Current Osteoporosis Reports (2019) 17:324–332
https://doi.org/10.1007/s11914-019-00529-7

THERAPEUTICS AND MEDICAL MANAGEMENT (S JAN DE BEUR AND B CLARKE, SECTION EDITORS)

When Low Bone Mineral Density and Fractures Is Not Osteoporosis

Smita Jha[1,2] · Marquis Chapman[3] · Kelly Roszko[4]

Published online: 29 August 2019

Abstract
Purpose of Review To review the differential diagnosis of low bone mineral density (BMD).
Recent Findings Osteoporosis is the most common cause of low BMD in adults; however, non-osteoporotic causes of low BMD should be considered in the differential diagnosis of patients with low BMD. Mild osteogenesis imperfecta, osteomalacia, and mineral and bone disorder of chronic kidney disease as well as several other rare diseases can be characterized by low BMD.
Summary This review summarizes the differential diagnosis of low BMD. It is important to differentiate osteoporosis from other causes of low BMD since treatment regimens can vary tremendously between these different disease processes. In fact, some treatments for osteoporosis could worsen or exacerbate the mineral abnormalities in other causes of low BMD.

Keywords Osteomalacia · Osteogenesis imperfecta · Rare diseases · CKD-MBD, DXA · Neurofibromatosis

Introduction

The International Society For Clinical Densitometry (ISCD) recommends testing for bone mineral density (BMD) using dual-energy x-ray absorptiometry (DXA) in all women aged 65 and older, younger post-menopausal women, and during menopausal transition in those with risk factors, men aged 70 and older, younger men with risk factors, and in all adults with history of fragility fracture or condition associated with low bone mass. Osteoporosis is the most common cause of low bone mass.

This article is part of the Topical Collection on *Therapeutics and Medical Management*

✉ Smita Jha
smita.jha@nih.gov

[1] Clinical and Investigative Orthopedics Surgery Unit, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, USA

[2] Section on Congenital Disorders, National Institutes of Health Clinical Center, 10 Center Drive, Bldg. 10-C RC, Room 1-5362, MSC-1504, Bethesda, MD 20892, USA

[3] National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD 20892, USA

[4] National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD 20892, USA

The World Health Organization (WHO) defines osteoporosis in post-menopausal white women without a previous history of fragility fracture as a bone mineral density (BMD) T-score at the spine, hip, or forearm of − 2.5 or less [1]. While originally described to include only post-menopausal white women, the WHO definition of osteoporosis has been extrapolated to include men older than age 50 [2]. The definition of osteoporosis in premenopausal women and men younger than age 50 in the absence of fragility fracture(s) is not well-established but is considered in patients with BMD Z-score ≤ − 2.0 [3]. However, as clinicians, we need to remember that diagnosis of the underlying medical condition is not simply based on the results of a diagnostic test but the complete clinical presentation. In practice, we not so uncommonly encounter patients who have a BMD measurement that meets the definition of osteoporosis, but an alternate diagnosis better describes the patient's condition. The aim of this paper is to review the differential diagnosis of low bone mineral density (Table 1). We do not intend to review the causes of secondary osteoporosis such as hypogonadism, Cushing's syndrome, nutritional disorders, drugs, and steroid-induced osteoporosis in this paper.

Osteomalacia

Reduced bone mineral density is characteristic of osteomalacia, although not necessary for diagnosis [4, 5]. It is crucial to

differentiate low bone density due to osteomalacia from that due to osteoporosis as the treatment regimens differ greatly. Treatment of osteomalacia varies based on the underlying cause. While we will not review treatment strategies here, it is important to note that bisphosphonates, denosumab, teriparatide, and other medications for osteoporosis are not appropriate treatments for osteomalacia, and in some cases, could exacerbate the underlying abnormalities of mineral homeostasis.

Osteomalacia is a disorder in which newly formed osteoid at the site of bone turnover is not properly mineralized. It can occur in adults or children, whereas rickets, the defective mineralization of cartilage in the epiphyseal growth plates, occurs only in children who have open growth plates [6]. Osteomalacia can be the result of an inherited genetic disease or an acquired disease. One main mechanism of osteomalacia is hypophosphatemia [7], typically due to loss of phosphate in the urine. In this section, we will group causes of osteomalacia into those mediated by parathyroid hormone (PTH) such as vitamin D deficiency; those mediated by fibroblast growth factor 23 (FGF23) such as X-linked hypophosphatemic rickets (XLH), autosomal dominant hypophosphatemic rickets (ADHR), and autosomal recessive hypophosphatemic rickets (ARHR); or those driven by renal-dependent loss of phosphate such as hereditary hypophosphatemic rickets with hypercalciuria (HHRH) or Fanconi syndrome [7]. (Table 2)

Presentation and Diagnosis

Osteomalacia can be asymptomatic or patients can present with symptoms such as bone pain, muscle weakness, fractures, and impaired gait [4, 8]. Patients may present with low bone mineral density on DXA, but it is important to note that the presentation on DXA can be extremely variable. For instance, BMD of the lumbar spine can even be higher in XLH patients as compared to age- and sex-matched controls [9, 10].

The diagnosis of osteomalacia is typically based on clinical symptoms and findings on laboratory and radiologic studies. While bone biopsy after double tetracycline labeling is the best diagnostic tool to confirm osteomalacia, this invasive procedure is rarely necessary.

Laboratory findings of osteomalacia are dependent on the underlying cause of the disease. Some common findings include elevated alkaline phosphatase, fibroblast growth factor 23 (FGF23), and parathyroid hormone and decreased serum calcium and phosphorous [4]. The most common radiological findings are reduced BMD with a thin cortex. Vertebral bodies can soften, leading to large, biconvex vertebral disks and concave vertebral bodies called codfish vertebrae. Looser zones refer to lucent lines 2–5 mm in width which form perpendicular to the cortex and can be bilateral. In diagnostically challenging cases, bone biopsy can be performed. On bone biopsy after double tetracycline labeling, osteomalacia is characterized by osteoid thickness > 12.5 μm and a mineralization lag time of > 100 days [11].

PTH-Dependent Osteomalacia

The most common cause of osteomalacia is vitamin D deficiency [12], specifically vitamin D deficiency due to dietary insufficiency and/or lack of sun exposure. Malabsorption, such as post-gastric bypass surgery or celiac sprue, is an important cause of vitamin deficiencies. Vitamin D is synthesized in the skin after exposure to sunlight (vitamin D3) or ingested as vitamin D2 or D3. Because of the risk of vitamin D deficiency and nutritional rickets, vitamin D supplementation is recommended for all infants until age 12 months [13]. Adequate vitamin D intake is also necessary for adults by either diet or supplementation. Vitamin D is 25-hydroxylated in the liver and 1,25-hydroxylated in the kidney to form the active metabolite, 1,25-$(OH)_2$-vitamin D_3, or calcitriol. Disorders of vitamin D metabolism include impaired 25-hydroxylation or 1,25-dihydroxylation of vitamin D into its active form due to liver or kidney illness respectively and insensitivity to vitamin D due to hereditary diseases. Lack of 1,25-$(OH)_2$-vitamin D_3 results in a decreased ability to absorb calcium and phosphate, which can lead to secondary hyperparathyroidism. PTH action in the kidney at the PTH-receptor leads to endocytosis of the renal phosphate transporter NPT2a, and thus, loss of phosphate in the urine [14].

FGF23-Mediated Osteomalacia

FGF23 is a hormone which promotes phosphate excretion. FGF23 is synthesized in osteoblasts and osteocytes [15], but new evidence also supports FGF23 production from erythroid progenitor cells in the bone marrow [16]. FGF23 binds to the FGF1R with the cofactor klotho and decreases the expression of NPT2a and NPT2c on the renal proximal tubule cell, resulting in decreased reabsorption of phosphate and subsequent phosphate excretion in the urine. Additionally, FGF23 inhibits 1 alpha-hydroxylase and stimulates 25-vitamin D-24 hydroxylase leading to a decrease in active 1,25-$(OH)_2$-vitamin D_3 levels.

Diseases of FGF23 excess can be acquired or inherited. Tumor-induced osteomalacia (TIO), an acquired disease of FGF23 overproduction, is caused by a mesenchymal tumor which secretes FGF23 autonomously and inappropriately given the level of blood phosphate [17]. Patients typically present with muscle and bone pain and weakness, and laboratory studies show low phosphate, renal phosphate wasting, and evidence of osteomalacia. While the best test to confirm renal phosphate wasting is tubular maximum reabsorption of phosphate to glomerular filtration rate (TmP/GFR), this test can be difficult to perform and thus the tubular reabsorption of phosphate (TRP) can be used as a surrogate [17]. Patients also have

a high or inappropriately normal FGF23 level. The tumors responsible for FGF23 secretion can be very small and located anywhere—making them notoriously difficult to find. Functional imaging modalities such as Octreotide scanning with ^{111}In-labeled pentatreotide, FDG PET/CT, and (^{68}Ga) DOTATATE PET/CT have each been useful in identifying these mesenchymal tumors. A recent study shows DOTATATE PET/CT to be superior to FDG PET/CT [18, 19]. The best treatment for TIO is surgical removal of the tumor with wide margins.

X-linked hypophosphatemic rickets (XLH) has a prevalence of 1 in 25,000, making it the most common inherited renal phosphate wasting disorder [12, 20]. XLH is caused by inactivating mutations in the *PHEX* gene on the X chromosome which encodes an endopeptidase [21], but the exact mechanism by which PHEX interacts with FGF23 is unknown. The clinical spectrum of XLH can be broad, but patients typically present very early in childhood.

Autosomal dominant hypophosphatemic rickets (ADHR) is caused by a mutation in the FGF23 gene which decreases cleavage of the protein into its inactive parts, leading to increased level of the intact, active FGF23 hormone [22]. The phenotype of ADHR is extremely varied with some patients developing symptoms such as rickets in childhood and others remaining generally asymptomatic. Studies have shown that states of low iron can increase symptoms in ADHR patients [23], which also might be related to increased levels of erythropoietin that have been shown to increase FGF23 expression [24].

Autosomal recessive hypophosphatemic rickets (ARHR) can be divided into type 1, caused by mutations in the *DMP1* gene, and type 2, due to mutations in the *ENPP1* gene [25]. ARHR typically presents during childhood with hypophosphatemia, elevated FGF23, and radiologic abnormalities. Inactivation of DMP-1 increases osteocyte production of FGF23 [26]. *ENPP1* encodes an enzyme that inhibits bone formation, and loss of this enzyme results in excessive calcification that can be fatal in the disease generalized arterial calcification of infancy (GACI) [27]. The bone mineral density can be higher in ARHR patients as compared to XLH or ADHR patients [28].

Biochemical markers of XLH, ADHR, and ARHR include hypophosphatemia, renal phosphate wasting, low or inappropriately normal $1,25(OH)_2D_3$ levels, and elevated serum alkaline phosphatase [12]. FGF23 levels are high or inappropriately normal for the degree of hypophosphatemia. While the characteristics surrounding the disease presentation might provide clues, the gold standard to differentiate between these genetic diseases is sequencing of the DNA.

Fibrous dysplasia/McCune Albright syndrome (FD/MAS) is a mosaic disease due to activating mutations in *GNAS*, which encodes Gsα. The disease can have varying severity depending on when in development the mutation was acquired, and fibrous dysplastic bone lesions can be monostotic or polyostotic. DXA findings are quite variable as the abnormal bone can have lucent and sclerotic areas, and the area of interest in the DXA scan may contain varying amounts of affected or normal bone. Patients who have McCune-Albright syndrome typically present in childhood and can be diagnosed by the syndrome of café au lait skin lesions and hyperactivity of various endocrine systems such as growth hormone excess, hyperthyroidism, and precocious puberty. A 99Tc-MDP bone scan should be used to identify areas of skeletal involvement. In cases of diagnostic difficulty, such as monostotic FD, genetic testing of *GNAS* can be performed to confirm the diagnosis. The bone lesions in FD, especially those with more extensive disease in childhood, can produce excess FGF23 leading to hypophosphatemia [15]. If not treated, the sequelae of excess FGF23 and hypophosphatemia can worsen the already fragile fibrous dysplastic bone [29]. Interestingly, the excess FGF23 in fibrous dysplasia was found to be largely inactive due to glycosylation abnormalities leading to excess cleavage of the molecule; therefore, these patients do not typically develop an overt rickets/osteomalacia phenotype [30, 31].

Other rare disorders of increased FGF23 which can lead to hypophosphatemia and osteomalacia include epidermal nevus syndrome (ENS) or cutaneous skeletal hypophosphatemia syndrome (CSHS) caused by somatic activating mutations in *HRAS*, *KRAS*, and *NRAS* [32, 33]. These patients have increased FGF23 levels which is thought to originate from a skeletal source [34]. Osteoglophonic dysplasia is a skeletal disorder caused by mutations in *FGFR1*. Patients can have elevated FGF23 levels, renal phosphate wasting, and hypophosphatemia [35]. Hypophosphatemic rickets with hyperparathyroidism is due to a translocation in chromosome 13 near the Klotho gene that causes high levels of klotho and FGF23 and increased PTH secretion [36]. Finally, intravenous iron therapy has also been reported to increase FGF23 levels and cause hypophosphatemia which can be prolonged [37].

Renal Causes of Phosphate Wasting

Two of the diseases which cause hypophosphatemia due to renal phosphate leaks are hereditary hypophosphatemic rickets with hypercalciuria (HHRH) and Fanconi's syndrome. HHRH is caused by autosomal recessive mutations in the *SLC34A3* gene, encoding NPT2c [38]. Loss of function of this phosphate transporter in the renal tubule leads to phosphate loss in the urine [39]. Since FGF23 is not directly affected in this disease, it is appropriately suppressed and $1,25(OH)_2D_3$ levels are increased. Patients thus have increased calcium absorption and hypercalciuria [26]. Fanconi's syndrome includes both inherited and acquired forms of renal proximal tubular dysfunction. It is characterized by aminoaciduria, glycosuria, and hyperchloremic metabolic acidosis. Phosphate,

calcium, magnesium, and other low-molecular-weight proteins can also be lost in the urine [40]. Inherited causes include inborn diseases in metabolism such as cystinosis, galactosemia, Dent disease, Wilson disease, and Lowe syndrome. Acquired Fanconi anemia can be due to several drugs and heavy metals, as well as dysproteinemias such as multiple myeloma [40]. Phosphate wasting in Fanconi's syndrome causes hypophosphatemia and osteomalacia, which has been shown to respond to calcium, phosphate, and vitamin D treatment [41].

In summary, osteomalacia can have variable presentation on DXA but should be considered in patients with low BMD and laboratory abnormalities such as low phosphate. While some of the diseases discussed above typically present in childhood, vitamin D deficiency, TIO, acquired Fanconi's syndrome, and variable penetrance of inherited diseases should be considered as each necessitates a tailored treatment regimen.

Osteogenesis Imperfecta and Other Connective Tissue Diseases

Osteogenesis imperfecta (OI), or brittle bone disease, is a rare (affecting one in 15–20,000 individuals) connective tissue disorder characterized by low bone mass and increased frequency of fractures [42]. Patients, typically children present with a history of frequent fractures, bowing of long bones, short stature, hearing loss, and/or scoliosis. Blue sclerae, macrocephaly, presence of wormian bones, basilar invagination (narrowing of foramen magnum), pulmonary function impairment, cardiac valve abnormalities, muscle weakness, ligamentous laxity, malocclusion, and dentinogenesis imperfecta (discolored and weaker teeth) may be noted on exam. The underlying pathophysiology in OI is a quantitative or qualitative defect in collagen production although some types of OI are not caused by mutations that affect the collagen pathway but by mutations in genes involved in bone mineralization and in the differentiation of osteoblasts [43]. However, about 85% of patients with OI have an autosomal dominant mutation in the type 1 collagen coding genes (*COL1A1* and *COL1A2)* [42, 43]. Mild manifestations of OI can be caused by stop, frame shift, or splice site mutations that result in a quantitative defect of type I collagen production [44]. Patients with moderate-severe OI or known family history of OI are typically diagnosed prenatally on sonographic imaging or in childhood. However, patients with mild OI may remain undiagnosed until adulthood and present with early-onset or accelerated osteoporosis, hearing loss, and poor dentition [45]. In addition, OI and osteoporosis can also co-exist in the same patient. Genetic testing for confirmation of diagnosis is performed when necessary, usually in the absence of a family history of OI.

Patients with OI demonstrate a low BMD on DXA scan [46]. It is important to distinguish OI from age-related osteoporosis as patients with OI need to be monitored for complications like hearing loss, restrictive lung pathology secondary to scoliosis and chest deformity, valvular dysfunction, and basilar invagination. Distinguishing mild OI from osteoporosis allows physicians to plan treatment thresholds and intensity. In addition, it offers patients and families the opportunity to participate in genetic counseling and understand risks associated with future pregnancies.

Ehlers-Danlos syndrome (EDS) is a sub-group of clinically and genetically heterogenous connective tissue diseases characterized by skin hyperextensibility, joint laxity, and easy bruisability. Although fractures and low BMD are not cardinal features in EDS, reduced BMD and bone quality with increased prevalence of fractures has been described in these patients [47]. Some types of EDS, commonly the vascular type, remain undiagnosed even into adulthood—awareness of these conditions could help in recognizing the disease [48]. Marfan syndrome is caused by an autosomal dominant mutation in the *FBN1* gene encoding the connective tissue protein fibrillin-1 leading to transforming growth factor-beta signaling dysfunction. Significantly low BMD has been described in patients with Marfan Syndrome [49, 50]. Given that patients with EDS and Marfan can have co-existing age-related osteoporosis, it is important to interpret the finding of low BMD in light of age of presentation, disease progression, and family history.

Chronic Kidney Disease-Mineral and Bone Disorder

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is a broader clinical syndrome which develops as a systemic disorder of mineral and bone metabolism due to chronic kidney disease (CKD) and is manifested by abnormalities in mineral metabolism (calcium, phosphorus, PTH, or vitamin D), bone mineralization, turnover, volume, linear growth, microarchitecture or strength, and/or extra-skeletal calcification [51]. Because of its wide spectrum, most patients with CKD develop CKD-MBD very early in their course.

Patients with CKD are at increased risk of fractures [52, 53]. However, the diagnosis of osteoporosis in patients with CKD is quite challenging as CKD-MBD needs to be excluded [54]. Moreover, patients can incur fractures due to CKD-MBD and/or osteoporosis and the two conditions can co-exist. Hence, the applicability of the WHO definition of presence of fragility fracture(s) or BMD ≤ -2.5 for diagnosis of osteoporosis remains uncertain in patients with CKD. Laboratory testing of PTH and bone-specific alkaline phosphatase may be used to exclude CKD-MDB although these surrogates are not as useful in the moderate range. Bone biopsy is the gold

standard to establish a diagnosis of osteoporosis [55] however because of its invasive nature and resource requirements, it is not commonly performed.

The risk with incorrect diagnosis of osteoporosis in patients with CKD lies in the use of anti-resorptives which are commonly prescribed as first-line agents for the management of osteoporosis but can further suppress bone turnover in patients with adynamic bone disease, if not reliably excluded. Moreover, the efficacy and safety of these drugs in patients with CKD is not well-established [56]. Hence, it is particularly important to exclude the diagnosis of CKD-MBD before diagnosing osteoporosis in a patient with CKD.

Rare Diseases

There are several rare metabolic bone diseases that can present with or include fractures and/or low BMD as part of the constellation of symptoms. We review some of these rare diseases below.

Type 1 neurofibromatosis (NF1) is an autosomal dominant disease with an incidence of 1: 3500 [57]. The gene responsible for NFI is involved in regulation of cellular growth and differentiation. Cardinal features of disease include cutaneous neurofibromas, café au lait spots on skin, and hamartoma of iris. Among the seven diagnostic criteria for diagnosing NF1, osseous defect is also included [58]. Common skeletal abnormalities noted in NF1 include long bone dysplasia resulting in fractures and non-union, sphenoid wing dysplasia, and scoliosis [59]. Low BMD and higher rates of fractures have been described in patients with and without osseous defects [60]. The conditional knockout (Nf1 cKO) mice display significantly increased FGF23 with altered calcium-phosphorus metabolism and an osteomalacia-like bone phenotype implicating FGF-23 in the pathophysiology of the mineralization defect in NF1 [61]. Decreased bone mineral density has also been reported in Noonan syndrome [62] and Costello syndrome [63] caused by genes of the RAS-MAPK pathway.

Hypophosphatasia is a disease which can have vastly varying phenotypes ranging from dental abnormalities with normal BMD to perinatal hypophosphatasia, which is fatal just after birth. Odonto hypophosphatasia is the mildest form of this disease and involves tooth loss, but no other systemic symptoms. Adult hypophosphatasia can present in the middle ages with osteomalacia and fractures, specifically metatarsal stress fractures, femoral pseudofractures, and subtrochanteric femur fractures [64]. Loss of dentition is a prevalent feature and a dental history should be taken in a suspected patient. Hypophosphatasia is caused by mutations in the gene for tissue-non-specific alkaline phosphatase (*TNSALP*) [65]. TNSALP is an enzyme located on the surface of bone and teeth, and in its absence, its substrate, inorganic pyrophosphatase (PPi), accumulates. PPi inhibits mineralization, and therefore, patients can suffer from osteomalacia and rickets [64]. One key finding on laboratory studies is low alkaline phosphate levels. Additionally, hydrolysis of a form of vitamin B6, pyridoxal 5′-phosphate (PLP) is inhibited; thus, serum PLP is elevated in hypophosphatasia. This can be assessed by ordering "vitamin B6" after holding any vitamin B6 supplements for 1 week [64]. Phosphoethanolamine (PEA) is also typically elevated in the serum and urine, as is inorganic pyrophosphate (PPi). Asfotase alpha, an enzyme replacement therapy for hypophosphatasia, has dramatically changed outcomes for patients with this disease [66].

Loeys-Dietz Syndrome (LDS) is a disease of vascular, skeletal, craniofacial, and dermatologic findings which is caused by mutations of *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, or *TGFBR2* [67]. LDS is typically diagnosed in childhood due to the vascular, skeletal, and craniofacial abnormalities. Arterial aneurysms are of particular concern in these patients. LDS patients have been found to have lower bone mineral density as well as a higher risk of fracture [68].

Cystic fibrosis (CF) is an autosomal recessive disease with a prevalence of 1 in 2500 live births [69]. It is caused by mutations in the CF transmembrane conductance regulator (CFTR) protein. Patients with CF can have low BMD due to a variety of factors: vitamin D and K malabsorption from exocrine pancreatic insufficiency, poor nutritional status, physical inactivity, chronic inflammation, glucocorticoid therapy, delayed puberty, and hypogonadism [70]. Risk factors for low BMD in patients with CF include male gender, poor lung function, low body weight, and low 25-hydroxy vitamin D levels [71]. The pooled prevalence of osteoporosis, osteopenia, radiographic vertebral fractures, and radiographic non-vertebral fractures were 23.5% (95% CI, 16.6–31.0), 38% (95% CI, 28.2–48.3), 14% (95% CI, 7.8–21.7), and 19.7% (95% CI, 6.0–38.8) [72] in a systematic literature review with meta-analysis. Bisphosphonates are the first-line medical treatment in patients with CF and low BMD. The effectiveness of teriparatide and sequential therapy are being investigated in these patients [73].

Acute bone involvement in sickle cell disease (SCD) is commonly due to vaso-occlusive crises or osteomyelitis [74]. However, 40–80% of patients with SCD have been described to have low BMD [75, 76]. Low levels of vitamin D and testosterone are predictors of low BMD in these patients [77]. BMI, ferritin level, hemoglobin type, and level have been reported to play an important role in determining bone health in these patients [76]. Significantly elevated RANKL/OPG ratios and lower osteocalcin in comparison to healthy controls has been described in patients with hemolytic anemia [78]. Patients with SCD can develop vertebral collapse either from osteoporosis or from vertebral infarction. Systematic review and meta-analysis of bone health in patients with

Table 1 Non-osteoporotic causes of low bone mineral density

1. Osteomalacia
   - PTH-mediated disorders
   - FGF23-mediated disorders
   - Renal-mediated disorders
2. Osteogenesis imperfect and other connective tissue diseases
   - Ehlers Danlos syndrome
   - Marfan syndrome
3. Chronic kidney disease—mineral and bone disorder
4. Rare diseases
   - Type 1 neurofibromatosis
   - Cystic fibrosis
   - Lowey Dietz syndrome
   - Fibrous dysplasia
   - Sickle cell disease
   - Autosomal dominant hyper IgE recurrent infection syndrome
   - Homocystinuria
   - Gaucher's disease

hematopoietic disorders of bone marrow origin show that abnormal proliferation of bone marrow cells is associated with bone loss, independent of hematopoietic lineage suggesting that iron metabolism may independently contribute to bone homeostasis [79]. These findings highlight the need to monitor BMD in patients with hemolytic anemia. Further studies are needed to define threshold for therapeutic interventions in this select population. These patients also develop CKD further complicating choice of therapy.

Autosomal dominant hyper IgE recurrent infection syndrome (AD-HIES or Job's syndrome) is a rare primary immunodeficiency disorder caused by mutations in signal transducer and activator of transcription 3 (*STAT3*) gene. Patients present with recurrent infections, eczemas, elevated serum immunoglobulin E, and pathological fractures. Bone manifestations include minimal trauma fractures predominantly on long bones, scoliosis, cystic bone changes, and low BMD [80]. The possible causes of low BMD in patients with AD-HIES include chronic inflammation, increased osteoclast function, nutritional and hormonal factors, and direct unknown effect(s) of STAT3 on bone metabolism [81]. In these patients, cells in the monocyte/macrophage family are activated to resorb bone contributing to the low BMD [82]. Case reports describing use of bisphosphonates to improve BMD in these patients have been published [83].

Homocystinuria (HCU) is an autosomal recessive disease due to mutations in cystathionine beta-synthetase characterized by developmental delay, intellectual impairment, dislocation of the optic lens, thromboembolism, and skeletal abnormalities. Low BMD is common in both children, and adults with HCU and routine assessment of bone health in these patients is recommended [84]. Good control of plasma homocysteine has been shown to optimize bone health in these patients [85].

Gaucher's disease (GD) is the most common lysosomal storage disease with an autosomal recessive inheritance. Patients lack the beta-glucocerebroside enzyme due to mutations at the glucosylceramide beta (GBA) gene resulting in accumulation of glucocerebroside in the lysosomes of macrophages. Patients typically present with hepatosplenomegaly and bone marrow

Table 2 Mechanisms of osteomalacia

Disease	Mechanism	Genetic vs acquired
PTH-mediated disorders		
Vitamin D Deficiency	Decreased 25-OH-D by poor intake	Acquired
Renal insufficiency	Decreased 1-alpha hydroxylase activity leads to decreased active 1,25-OH_2-D	Acquired
Hepatic insufficiency	Decreased 25-hydroxylation of vitamin D in the liver leads to decreased active 1,25-OH_2-D	Acquired
FGF23-mediated disorders		
Tumor-induced osteomalacia	Mesenchymal tumor autonomously secretes FGF23	Acquired
X-linked hypophosphatemic rickets	Mutation in *PHEX*	Genetic
Autosomal dominant hypophosphatemic rickets	Mutation in *FGF23* causes decreased cleavage and inactivation	Genetic
Autosomal recessive hypophosphatemic rickets (type 1 and 2)	Mutations in *DMP1* and *ENPP1*	Genetic
Renal-mediated disorders		
Fanconi anemia	Renal proximal tubule damage	Genetic or acquired
Hereditary hypophosphatemic rickets with hypercalciuria	Mutation of SLC23A3 (renal phosphate channel)	Genetic

involvement. Recurrent fractures, low BMD, growth retardation, lytic lesions, and infarct of the cortico-medullary bone are some of the skeletal manifestations of the disease [86]. Bisphosphonate therapy has been reported to improve bone density in conjunction with enzyme replacement for GD [86].

Conclusions

While post-menopausal osteoporosis is the most common cause of low BMD, clinicians are encouraged to review the differential diagnosis of low BMD to establish a diagnosis in clinical setting. With continued advances in the study of rare bone diseases and availability of high-resolution peripheral quantitative computed tomography to measure BMD, new information and treatments will continue to emerge.

Compliance with Ethical Standards

Conflict of Interest This research was supported by the Division of Intramural Research of the National Institutes of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Dental and Craniofacial Research and the National Institutes of Health Clinical Center. Smita Jha, Marquis Chapman, and Kelly Roszko declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group Osteoporos Int. 1994;4(6):368–81.
2. Kanis JA, McCloskey EV, Johansson H, Oden A, Melton LJ 3rd, Khaltaev N. A reference standard for the description of osteoporosis. Bone. 2008;42(3):467–75. https://doi.org/10.1016/j.bone.2007.11.001.
3. 2013 ISCD Official Position - Adults. Internation Society of Clinical Densitometry. 2013. http://www.iscd.org/official-positions/2013-iscd-official-positions-adult/. Accessed November 11th, 2018 2018.
4. Bhambri R, Naik V, Malhotra N, Taneja S, Rastogi S, Ravishanker U, et al. Changes in bone mineral density following treatment of osteomalacia. J Clin Densitom. 2006;9(1):120–7. https://doi.org/10.1016/j.jocd.2005.11.001.
5. Saghafi M, Azarian A, Hashemzadeh K, Sahebari M, Rezaieyazdi Z. Bone densitometry in patients with osteomalacia: is it valuable? Clinical Cases in Mineral and Bone Metabolism : the official journal of the Italian Society of Osteoporosis, Mineral Metabolism, and Skeletal Diseases. 2013;10(3):180–2.
6. Elder CJ, Bishop NJ. Rickets. Lancet (London, England). 2014;383(9929):1665–76. https://doi.org/10.1016/s0140-6736(13)61650-5.
7. Tiosano D, Hochberg Z. Hypophosphatemia: the common denominator of all rickets. J Bone Miner Metab. 2009;27(4):392–401. https://doi.org/10.1007/s00774-009-0079-1.
8. Basha B, Rao DS, Han ZH, Parfitt AM. Osteomalacia due to vitamin D depletion: a neglected consequence of intestinal malabsorption. Am J Med. 2000;108(4):296–300.
9. Colares Neto GP, Pereira RM, Alvarenga JC, Takayama L, Funari MF, Martin RM. Evaluation of bone mineral density and microarchitectural parameters by DXA and HR-pQCT in 37 children and adults with X-linked hypophosphatemic rickets. Osteoporos Int. 2017;28(5):1685–92. https://doi.org/10.1007/s00198-017-3949-8.
10. Rosenthall L. DEXA bone densitometry measurements in adults with X-linked hypophosphatemia. Clin Nucl Med. 1993;18(7):564–6.
11. Bhan A, Qiu S, Rao SD. Bone histomorphometry in the evaluation of osteomalacia. Bone Rep. 2018;8:125–34. https://doi.org/10.1016/j.bonr.2018.03.005.
12. Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. J Bone Miner Res. 2011;26(7):1381–8. https://doi.org/10.1002/jbmr.340.
13. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, et al. Global consensus recommendations on prevention and management of nutritional rickets. J Clin Endocrinol Metab. 2016;101(2):394–415. https://doi.org/10.1210/jc.2015-2175.
14. Christov M, Juppner H. Phosphate homeostasis disorders. Best Pract Res Clin Endocrinol Metab. 2018;32(5):685–706. https://doi.org/10.1016/j.beem.2018.06.004.
15. Riminucci M, Collins MT, Fedarko NS, Cherman N, Corsi A, White KE, et al. FGF-23 in fibrous dysplasia of bone and its relationship to renal phosphate wasting. J Clin Invest. 2003;112(5):683–92. https://doi.org/10.1172/jci18399.
16. Toro L, Barrientos V, Leon P, Rojas M, Gonzalez M, Gonzalez-Ibanez A, et al. Erythropoietin induces bone marrow and plasma fibroblast growth factor 23 during acute kidney injury. Kidney Int. 2018;93(5):1131–41. https://doi.org/10.1016/j.kint.2017.11.018.
17. Florenzano P, Gafni RI, Collins MT. Tumor-induced osteomalacia. Bone Rep. 2017;7:90–7. https://doi.org/10.1016/j.bonr.2017.09.002.
18. El-Maouche D, Sadowski SM, Papadakis GZ, Guthrie L, Cottle-Delisle C, Merkel R, et al. (68)Ga-DOTATATE for tumor localization in tumor-induced osteomalacia. J Clin Endocrinol Metab. 2016;101(10):3575–81. https://doi.org/10.1210/jc.2016-2052.
19. Agrawal K, Bhadada S, Mittal BR, Shukla J, Sood A, Bhattacharya A, et al. Comparison of 18F-FDG and 68Ga DOTATATE PET/CT in localization of tumor causing oncogenic osteomalacia. Clin Nucl Med. 2015;40(1):e6–e10. https://doi.org/10.1097/rlu.0000000000000460.
20. Cagnoli M, Richter R, Bohm P, Knye K, Empting S, Mohnike K. Spontaneous growth and effect of early therapy with calcitriol and phosphate in X-linked hypophosphatemic rickets. Pediatr Endocrinol Rev. 2017;15(Suppl 1):119–22. https://doi.org/10.17458/per.vol15.2017.crb.spontaneousgrowtheffect.
21. A gene (PEX) with homologies to endopeptidases is mutated in patients with X-linked hypophosphatemic rickets. The HYP Consortium. Nat Genet. 1995;11(2):130–6. https://doi.org/10.1038/ng1095-130.
22. Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. Nat Genet. 2000;26(3):345–8. doi:https://doi.org/10.1038/81664.
23. Imel EA, Peacock M, Gray AK, Padgett LR, Hui SL, Econs MJ. Iron modifies plasma FGF23 differently in autosomal dominant hypophosphatemic rickets and healthy humans. J Clin Endocrinol Metab. 2011;96(11):3541–9. https://doi.org/10.1210/jc.2011-1239.
24. Clinkenbeard EL, Hanudel MR, Stayrook KR, Appaiah HN, Farrow EG, Cass TA, et al. Erythropoietin stimulates murine and human fibroblast growth factor-23, revealing novel roles for bone and bone marrow. Haematologica. 2017;102(11):e427–e30. https://doi.org/10.3324/haematol.2017.167882.

25. Levy-Litan V, Hershkovitz E, Avizov L, Leventhal N, Bercovich D, Chalifa-Caspi V, et al. Autosomal-recessive hypophosphatemic rickets is associated with an inactivation mutation in the ENPP1 gene. Am J Hum Genet. 2010;86(2):273–8. https://doi.org/10.1016/j.ajhg.2010.01.010.
26. Marcucci G, Masi L, Ferrari S, Haffner D, Javaid MK, Kamenicky P, et al. Phosphate wasting disorders in adults. Osteoporos Int. 2018;29(11):2369–87. https://doi.org/10.1007/s00198-018-4618-2.
27. Lorenz-Depiereux B, Schnabel D, Tiosano D, Hausler G, Strom TM. Loss-of-function ENPP1 mutations cause both generalized arterial calcification of infancy and autosomal-recessive hypophosphatemic rickets. Am J Hum Genet. 2010;86(2):267–72. https://doi.org/10.1016/j.ajhg.2010.01.006.
28. Carpenter TO. The expanding family of hypophosphatemic syndromes. J Bone Miner Metab. 2012;30(1):1–9. https://doi.org/10.1007/s00774-011-0340-2.
29. Collins MT, Chebli C, Jones J, Kushner H, Consugar M, Rinaldo P, et al. Renal phosphate wasting in fibrous dysplasia of bone is part of a generalized renal tubular dysfunction similar to that seen in tumor-induced osteomalacia. J Bone Miner Res. 2001;16(5):806–13. https://doi.org/10.1359/jbmr.2001.16.5.806.
30. Bhattacharyya N, Wiench M, Dumitrescu C, Connolly BM, Bugge TH, Patel HV, et al. Mechanism of FGF23 processing in fibrous dysplasia. J Bone Miner Res. 2012;27(5):1132–41. https://doi.org/10.1002/jbmr.1546.
31. Boyce AM, Bhattacharyya N, Collins MT. Fibrous dysplasia and fibroblast growth factor-23 regulation. Curr Osteoporos Rep. 2013;11(2):65–71. https://doi.org/10.1007/s11914-013-0144-5.
32. Lim YH, Ovejero D, Sugarman JS, Deklotz CM, Maruri A, Eichenfield LF, et al. Multilineage somatic activating mutations in HRAS and NRAS cause mosaic cutaneous and skeletal lesions, elevated FGF23 and hypophosphatemia. Hum Mol Genet. 2014;23(2):397–407. https://doi.org/10.1093/hmg/ddt429.
33. Lim YH, Ovejero D, Derrick KM, Collins MT, Choate KA. Cutaneous skeletal hypophosphatemia syndrome (CSHS) is a multilineage somatic mosaic RASopathy. J Am Acad Dermatol. 2016;75(2):420–7. https://doi.org/10.1016/j.jaad.2015.11.012.
34. Ovejero D, Lim YH, Boyce AM, Gafni RI, McCarthy E, Nguyen TA, et al. Cutaneous skeletal hypophosphatemia syndrome: clinical spectrum, natural history, and treatment. Osteoporos Int. 2016;27(12):3615–26. https://doi.org/10.1007/s00198-016-3702-8.
35. White KE, Cabral JM, Davis SI, Fishburn T, Evans WE, Ichikawa S, et al. Mutations that cause osteoglophonic dysplasia define novel roles for FGFR1 in bone elongation. Am J Hum Genet. 2005;76(2):361–7. https://doi.org/10.1086/427956.
36. Brownstein CA, Adler F, Nelson-Williams C, Iijima J, Li P, Imura A, et al. A translocation causing increased alpha-klotho level results in hypophosphatemic rickets and hyperparathyroidism. Proc Natl Acad Sci U S A. 2008;105(9):3455–60. https://doi.org/10.1073/pnas.0712361105.
37. Schouten BJ, Hunt PJ, Livesey JH, Frampton CM, Soule SG. FGF23 elevation and hypophosphatemia after intravenous iron polymaltose: a prospective study. J Clin Endocrinol Metab. 2009;94(7):2332–7. https://doi.org/10.1210/jc.2008-2396.
38. Lorenz-Depiereux B, Benet-Pages A, Eckstein G, Tenenbaum-Rakover Y, Wagenstaller J, Tiosano D, et al. Hereditary hypophosphatemic rickets with hypercalciuria is caused by mutations in the sodium-phosphate cotransporter gene SLC34A3. Am J Hum Genet. 2006;78(2):193–201. https://doi.org/10.1086/499410.
39. Bergwitz C, Roslin NM, Tieder M, Loredo-Osti JC, Bastepe M, Abu-Zahra H, et al. SLC34A3 mutations in patients with hereditary hypophosphatemic rickets with hypercalciuria predict a key role for the sodium-phosphate cotransporter NaPi-IIc in maintaining phosphate homeostasis. Am J Hum Genet. 2006;78(2):179–92. https://doi.org/10.1086/499409.
40. Foreman JW. Fanconi syndrome. Pediatr Clin N Am. 2019;66(1):159–67. https://doi.org/10.1016/j.pcl.2018.09.002.
41. Clarke BL, Wynne AG, Wilson DM, Fitzpatrick LA. Osteomalacia associated with adult Fanconi's syndrome: clinical and diagnostic features. Clin Endocrinol. 1995;43(4):479–90.
42. Forlino A, Marini JC. Osteogenesis imperfecta. Lancet (London, England). 2016;387(10028):1657–71. https://doi.org/10.1016/s0140-6736(15)00728-x.
43. Marini JC, Forlino A, Bachinger HP, Bishop NJ, Byers PH, Paepe A, et al. Osteogenesis imperfecta. Nat Rev Dis Primers. 2017;3:17052. https://doi.org/10.1038/nrdp.2017.52.
44. Arundel P. Osteogenesis imperfecta. Paediatr Child Health (United Kingdom). 2015;25(12):574–9. https://doi.org/10.1016/j.paed.2015.07.007.
45. Bishop NJ, Walsh JS. Osteogenesis imperfecta in adults. J Clin Invest. 2014;124(2):476–7. https://doi.org/10.1172/JCI74230.
46. Davie MW, Haddaway MJ. Bone mineral content and density in healthy subjects and in osteogenesis imperfecta. Arch Dis Child. 1994;70(4):331–4. https://doi.org/adc.70.4.331%J/adc.70.4.331%J.
47. Eller-Vainicher C, Bassotti A, Imeraj A, Cairoli E, Ulivieri FM, Cortini F, et al. Bone involvement in adult patients affected with Ehlers-Danlos syndrome. Osteoporos Int. 2016;27(8):2525–31. https://doi.org/10.1007/s00198-016-3562-2.
48. Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. N Engl J Med. 2000;342(10):673–80. https://doi.org/10.1056/NEJM200003093421001.
49. Moura B, Tubach F, Sulpice M, Boileau C, Jondeau G, Muti C, et al. Bone mineral density in Marfan syndrome. A large case-control study. Joint Bone Spine. 2006;73(6):733–5. https://doi.org/10.1016/j.jbspin.2006.01.026.
50. Haine E, Salles JP, Khau Van Kien P, Conte-Auriol F, Gennero I, Plancke A, et al. Muscle and bone impairment in children with Marfan syndrome: correlation with age and FBN1 genotype. J Bone Miner Res. 2015;30(8):1369–76. https://doi.org/10.1002/jbmr.2471.
51. Moe S, Drueke T, Cunningham J, Goodman W, Martin K, Olgaard K, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from kidney disease: improving global outcomes (KDIGO). Kidney Int. 2006;69(11):1945–53. https://doi.org/10.1038/sj.ki.5000414.
52. Coco M, Rush H. Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. Am J Kidney Dis. 2000;36(6):1115–21. https://doi.org/10.1053/ajkd.2000.19812.
53. Kim SM, Long J, Montez-Rath M, Leonard M, Chertow GM. Hip fracture in patients with non-dialysis-requiring chronic kidney disease. J Bone Miner Res. 2016;31(10):1803–9. https://doi.org/10.1002/jbmr.2862.
54. Ketteler M, Block GA, Evenepoel P, Fukagawa M, Herzog CA, McCann L, et al. Executive summary of the 2017 KDIGO chronic kidney disease-mineral and bone disorder (CKD-MBD) guideline update: what's changed and why it matters. Kidney Int. 2017;92(1):26–36. https://doi.org/10.1016/j.kint.2017.04.006.
55. Malluche HH, Mawad HW, Monier-Faugere MC. Renal osteodystrophy in the first decade of the new millennium: analysis of 630 bone biopsies in black and white patients. J Bone Miner Res. 2011;26(6):1368–76. https://doi.org/10.1002/jbmr.309.
56. Wilson LM, Rebholz CM, Jirru E, Liu MC, Zhang A, Gayleard J, et al. Benefits and harms of osteoporosis medications in patients with chronic kidney disease: a systematic review and meta-analysis. Ann Intern Med. 2017;166(9):649–58. https://doi.org/10.7326/M16-2752.
57. Lammert M, Kappler M, Mautner VF, Lammert K, Storkel S, Friedman JM, et al. Decreased bone mineral density in patients with

neurofibromatosis 1. Osteoporos Int. 2005;16(9):1161–6. https://doi.org/10.1007/s00198-005-1940-2.
58. Friedman JM. Neurofibromatosis 1: clinical manifestations and diagnostic criteria. J Child Neurol. 2002;17(8):548–54; discussion 71–2, 646–51. https://doi.org/10.1177/088307380201700802.
59. Stevenson DA, Moyer-Mileur LJ, Murray M, Slater H, Sheng X, Carey JC, et al. Bone mineral density in children and adolescents with neurofibromatosis type 1. J Pediatr. 2007;150(1):83–8. https://doi.org/10.1016/j.jpeds.2006.10.048.
60. Tucker T, Schnabel C, Hartmann M, Friedrich RE, Frieling I, Kruse HP, et al. Bone health and fracture rate in individuals with neurofibromatosis 1 (NF1). J Med Genet. 2009;46(4):259–65. https://doi.org/10.1136/jmg.2008.061895.
61. Kamiya N, Yamaguchi R, Aruwajoye O, Kim AJ, Kuroyanagi G, Phipps M, et al. Targeted disruption of NF1 in osteocytes increases FGF23 and osteoid with osteomalacia-like bone phenotype. J Bone Miner Res. 2017;32(8):1716–26. https://doi.org/10.1002/jbmr.3155.
62. Choudhry KS, Grover M, Tran AA, O'Brian Smith E, Ellis KJ, Lee BH. Decreased bone mineralization in children with Noonan syndrome: another consequence of dysregulated RAS MAPKinase pathway? Mol Genet Metab. 2012;106(2):237–40. https://doi.org/10.1016/j.ymgme.2012.04.003.
63. Leoni C, Stevenson DA, Martini L, De Sanctis R, Mascolo G, Pantaleoni F et al. Decreased bone mineral density in Costello syndrome. Mol Genet Metab 2014;111(1):41–45. doi:https://doi.org/10.1016/j.ymgme.2013.08.007.
64. Whyte MP. Hypophosphatasia: an overview for 2017. Bone. 2017;102:15–25. https://doi.org/10.1016/j.bone.2017.02.011.
65. Henthorn PS, Raducha M, Fedde KN, Lafferty MA, Whyte MP. Different missense mutations at the tissue-nonspecific alkaline phosphatase gene locus in autosomal recessively inherited forms of mild and severe hypophosphatasia. Proc Natl Acad Sci U S A. 1992;89(20):9924–8.
66. Whyte MP, Greenberg CR, Salman NJ, Bober MB, McAlister WH, Wenkert D, et al. Enzyme-replacement therapy in life-threatening hypophosphatasia. N Engl J Med. 2012;366(10):904–13. https://doi.org/10.1056/NEJMoa1106173.
67. Loeys BL, Dietz HC. Loeys-Dietz syndrome. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K et al., editors. GeneReviews((R)). Seattle (WA): University of Washington, Seattle University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved; 1993.
68. Tan EW, Offoha RU, Oswald GL, Skolasky RL, Dewan AK, Zhen G, et al. Increased fracture risk and low bone mineral density in patients with loeys-dietz syndrome. Am J Med Genet A. 2013;161a(8):1910–4. https://doi.org/10.1002/ajmg.a.36029.
69. Ratjen F, Doring G. Cystic fibrosis. Lancet. 2003;361(9358):681–9. https://doi.org/10.1016/S0140-6736(03)12567-6.
70. Siwamogsatham O, Alvarez J, Tangpricha V. Diagnosis and treatment of endocrine co-morbidities in ptaients with cystic fibrosis. Current opinion in endocrinology, diabetes, and obesity. 2015. https://doi.org/10.1097/MED.
71. 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):180–5. https://doi.org/10.1007/s00774-014-0572-z.
72. Paccou J, Zeboulon N, Combescure C, Gossec L, Cortet B. The prevalence of osteoporosis, osteopenia, and fractures among adults with cystic fibrosis: a systematic literature review with meta-analysis. Calcif Tissue Int. 2010;86(1):1–7. https://doi.org/10.1007/s00223-009-9316-9.
73. Siwamogsatham O, Stephens K, Tangpricha V. Evaluation of teriparatide for treatment of osteoporosis in four patients with cystic fibrosis: a case series. Case Rep Endocrinol. 2014;2014:893589–4. https://doi.org/10.1155/2014/893589.
74. Almeida A, Roberts I. Bone involvement in sickle cell disease. Br J Haematol. 2005;129(4):482–90. https://doi.org/10.1111/j.1365-2141.2005.05476.x.
75. Meeuwes M, Souza de Carvalho TF, Cipolotti R, Gurgel RQ, Ferrao TO, Peters M, et al. Bone mineral density, growth, pubertal development and other parameters in Brazilian children and young adults with sickle cell anaemia. Tropical Med Int Health. 2013;18(12):1539–46. https://doi.org/10.1111/tmi.12211.
76. Sarrai M, Duroseau H, D'Augustine J, Moktan S, Bellevue R. Bone mass density in adults with sickle cell disease. Br J Haematol. 2007;136(4):666–72. https://doi.org/10.1111/j.1365-2141.2006.06487.x.
77. Garadah TS, Hassan AB, Jaradat AA, Diab DE, Kalafalla HO, Kalifa AK, et al. Predictors of abnormal bone mass density in adult patients with homozygous sickle-cell disease. Clin Med Insights Endocrinol Diabetes. 2015;8:35–40. https://doi.org/10.4137/CMED.S24501.
78. Schundeln MM, Goretzki SC, Hauffa PK, Wieland R, Bauer J, Baeder L, et al. Impairment of bone health in pediatric patients with hemolytic anemia. PLoS One. 2014;9(10):e108400. https://doi.org/10.1371/journal.pone.0108400.
79. Steer K, Stavnichuk M, Morris M, Komarova SV. Bone health in patients with hematopoietic disorders of bone marrow origin: systematic review and meta-analysis. J Bone Miner Res. 2017;32(4):731–42. https://doi.org/10.1002/jbmr.3026.
80. Scheuerman O, Hoffer V, Cohen AH, Woellner C, Grimbacher B, Garty BZ. Reduced bone density in patients with autosomal dominant hyper-IgE syndrome. J Clin Immunol. 2013;33(5):903–8. https://doi.org/10.1007/s10875-013-9895-0.
81. Sowerwine KJ, Shaw PA, Gu W, Ling JC, Collins MT, Darnell DN, et al. Bone density and fractures in autosomal dominant hyper IgE syndrome. J Clin Immunol. 2014;34(2):260–4. https://doi.org/10.1007/s10875-013-9982-2.
82. Leung DY, Key L, Steinberg JJ, Young MC, Von Deck M, Wilkinson R, et al. Increased in vitro bone resorption by monocytes in the hyper-immunoglobulin E syndrome. J Immunol. 1988;140(1):84–8.
83. Staines Boone AT, Alcantara-Montiel JC, Sanchez-Sanchez LM, Arce-Cano M, Garcia-Campos J, Lugo Reyes SO. Zoledronate as effective treatment for minimal trauma fractures in a child with STAT3 deficiency and osteonecrosis of the hip. Pediatr Blood Cancer. 2016;63(11):2054–7. https://doi.org/10.1002/pbc.26119.
84. Weber DR, Coughlin C, Brodsky JL, Lindstrom K, Ficicioglu C, Kaplan P, et al. Low bone mineral density is a common finding in patients with homocystinuria. Mol Genet Metab. 2016;117(3):351–4. https://doi.org/10.1016/j.ymgme.2015.12.003.
85. Lim JS, Lee DH. Changes in bone mineral density and body composition of children with well-controlled homocystinuria caused by CBS deficiency. Osteoporos Int. 2013;24(9):2535–8. https://doi.org/10.1007/s00198-013-2351-4.
86. Demirci U, Cizmecioglu A, Aydogdu I. Actual reason for bone fractures in the case of a patient followed-up with the osteogenesis imperfecta: Gaucher's disease. Clin Cases Miner Bone Metab. 2017;14(3):336–9. https://doi.org/10.11138/ccmbm/2017.14.3.336.