 2001; 139(4):516–521. [PubMed: 11598597]
23. Trovato CM, Albanese CV, Leoni S, et al. Lack of clinical predictors for low mineral density in children with celiac disease. J Pediatr Gastroenterol Nutr. 2014; 59(6):799–802. [PubMed: 25162363]
24. Fouda MA, Khan AA, Sultan MS, et al. Evaluation and management of skeletal health in celiac disease: position statement. Can J Gastroenterol. 2012; 26(11):819–829. [PubMed: 23166906]
25. Mora S. Celiac disease in children: impact on bone health. Rev Endocr Metab Disord. 2008; 9(2):123–130. [PubMed: 18247120]
26. Jansen MA, Kiefte-de Jong JC, Gaillard R, et al. Growth trajectories and bone mineral density in anti-tissue transglutaminase antibody-positive children: the Generation R Study. Clin Gastroenterol Hepatol. 2015; 13(5):913.e915–920.e915. [PubMed: 25245626]
27. Jatla M, Zemel BS, Bierly P, et al. Bone mineral content deficits of the spine and whole body in children at time of diagnosis with celiac disease. J Pediatr Gastroenterol Nutr. 2009; 48(2):175–180. [PubMed: 19179879]
28. Simmons KM, McFann K, Taki I, et al. Reduced bone mineral density is associated with celiac disease autoimmunity in children with type 1 diabetes. J Pediatr. 2015; 169:44.e1–48.e1. [PubMed: 26561381]
29. Scott E, Gayood I, Scott B. Guidelines for osteoporosis in coeliac disease and inflammatory bowel disease. Gut. 2000; 46(Suppl 1):I1–I8. [PubMed: 10647595]
30. Compston J. Is fracture risk increased in patients with coeliac disease? Gut. 2003; 52:459–460. [PubMed: 12631649]
31. Zhukouskaya VV, Eller-Vainicher C, Shepelkevich AP, et al. Bone health in type 1 diabetes: focus on evaluation and treatment in clinical practice. J Commun Inq. 2015; 38:941–950.

32. Abdalrahaman N, McComb C, Foster JE, et al. Deficits in trabecular bone microarchitecture in young women with type 1 diabetes. J Back Musculoskeletal Rehabil. 2015; 30(8):1386–1393.
33. Khan TS, Fraser LA. Type 1 diabetes and osteoporosis: from molecular pathways to bone phenotype. J Osteoporos. 2015; 2015:174186. [PubMed: 25874154]
34. Neuman T, Lodes S, Kastner B, et al. Osteocalcin, adipokines and their associations with glucose metabolism in type 1 diabetes. Bone. 2016; 82:50–55. [PubMed: 25888930]
35. Starup-Linde J, Vestergaard P. Diabetes and osteoporosis: cause for concern? Eur J Endocrinol. 2015; 173:R93–R99. [PubMed: 26243638]
36. Ingberg CM, Palmer M, Aman J, et al. Body composition and bone mineral density in long-standing type 1 diabetes. J Intern Med. 2004; 255:392–398. [PubMed: 14871464]
37. Farlay D, Armas LAG, Gineyts E, et al. Nonenzymatic glycation and degree of mineralization are higher in bone from fracture patients with type 1 diabetes. J Bone Miner Res. 2016; 31(1):190–195. [PubMed: 26234180]
38. Hough S. Mechanism and evaluation of bone fragility in type 1 diabetes mellitus. Eur J Endocrinol. 2015 [Epub ahead of print].
39. Shah VN, Shah CS, Snell-Bergeon JK. Type 1 diabetes and risk of fracture: meta analysis and review of the literature. Diabet Med. 2015; 32:1134–1142. [PubMed: 26096918]
40. Turner J, Pellerin G, Mager D. Prevalence of metabolic bone disease in children with celiac disease is independent of symptoms at diagnosis. J Pediatr Gastroenterol Nutr. 2009; 49(5):589–593. [PubMed: 19644400]

KEY POINTS

- Chronic illness is associated with impaired bone health due to decreased bone mineral accrual and increased resorption.
- Common pediatrics disorders, including celiac disease (CD), type 1 diabetes mellitus (T1DM), and cystic fibrosis (CF), have associated low bone mineral density (BMD) and significant fracture risk in adolescence and adulthood.
- The risk of low bone accrual can be attributed to malabsorption.
- Dual-energy x-ray absorptiometry (DXA) when adjusted for body size, is the preferred imaging modality in pediatrics to assess risk of bone fragility; however, fractures have been observed in absence of low mineralization.
- Treatment strategies for poor bone health include optimizing nutrition and vitamin intake, increased weight-bearing exercise, and treating the underlying disorder to prevent further bone impairment.

Table 1

Pediatric disorders associated with bone disease

Endocrine	Growth hormone deficiency Hypogonadism Type 1 Diabetes Mellitus
Gastrointestinal/nutritional	Anorexia Celiac Disease Inflammatory bowel disease Liver disease
Hematology/oncology	Neoplasm Sickle cell disease Thalassemia Transplant – solid organ and bone marrow
Pulmonary	Asthma Cystic Fibrosis
Other	Chronic kidney disease Neuromuscular disorders Primary bone disease Seizure disorders