

# Rare causes of osteoporosis

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## Summary

**Osteoporosis is a metabolic bone disease characterized by loss of bone mass and strength, resulting in increased risk of fractures. It is classically divided into primary (postmenopausal or senile), secondary and idiopathic forms. There are many rare diseases, that cause directly or indirectly osteoporosis. The identification and classification of most of these rare causes of osteoporosis is crucial for the specialists in endocrinology and not, in order to prevent this bone complication and to provide for an early therapy. Several pathogenic mechanisms are involved, including various aspects of bone metabolism such as: decreased bone formation, increased bone resorption, altered calcium, phosphorus and/or vitamin D homeostasis, and abnormal collagen synthesis. In this review, less common forms of primary and secondary osteoporosis are described, specifying, if applicable: genetic causes, epidemiology, clinical features, and pathogenic mechanisms causing osteoporosis. A greater awareness of all rare causes of osteoporosis could reduce the number of cases classified as idiopathic osteoporosis and allow the introduction of appropriate and timely treatments.**

**KEY WORDS:** *osteoporosis; secondary osteoporosis; rare disease.*

## Introduction

Osteoporosis is a systemic skeletal disease characterized by decreased bone mass and impaired bone microstructure, with a consequent compromised bone strength, predisposing to an increased risk of fractures (1). The diagnosis of osteoporosis is established with measurement of bone mineral density (BMD) by dual-energy x-ray absorptiometry (DEXA) of the spine, hip,

and/or forearm (T-score of  $\leq -2.5$ ). In addition, the clinical diagnosis can be made in individuals who sustain a low trauma or fragility fracture (1). Osteoporosis is classified as primary (postmenopausal women and people over 70 years old), secondary (caused at least in part by others diseases or therapies), or idiopathic. The most common forms of primary osteoporosis occurs as result of menopause and aging process. The less common forms of primary osteoporosis, instead, include: juvenile and adult idiopathic osteoporosis, pregnancy and lactation-associated osteoporosis, and localized osteoporosis (disuse, paralysis, atrophy of Sudek, peri-prosthesis, transient by unknown cause). Secondary osteoporosis result from one or more of the following causes: systemic diseases, endocrine diseases, malignant neoplasms, chronic use of glucocorticoids and other drugs, lifestyle conditions and habits, and finally major depression. The pathogenesis of secondary osteoporosis is almost always multifactorial, and usually it is diagnosed after an atraumatic fracture (2). Considering the lack of symptoms in the early phases, secondary osteoporosis tends to be underestimated. In this review, rare forms of primary osteoporosis, and rare diseases resulting in secondary osteoporosis, are described.

## Rare forms of primary osteoporosis

### *Juvenile idiopathic osteoporosis*

Juvenile idiopathic osteoporosis (JIO) is a very rare condition of primary bone demineralization (3). The exact prevalence is unknown. Diagnosis of JIO is based on clinical presentation, skeletal X-rays, BMD, and exclusion of other common causes of osteoporosis in this age. It is characterized by prepubertal onset, without sex predilection, and spontaneous remission with progression of puberty (4). The exact pathogenesis of this disease is not known, but very low bone formation rate and decreased cancellous bone volume have been described (5). The main presenting symptoms include: recurrent long-bone fractures, back pain, and difficulty or inability to walk (6). Typical radiological changes show generalized osteoporosis, vertebral collapse and metaphyseal compression fractures of the long bones. Although the disease is self-limiting with spontaneous resolution after the onset of puberty, in more severe cases, permanent disability, kyphoscoliosis and rib deformity can develop. Many treatments such as calcium and vitamin D supplementations, bisphosphonates, fluorides and calcitonin have been used with equivocal results (7).

## Pregnancy and lactation-associated osteoporosis

Pregnancy and lactation-associated osteoporosis (PLaOs) is an uncommon and rare disease, characterized by the occurrence of fragility fracture(s), most commonly vertebral, in late pregnancy or during the postpartum period. The diagnosis of PLaOs is usually based on clinical history, supported by imaging findings of osteopenia and/or fragility fractures, and exclu-

sion of other causes (8). The etiology and pathogenesis of this condition is not clear. It is known that pregnancy and lactation are characterized by significant changes in calcium and bone homeostasis, and apparently this occurs due to increased fetal demand of calcium for skeletal bone calcification (9). In some cases, the decrease in BMD during a physiological pregnancy can lead to dramatic microarchitectural changes. PLaOs occur mostly in primigravidas and in the third decade of life (10). No established treatment has been proposed for PLaOs, except mechanical measures, such as rest, avoidance of weight lifting, and supportive means for the spine (corset) (11). Exercise as well as supplementation with vitamin D and calcium could cope for the losses and/or higher requirements, and lactating is not recommendable (12). At present, data on the effects of bisphosphonates, and long-term outcomes in PLaOs are limited. However, bisphosphonate therapy administered within 1 year of presentation, substantially, appears to increase spinal BMD in patients with PLaOs (13). The safety of bisphosphonates in human pregnancy has not been well established. However, to date, regarding treatment, no maternal and fetal adverse outcomes from the use of bisphosphonates before pregnancy and during the first trimester of pregnancy have been noted. Recently, Levy et al. have conducted a cohort study with a comparison group to examine pregnancy outcome after bisphosphonate exposure (14). The inclusion criterion for the bisphosphonate-exposed group was the use of bisphosphonates during or within 12 months before pregnancy. They did not observe an increased risk of major birth defects from intrauterine exposure to bisphosphonates prior to conception and during the first trimester of pregnancy (14). Coupled with existing data in the literature, their findings suggest that preconceptional and first trimester use of bisphosphonates may not pose substantial fetal risks, but further studies are necessary.

## Rare causes of secondary osteoporosis

### Miscellaneous chronic diseases

#### Cystic Fibrosis

Cystic Fibrosis (CF) is a genetic disorder characterized by the production of sweat with a high salt content and mucus secretions with an abnormal viscosity. CF is caused by mutations in the cystic fibrosis transmembrane regulator (*CFTR*) gene (15). The exact prevalence in Europe is unknown, but estimates range between 1/8.000 and 1/10.000 individuals (16). CF affects many organs (e.g. lung and pancreas), but also commonly leads to reduced BMD, increasing the risk of fractures (17). Osteoporosis occurs in about one third of adults with CF (18). An imbalance of increased bone resorption and decreased bone formation has been observed, even in young prepubertal patients. The etiology of CF-related bone disease is likely multifactorial (e.g. malnutrition, exocrine pancreatic insufficiency, vitamin D, vitamin K or calcium deficiency etc.) (19). Furthermore, BMD has been positively associated with pulmonary and physical function, nutritional status and negatively associated with chronological age and recurrent pulmonary exacerbations (20). Mutation of the *CFTR* gene itself may have a direct role in the pathogenesis of CF-related bone disease (17). Some studies have indicated that the loss of CFTR activity in osteoblasts decreases the secretion of osteoprotegerin (OPG) resulting in accentuated inflammation-driven bone resorption (21). The evidence available about the use of bisphosphonates for osteoporosis in individuals with CF is limited. The last update of a previous Cochrane review on bis-

phosphonates use for osteoporosis in people with CF reported that oral and intravenous bisphosphonates increase BMD, at the lumbar spine, and at the hip or femur. Data showed that there was no significant reduction in fractures between treatment and control groups at 12 months. Severe bone pain and flu-like symptoms may occur with intravenous agents, and additional trials are needed to determine if bone pain is more common or severe with the zoledronate and if corticosteroids ameliorate or prevent these adverse events. Others trials are also required to assess gastrointestinal adverse effects associated with oral bisphosphonates (18).

#### Thalassemia major

Thalassemia is an inherited blood disorder characterized by a defect in globin chain synthesis in red blood cells. Metabolic bone disease represents a major cause of morbidity in patients with thalassemia major (the most severe form). Chronic anemia, iron toxicity and endocrine complications, via a complex mechanism, lead to alterations in the RANK/RANKL (Receptor activator of nuclear factor kappa-B - ligand)/OPG system, increasing osteoclastic activity and enhancing osteoblast dysfunction (22). There are several endocrine complications in patients with thalassemia major, such as: hypogonadotropic hypogonadism, delayed puberty, GH (Growth hormone) secretory dysfunction, hypoparathyroidism, vitamin D deficiency, hypothyroidism and diabetes mellitus, and all these contribute to development of osteopenia and osteoporosis, present in more than 50% of patients (22). Regarding the high prevalence of osteopenia/osteoporosis in patients with thalassemia major, all patients should be screened periodically for bone disease. No smoking, a calcium-rich diet, correction of hypogonadism by sex hormone replacement therapy at a proper age and regular exercise should be recommended like prevention of osteoporosis. Oral calcium supplements should be used with caution because of the risk of renal stones. Bisphosphonates have been used in thalassemia patients for the treatment of osteoporosis with promising outcomes. Alendronate, pamidronate, and zoledronate seem to be effective in increasing BMD and normalizing bone turnover. Further controlled trials are necessary to evaluate their real efficacy in reducing fracture risks (23).

#### Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is a chronic autoimmune liver disease, characterized by progressive cholestasis, biliary fibrosis and eventually cirrhosis. Its incidence is estimated to be 5/100.000 persons/year, while the prevalence is 50-250/1.000.000 (24). Osteoporosis is a frequent complication of PBC, mostly in the advanced stages of PBC (25). The pathogenesis of osteoporosis in PBC is still not exactly known, although it appears to be associated with high bone resorption and a slowdown in internal modelling. Malnutrition and vitamin deficiencies, especially vitamins D and K could contribute to development of osteoporosis (26). To date, there is not still medical evidence to support or refute the use of bisphosphonates for patients with PBC (27).

#### Mastocytosis

Mastocytosis is a clonal disorder of the mast cell and its precursor cells, and is characterized by proliferation and accumulation of mast cells within various organs, most commonly the skin but also the bone marrow. The worldwide prevalence is estimated at between 1/20.000 and 1/40.000. Systemic mastocytosis is a rare disease but well-recognised cause of secondary osteoporosis. The pathophysiological mechanism is

probably multifactorial, including increased osteoclastic activity, and a direct effect of mast cell mediators like histamine, heparin, tryptase and cytokines (28). The risk of osteoporotic fractures is elevated, especially at the spine and in men. Bisphosphonates represent the first-line treatment for osteoporosis-related mastocytosis (29), but there are reports of successful use of interferon  $\alpha$  2B to treat severe resistant cases (30). Other skeletal manifestations include osteolytic or osteosclerotic bone lesions due to mast cell infiltration (31).

### Mucopolysaccharidoses

The mucopolysaccharidoses (MPS) are a group of inherited lysosomal storage disorders caused by deficiencies in enzymes catalyzing the degradation of glycosaminoglycans (GAGs). Eleven known enzyme deficiencies give rise to 7 distinct types of MPS (I, II, III, IV, VI, VII, and IX). All are inherited in an autosomal recessive manner except for MPS II, which is an X-linked recessive disorder, occurring almost exclusively in males. Each MPS type exhibits a wide spectrum of clinical severity (32, 33). The prevalence of MPS is reported to be 1.9-4.5/100.000 live births with geographical differences in the frequencies of specific types (34). MPS is associated with poor bone growth and low BMD, but the pathophysiologic basis for skeletal findings is not completely understood. In some cases, with MPS I, II or VI treated with enzyme replacement therapy, improvement of BMD has been described. It is probably due to multiple mechanisms, such as reduced GAGs storage in the bones, increased muscle strength and endurance, and improved pulmonary function and mobility (35).

### Gaucher disease

Gaucher disease (GD) is a lysosomal storage disorder encompassing three main forms (types 1, 2 and 3). GD is an autosomal recessive disorder, characterized by the accumulation of glucosylceramide, mainly in cells of the reticuloendothelial system, due to mutations in the acid  $\beta$ -glucocerebrosidase (*GBA*) gene (36). The prevalence is approximately 1/100.000. Bone complications, including osteopenia/osteoporosis, increased fracture risk, Erlenmeyer flask deformity, bone crises, osteonecrosis, lytic bone lesions, osteosclerosis, cortical thinning, acute osteomyelitis, and growth retardation, affect up to 90% of GD patients, mainly present in type 1 (the chronic non-neurological form) and type 3 (the subacute neurological form). The pathophysiology of bone disease includes several factors such as: alterations of bone marrow and vascularity, immune cells, inflammation, macrophage-derived factors, cytokines, and hormones. Some reports appear to indicate that bisphosphonates may have a role in the treatment of bone manifestations, but further data on fracture risk reduction, changes of bone biomarkers, and BMD assessment would be necessary, evaluating also the potential risk of osteonecrosis of the jaw, a severe bone complication of GD (36).

### Classic galactosemia

Classic galactosemia is an autosomal recessive disorder resulting in a deficiency of the galactose-1-phosphate uridylyltransferase (GALT) enzyme, caused by homozygous or compound heterozygous mutation in the *GALT* gene. Classic galactosemia occurs in approximately 1/40.000 - 50.000 Caucasian newborns (37). GALT deficiency leads to an accumulation of galactose-1-phosphate, resulting in increased production of galactitol and galactonate metabolites, that may have adverse effects on the ovaries and bone, among other tissues (37). De-

creased BMD is frequently encountered in classic galactosemia. This decrease in bone mass is most prominent in adults, but is already described in prepubertal children (38). Although the pathophysiological mechanism is still not fully understood, several factors could negatively affect bone metabolism in this disease, such as: dietary restriction, primary ovarian insufficiency in women, abnormal glycosylation of collagen or other glycoproteins involved in bone metabolism, and the decreased insulin-like growth factor (IGF-I) and Insulin-like growth factor-binding protein-3 concentrations (39).

### Systemic sclerosis

Systemic Sclerosis (SSc) is an uncommon connective tissue disease characterized by excessive collagen deposition and damage to skin and internal organs, vasculopathy, and immune activation. The prevalence is estimated at around 1/6.500 adults. A recent systematic review on data about the prevalence of low BMD, risk factors for low BMD, and occurrence of fracture and fracture-related mortality in SSc, has suggested that patients with SSc are at a higher risk of losing bone density, especially when other osteoporosis risk factors are present (40). However, the effect of SSc on bone is still not well understood (40). SSc-specific factors that may increase the risk of osteoporosis include: chronic inflammation, early menopause, immobilization, soft tissue calcification depleting calcium stores, and alteration of vitamin D metabolism in the skin, kidney, and gastrointestinal tract (41). Hypothyroidism, a common endocrine complication in SSc, can contribute to the low BMD (42). Regarding therapy of osteoporosis, the elevated sRANKL level in SSc, found by Dovio et al. is a potential target of denosumab, which could be an appropriate alternative to bisphosphonates when there is failure or gastrointestinal intolerance (43).

### Neuromuscular Diseases

#### Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is the most common muscular dystrophy in childhood, affecting 1/5.600-7.700 males between ages 5 and 24 years. It is caused by mutations in the gene encoding the dystrophin protein, located on the short arm of the X chromosome (44). Patients affected by DMD have low BMD and are at high risk for fractures. In DMD, osteoporosis has a multifactorial pathogenesis, including treatment with glucocorticoids, immobility, delayed puberty, lack of sun exposure with low vitamin D production, and inflammatory changes (45). There are few retrospective studies in persons with DMD, regarding the use of alendronate, pamidronate, zoledronate and no controlled study. However, preliminary results are supportive (46-48).

#### Rett Syndrome

Rett Syndrome (RS) is a severe neurological disease, characterized by arrest of brain development. It is caused by an X chromosome mutation (49). The prevalence is estimated at 1/9.000 in girls under the age of 12, whereas the prevalence in the general population is estimated at approximately 1/30.000. Individuals affected by RS have usually low BMD, high risk of fractures, seriously impairing the mobility and quality of life at a young age (49). Immobility, development of epilepsy and anti-convulsant medications are all factors that can contribute to the development of osteoporosis (49).

## Endocrine and Reproductive Disorders

### Primary hyperparathyroidism

Primary hyperparathyroidism is due to increased intrinsic activity of the parathyroid gland, altering the secretion of parathyroid hormone (PTH), in the absence of a known or recognized stimulus affecting calcium homeostasis (50). Primary hyperparathyroidism is a common endocrine disorder, but there are some rare forms of this disease such as: family isolated hyperparathyroidism, hyperparathyroidism familial not isolated, parathyroid cancer, hyperparathyroidism-jaw tumor syndrome, and ectopic hyperparathyroidism associated to carcinomas (50). Family isolated hyperparathyroidism and parathyroid cancer can be caused by heterozygous mutation in the cell division cycle protein 73 (*CDC73*) gene (prevalence unknown). Hyperparathyroidism familial not isolated is associated to multiple endocrine neoplasias, such as multiple endocrine neoplasia (MEN) type 1, 2A and 4 (prevalence respectively of: 1-9/100.000, 1/30.000, and unknown). Hyperparathyroidism-jaw tumor syndrome (HPT-JT) is a rare, autosomal-dominant disease secondary to germline-inactivating mutations of the tumor suppressor gene *CDC73* (prevalence unknown). Furthermore, ectopic hyperparathyroidism can be associated to carcinomas, such as clear cell carcinoma of the ovary, small cell lung carcinoma and thymoma. It is known that high levels of PTH enhances the osteoclast differentiation and activity via RANKL-OPG system, resulting in bone resorption, mainly in cortical bones, and the net effect is bone loss and increased fracture risk (50).

### Metabolic bone disease

Osteogenesis imperfecta (OI) is a group of clinically and genetically heterogeneous disorders characterized by high risk of bone fractures, with variable degree of severity and presumed or proven defects in collagen type 1 biosynthesis (51). The incidence of the different types of OI is approximately 1/15.000-20.000 births and most cases are due to autosomal dominant inheritance with mutations in collagen, type 1 alpha-1, type 1 alpha-2 (*COL1A1* or *COL1A2*) genes, which encode the alpha 1 and alpha 2 chains of type 1 collagen (51). Mutations in *COL1A1* and *COL1A2* genes altering the structure or the amount of type 1 collagen, result in a skeletal phenotype that ranges from subclinical to lethal (51). Furthermore, there are several mutant noncollagen genes causing the 5-10% of recessive cases, such as *CRTAP*, *LEPRE1*, *PPIB*, *PLOD2*, *FKBP10*, *SERPIN H1*, *SERPIN F1*, *BMP1*, *IFITM5* genes. All types of OI cause fragile bone, which can include overmineralization or under-mineralization defects as well as abnormal collagen post-translational modifications (52).

Hypophosphatasia is an inheritable disorder characterized by defective mineralisation of bones and teeth, due to inactivating mutations of the alkaline phosphatase (*ALPL*) gene, with consequent impaired activity of tissue-non-specific alkaline phosphatase (53). The frequency of the disease has been estimated to be 1/100.000 for severe forms, also if mild forms of hypophosphatasia may be more common (53). The prevalence of hypophosphatasia as a cause of bone fragility is likely underestimated. The disease is highly variable in its clinical expression, classified into six major forms, which ranges from stillbirth without mineralized bone to early tooth loss without bone symptoms (53). During childhood, the main manifestations include rickets, growth delay and dental problems (54). The adult form of hypophosphatasia is mainly characterized by osteomalacia, pseudofractures, and pathologic fractures after minimal

trauma, as well as by muscle and joint pain (55). In addition, a study demonstrated that histomorphometry and quantitative backscattered electron microscopy of iliac crest biopsies from patients with adult hypophosphatasia confirmed the expected enrichment of non-mineralized osteoid, but also showed an altered trabecular microarchitecture, an increased number of osteoblasts, and an impaired calcium distribution within the mineralized bone matrix (56).

Hypophosphatemic nephrolithiasis/osteoporosis-1 (NPHLOP1) is caused by heterozygous mutation in the sodium/phosphate co-transporter type 2 (*SLC34A1*) gene (prevalence <1/1.000.000). It has been described that heterozygous mutations in the *SLC34A1* gene may be responsible for hypophosphatemia and urinary phosphate loss in persons with urolithiasis or bone demineralization (57).

Osteoporosis-pseudoglioma syndrome (OPPG) is a rare autosomal recessive disease of severe juvenile osteoporosis and congenital blindness, due to mutations in the low-density lipoprotein receptor-related protein 5 (*LRP5*) gene. Approximately 50 cases of OPPG have been reported, most with onset of fractures after age 2 years, and congenital blindness (58, 59). *LRP5* is a membrane co-receptor in the canonical Wnt signaling pathway. *LRP5* mutations, preventing Wnt from binding to *LRP5*, lead to pathway inactivation and OPPG, while mutations that prevent *LRP5* from binding to co-factor Dkkopf lead to pathway activation and excessive bone formation (60). Some cases have been treated with bisphosphonates with beneficial response (61).

### Acromegaly

Acromegaly is a rare endocrine disorder, characterized by excess GH levels and consequently high IGF-1 concentration, due to a GH-secreting pituitary adenoma, in more than 95% of cases. The estimated annual incidence is of 3-4/1.000.000 and a current estimated prevalence is of 40-130/1.000.000 (62). The gene aryl hydrocarbon receptor interacting protein (*AIP*) has been identified as a major susceptibility factor, particularly in cases of familial acromegaly or when acromegaly begins in childhood or adolescence. Patients affected by acromegaly have an increased risk significantly higher (39-59% in cross-sectional studies) than prevalence of vertebral fractures in general population (approximately 14%) (63). BMD can be normal, increased or decreased, and it is usually discordant with occurrence of morphometric vertebral fractures (64). The pathogenesis of osteoporosis in this disease is not clear, however increased bone turnover and impaired trabecular bone microarchitecture have been described (64). The risk of fractures seems correlate with acromegaly activity, its duration, coexistent hypogonadism, diabetes mellitus, and glucocorticoid therapy (56). There are no specific recommendations, but screening with thoracic and lumbar vertebral radiographs is indicated in patients affected by acromegaly (64).

### Growth Hormone Deficiency

Isolated GH deficiency (IGHD) refers to conditions associated with growth failure due to lack of growth hormone (GH) action. It is estimated to occur in 1/3.480-10.000 individuals (65). Although most cases are considered to be sporadic, a genetic cause is found in about 10-15% of the patients (66). Many Authors have observed low BMD in GHDeficient patients (67). It is known that GH has a key role in longitudinal bone growth and in reaching peak bone mass (PBM) during childhood and adolescence. GH regulates bone remodeling and increases the bone mass through not only the circulating IGF, but also the locally



produced IGF in the skeleton, where it acts in an autocrine or paracrine mode. Subsequently, despite closure of epiphyseal growth plates, effect of GH/IGF on bone turnover, bone mass, bone density and strength persist (68). It is recognized that decrease in bone growth and PBM influences incidence of vertebral and nonvertebral fractures in elderly patients, and GHD in adults results in low bone turnover osteoporosis with high risk of fractures. At a young age, GH therapy should minimize, if not prevent, osteoporosis in adulthood (67), subsequently low bone mass can only be partially reversed by GH replacement therapy (68).

### Cushing's Syndrome (ACTH-dependent and independent)

Cushing syndrome (CS) encompasses a group of hormonal disorders caused by prolonged and high exposure levels to glucocorticoids, that may be due to ACTH-dependent (80% cases), or – independent (20% cases) causes. ACTH overproduction may be of pituitary origin (85% cases), chronic over-secretion of ACTH by a pituitary corticotroph adenoma, or result from ectopic tumor secretion (15% cases). ACTH - independent Cushing syndrome may result from excess secretion of cortisol by either a unilateral and benign (adrenocortical adenoma: 55-60%) or malignant (adrenocortical carcinoma: 35-40%) adrenocortical tumor or by bilateral adrenal secretion by macronodular adrenal hyperplasia (AIMAH), as an isolated disease or as part of McCune-Albright syndrome (MAS), or by primary pigmented nodular adrenocortical disease (PPNAD), as an isolated disease or as part of Carney complex (CNC). The incidence of Cushing's syndrome is estimated to be equal to 1-3/1.000.000 inhabitants per year, whereas its prevalence is about 40/1.000.000 inhabitants (69). Several studies, evaluating the effect of endogenous hypercortisolism on the skeleton, describe that this leads to a decline in BMD, also in patients with subclinical hypercortisolism (70). Structural and functional impairment of skeleton is a relevant cause of morbidity and disability in patients with CS. Approximately 30-50% of patients with CS experience fractures, mostly at the spinal column, consistent with the 50% incidence of osteoporosis (71). CS causes osteopenia and osteoporosis through a variety of synergistic mechanisms, including decreased osteoblastic activity and increased apoptosis of osteoblasts, probable loss of cortical osteocytes and thus prevent bone repair, increased sensitivity to PTH, decreased renal calcium reabsorption and calcium absorption from the gut, muscular atrophy, secondary hypogonadism, inhibition of GH secretion with growth failure, pubertal arrest and reduced peak bone mass. In addition, cortisol hypersecretion alters the secretion of cytokines, and growth factors influencing bone mass (72). It is recommendable to measure BMD (possibly with DEXA at lumbar spine) in all patients affected by CS, considering the preferential bone loss in the cancellous skeleton (71). Successful treatment of CS is associated with a slow improvement in BMD, taking approximately 10 years to become complete. Bisphosphonates and recombinant human PTH can induce a more rapid improvement in BMD decreasing the fracture risk (71).

### Hypogonadism

There are several rare forms of male and female hypogonadism, including females and male congenital hypergonadotropic hypogonadism, and hypogonadism due to reduced gonadal steroids synthesis or action. Hypogonadism, regardless of etiology, can result in osteoporosis. Sex steroids are major hormonal regulators of bone turnover in both sexes, and there are many studies on the roles of gonadal steroids in bone

metabolism. Estrogen deficiency increases the life span of osteoclasts and bone resorption, decreasing OPG production and increasing RANKL and cytokines (IL-6 and TNF- $\alpha$ ) levels, that promote osteoclastogenesis (73, 74). Moreover, estrogen deficiency induces osteoblasts apoptosis and impairs Wntless-beta catenin signaling, regulating osteoblastic activity (75). At last, androgen deficiency inhibits the proliferation and differentiation of osteoblasts and promotes the osteoclastogenic activity (74).

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