Osteoporosis in Pediatrics

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Osteoporosis is a complex multifactorial condition characterized by progressive loss of bone mass and microarchitectural deterioration, leading to increased bone fragility and susceptibility to fractures [1]. Although it occurs most commonly in the elderly (women and men alike) as a result of sex hormone deficiency (primary, involutional osteoporosis), it is increasingly recognized that osteoporosis also affects other high risk pediatric and adult populations (secondary osteoporosis).

Bone development during childhood and adolescence is a key determinant of adult skeleton health. A reduced bone mass is associated with increased fracture risk in adults as well as in children. Peak bone mass, which is reached by early adulthood, serves as a bone reserve for the remainder of life, therefore childhood and adolescence are crucial periods for bone development. Strategies implemented for optimization of bone acquisition, as well as factors adversely affecting bone growth during these susceptible periods can have potentially long-standing consequences.

Bone formation and remodeling

Bone is a mineralized tissue that performs the multiple mechanical and metabolic functions of the skeleton. The mineralized extracellular component, which builds over 99% of bone tissue, is composed of 30% organic matrix, mostly type I collagen, and 70% mineral represented by calcium and phosphorus in the form of hydroxyapatite crystals [$Ca_{10}(Ph_4)_6(OH)_2$]. Bone contains two distinct cell types, both derived from bone marrow: the osteoblasts, or bone forming cells, from mesenchymal lineage, and the osteoclasts, or bone resorbing cells, from hematopoietic cells of the monocyte/macrophage family [Figure 1] [2]. During skeletal development and throughout life, the coupled function of these cells is responsible for bone formation, mineralization and remodeling. Bone metabolism is controlled by numerous systemic and local endocrine and paracrine factors [Table 1]. The local factors are represented by a myriad of immune and hematopoietic cytokines and growth factors present in the bone microenvironment and involved in the direct communication between osteoblasts and osteoclasts [3]. Although multiple hormones and cytokines regulate various aspects of bone remodeling, it was recently hypothesized that the final effectors are represented by several peptides, members of the tumor necrosis factor and TNF receptor superfamilies. These peptides are osteoprotegerin/osteoclastogenesis-inhibition factor and osteoprotegerin-ligand/osteoclast differentiation factor, produced by osteoblast lineage cells, and the receptor for activation of nuclear factor kappa B, present on osteoclast

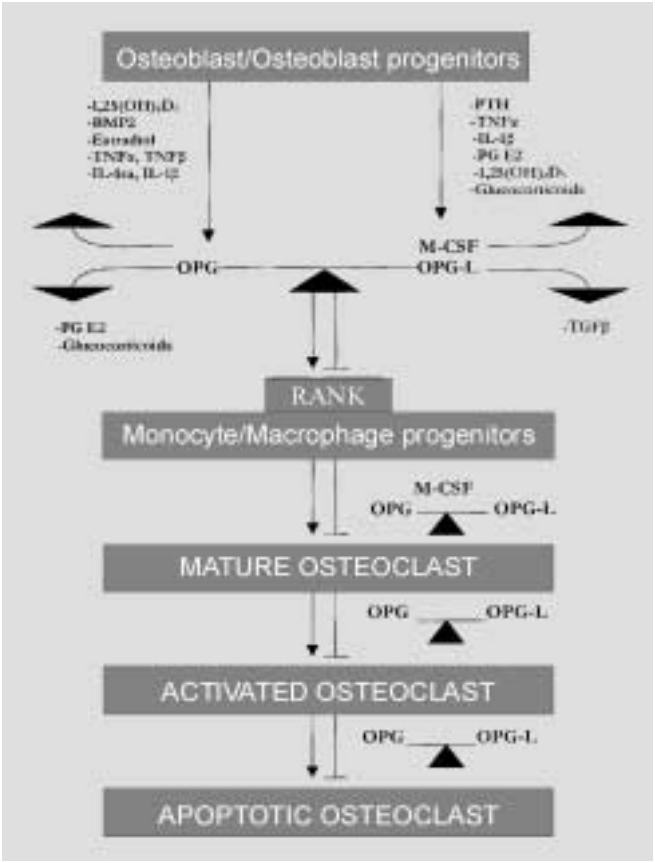

Figure 1. Osteoclast differentiation and activation is accomplished through a common pathway represented by the OPG/ODF (osteoprotegerin/osteoclast differentiation factor), OPG-L/OIF (osteoprotegerin-ligand/osteoclastogenesis inhibitory factor) and RANK receptor. M-CSF (monocytes colony-stimulating factor), OPG/ODF and OPG-L/OIF secreted by osteoblasts or stromal cells are essential for osteoclasts' initial differentiation from their precursors. All steps of osteoblast formation and activation are regulated (stimulated (↓) or inhibited (⊥) by the relative ratio of OPG/OPG-L in the bone microenvironment. The "convergence" hypothesis speculates that the proresorptive and antiresorptive effects of most calcitropic cytokines and hormones are mediated through regulation (stimulation ↶ or inhibition ↷) of OPG and OPG-L production, the final effector system that modulates the differentiation, activation and apoptosis of osteoclasts.

TNF = tumor necrosis factor

Table 1. Systemic and local factors controlling bone remodeling

Systemic factors
Parathyroid hormone
Vitamin D
Calcitonin
Thyroid hormones
Growth hormone and IGF-1
Gonadal and adrenal sex steroids
Insulin
Leptin
Local factors
Cytokines
Interleukins (IL-1, IL-6, IL-11, IL-18)
Tumor necrosis factors (TNF-α)
Transforming growth factors (TGFβ, FGF)
Colony-stimulating factors (M-CSF)
Insulin-like growth factors
Prostaglandins (PG E_2)
Nitric oxide

lineage cells. The interaction between OPG-L, OPG and RANK ultimately dictates the balance between bone resorption and formation [Figure 1] [4].

Peak bone mass

Bone mass is accumulated progressively from infancy through the end of adolescence and beyond, in a process that generally parallels linear growth. During childhood and adolescence, up until the acquisition of adult stature, bone growth and remodeling occur simultaneously – the final result being the acquisition and maintenance of body bone mass. Bone acquisition is unequally distributed during childhood and adolescence, with about 40–60% of peak bone mass being achieved during the adolescent growth spurt. The increase in bone mass in early puberty is due to an increase in bone size, whereas a smaller increase in bone mineral content independent of increase in bone size occurs in late puberty [5]. An increase in serum insulin-like growth factor-1, stimulated by growth hormone and sex steroids, is probably the main facilitator of increase in bone size during puberty [6].

Peak bone mass appears to be mainly under genetic control but is also influenced by lifestyle factors including diet, exercise, alcohol intake and tobacco use, as well as hormonal factors and exposure to risk factors such as disease and medication. Family and animal studies suggest that genetic factors are responsible for 60–80% of variance in bone phenotype (bone structural characteristics and skeletal size) and that these heritable effects are already programmed before puberty. A common allelic variation in vitamin D receptor was the first of several genes and chromosomal loci to be implicated in the genetic determination of bone phenotype. In addition, intronic polymorphism of the collagen-I alpha gene, allelic variations for the estrogen receptor, TGF-β1 and TGF-β receptor, IGF-1 pathway, interleukin-4 and 6 and the IL-1 receptor antagonist, calcitonin and the parathormone receptors have been shown to be related to bone density and fracture risk in different studies. The great variability in genetic findings is probably related to the interaction of particular loci with specific environmental or other genetic factors as race and gender, which have additional influence on bone mass [7].

Although genetic factors exert a predominant influence on peak bone mass, environmental and modifiable lifestyle factors also play a significant role. Among the environmental factors, the relationship between calcium intake and bone mass has been the most extensively studied. An adequate calcium supply is essential for the developing skeleton in order to reach its genetically programmed bone density. There is evidence from retrospective studies that high calcium intake in the form of dairy products in early life is associated with greater peak bone mass and fewer hip fractures in adult life [8]. Moreover, several prospective studies showed that increased calcium or dairy product supplementation in children resulted in short-term greater skeletal mineral acquisition, and supplementation with calcium and dairy products was shown to prevent bone loss in pre- and postmenopausal women [9,10]. However, it remains intriguing that some studies have failed to show a relationship between calcium intake and bone mass. The American Academy of Pediatrics Committee on Nutrition recently published its statement regarding calcium requirements of infants, children and adolescents, based on recent studies that "identified a relationship between childhood calcium intake and bone mineralization, and the potential relationship of these data to fractures in adolescents and the development of osteoporosis in adulthood" [11]. General nutrition in addition to calcium intake is also important, as reflected by the 25% reduction of trabecular bone density in the lumbar spine in girls with anorexia and the reduced bone mineral density in malnourished and hypoalbuminemic aged people [12].

Numerous studies have addressed the effect of vitamin D supplementation on bone mineral acquisition and the risk of fracture, with variable results. Whereas some reported positive results and significant improvement in bone mass accumulation and diminution of fracture incidence, others failed to find any effect [13,14]. The main effects of vitamin D are enhanced intestinal calcium absorption and renal reabsorption, in addition to the direct and indirect effects on bone metabolism. These effects imply a complex relationship between bone and vitamin D [15].

Recently, interest has emerged on the potential beneficial effects of phytoestrogens (non-steroidal plant-derived compounds) on bone health. Several epidemiologic studies in humans and studies in animal models suggest a protective effect of isoflavones (the main phytoestrogens class present in soyfoods) on bone in a state of estrogen deficiency [16,17].

In conclusion, nutrition is an important modifiable factor in the development and maintenance of bone mass. Nevertheless, many

OPG-L = osteoprotegerin-ligand
OPG = osteoprotegerin
RANK = receptor for activation of nuclear factor kappa B

IGF = insulin-like growth factor
IL = interleukin

nutrients are co-dependent and simultaneously interact with genetic and environmental factors. Unraveling the interactions between different factors – nutritional, environmental, lifestyle and heredity – will help us understand the complexity of the development of osteoporosis and subsequent fractures.

Biochemical markers of bone remodeling (turnover)

Bone is a dynamic tissue that undergoes constant remodeling in response to environmental modifications, through bone formation and resorption. Their assessment during growth periods in childhood and adolescence should take into consideration that their values depend on numerous variables (age, pubertal stage, growth velocity, nutritional status, circadian and day-to-day variations). Biochemical markers of bone remodeling are divided into markers of bone formation, usually measured in serum, and markers of bone resorption, determined in serum or urine [Table 2]. Biochemical evaluation of bone metabolism should also include assessment of blood ions (calcium and phosphorus) and calcium-regulating hormones: intact parathyroid hormone, 25-OH vitamin D, 1,25-$(OH)_2$ vitamin D and calcitonin [18].

Diagnosis of osteoporosis

Since it is not possible to measure bone strength *in vivo*, bone mineral density is mostly used as a proxy measure since it accounts for approximately 70% of bone strength. Several non-invasive methods with varying accuracy and precision are currently available for bone mass measurement [19].

Dual energy X-ray absorptiometry

Measurement of bone mineral density and bone mineral content using DXA has become the standard method for assessing bone mineral content in the spine and other skeletal regions. The technique provides an apparent areal density (BMD) calculated as bone mineral content/bone area (g/cm^2). In addition to BMD absolute values (g/cm^2), most centers also provide z scores and T scores for each anatomic site (usually hip and spine). The z score compares the patient with a population adjusted for age, gender and weight, whereas the T score compares the patient with a gender-matched young adult population (at peak bone mass). The World Health Organization set the diagnostic criteria for the diagnosis of osteopenia and osteoporosis in postmenopausal women, as a T score at the spinal site between -1 SD and -2.5 SD, and more than -2.5 SD respectively [1]. The technique's advantages are high precision and accuracy, low radiation dose and increased speed of scan. The disadvantages of DXA are the high cost and the scarcity of centers performing the study. Another disadvantage, especially significant for growing children, is that DXA gives a two-dimensional reading for a three-dimensional bone, and expresses bone density as g/cm. In this way, when comparing two bones of a different size, the larger will show an artificially higher BMD than the smaller one. This is even more important when assessing a chronically ill population of children, who are often shorter or taller, heavier or lighter than average healthy children. At present, pediatric reference values are available for DXA of the lumbar spine and total body, but no normative values for hip are available. Accurate interpretation of DXA data in children requires the consideration of body and bone size, pubertal stage, skeletal maturation, ethnicity, and body composition. In order to overcome this problem, anthropometric based prediction models for whole-body BMC have been proposed and are being validated in children [20,21].

Table 2. Biochemical markers of bone remodeling

Marker	Comments
Markers of bone formation Alkaline phosphatase	Bone-specific alkaline phosphatase (bAP) is a constituent of osteoblast membrane. Its principal role is phosphate hydrolysis, which permits growth of hydroxyapatite crystals. In children bAP is increased until mid-puberty and decreased in late puberty.
Osteocalcin	Sensitive and specific marker of bone formation. OC is synthesized by osteoblasts and odontoblasts and incorporated directly into bone matrix, but some circulates in blood. Serum OC levels vary by age and pubertal stage and correlate with height and height velocity in pubertal children.
Procollagen I extension peptides	N-terminal and C-terminal extension peptides are cleaved during the extracellular processing of type I collagen, prior to fibril formation. Procollagen I carboxy-terminal peptide can be measured in plasma and correlates with growth velocity and with bone mineral aquisition.
Markers of bone resorption Tartrate-resistant acid phosphatase	Enzyme present in the osteoclasts and released during osteoclastic activity, however serum TRAP is not bone-specific.
Hydroxyproline	HP is a product of post-translational hydroxylation of proline in the procollagen chain and reflects bone resorption. HP is not specific for bone collagen, and non-collagenous proteins and dietary proteins may be a source for urinary HP. Urinary HP is very high during periods of rapid growth such as infancy and puberty.
Collagen pyridinium cross-links	Pyridinoline and deoxypyridinoline are generated from hydroxylisine and lisine during post-translational modification of collagen. Pyr and DPyr are released during matrix resorption and are excreted in urine. DPyr is more specific for bone. A marked age-related variation in urinary Pyr and DPyr occurs in children and adolescents and correlates with growth velocity.
Collagen type I cross-linked telopeptides	Same as pyridinium cross-links

AP = alkaline phosphatase, OC = osteocalcin, TRAP = tartrate-resistant acid phosphatase, HP = hydroxyproline, Pyr = pyridinoline, DPyr = deoxypyridinoline

Quantitative computed tomography

QCT enables, at least in theory, a direct measurement of bone density (g/cm^3) at any skeletal site. QCT's major advantage in the

DXA = dual energy X-ray absorptiometry
BMD = bone mineral density
BMC = bone mineral content
QCT = quantitative computed tomography

assessment of bone density is that it provides a true volumetric density, rather than an areal-adjusted result as DXA. Its major drawbacks are radiation exposure and cost [19].

Quantitative ultrasound

QUS methods have been introduced in recent years for the assessment of skeletal status in osteoporosis. This technique uses the ability of the ultrasound wave to provide information about the medium through which it is being propagated. Bone tissue can induce two types of alterations in the ultrasound waves: change the velocity of the wave (speed of sound) or reduce the amount of energy transmitted and attenuate the wave (ultrasound attenuation). The most investigated ultrasound parameters are speed of sound (or ultrasound velocity) and broad-band ultrasound attenuation as alternatives to BMD. Several studies suggest that ultrasound may provide additional information on skeletal status besides BMD (namely, microarchitecture, stiffness/elasticity) that cannot be measured using absorptiometry techniques alone, which may also be important for the assessment of fracture risk. In addition, the ultrasound technique has the advantage of being radiation-free, non-invasive, mobile and friendly to user and patient alike, making it ideal for use in children [19].

Assessment of bone status during childhood and adolescence is challenged by several problems, partially related to the limits of the available techniques (all of which were developed for use in adults) and absence or discrepancy in pediatric reference data. In addition, heterogeneous bone growth and acquisition during different stages of development, as well as the changes induced by disease or drugs used in their treatment, make assessment of bone status in healthy and sick children more difficult. The application of new approaches for the interpretation of bone densitometry data will help to determine whether different BMC values in children are related to bone length, width or bone density [20,21].

Table 3. Pediatric disorders associated with osteopenia and osteoporosis

Disease	Pathophysiology of bone disease
Connective tissue disorders Juvenile rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, scleroderma	Pro-inflammatory cytokines, glucocorticoid use, growth failure and delayed puberty, inactivity, reduced sun exposure, insufficient calcium and vitamin D
Gastrointestinal disorders Inflammatory bowel disease, celiac disease, cholestatic liver disorders, lactose intolerance, cirrhosis, post-liver transplantation	Same as above, in addition to calcium and vitamin D malabsorption
Respiratory disorders Cystic fibrosis, steroid-dependent asthma	Same as above
Endocrine disorders Insulin-dependent diabetes mellitus, hypothyroidism, hyperparathyroidism, Cushing syndrome, growth hormone deficiency, hypogonadism of all etiologies	Deficiency or excess of hormones with key roles in bone metabolism
Blood disorders Thalassemia	Hormonal deficiencies, bone marrow expansion, nutritional deficiency, desferral toxicity
Neoplastic disorders and bone marrow transplant	Chemotherapy, glucocorticoids, radiotherapy, growth failure, pubertal delay and nutritional deficits, systemic parathyroid hormone-related protein, and local cytokines
Renal disorders Chronic renal failure, nephrotic syndrome	Growth failure, nutritional deficiencies, parathormone, vitamin D, calcium and phosphor metabolism abnormalities
Eating disorders Anorexia nervosa, bulimia	Low body mass index, low calcium and vitamin D intake, hypogonadism, elevated cortisol levels
Metabolic disorders Homocystinuria, Gaucher disease	Reduced cross-linking of collagen type I fibrils (homocystinuria), infiltration by lipid-laden Gaucher cells, dislocation of hematopoietic cells, inflammatory cytokines
Neurologic and neuromuscular disorders Cerebral palsy, convulsive disorders, spina bifida, myopathies	Immobilization, decreased sun exposure, nutritional deficiencies, growth failure, pubertal delay, anticonvulsant therapy
Prematurity	Poor mineral intake, poor growth
Bone disorders Osteogenesis imperfecta, idiopathic juvenile osteoporosis, hypophosphatasia, polyostotic fibrous dysplasia	Collagen type I defect (osteogenesis imperfecta) Impaired osteoblast function (idiopathic juvenile osteoporosis)

Pediatric disorders associated with osteoporosis

Osteoporosis in an otherwise healthy child or adolescent is rare, although cases of idiopathic osteoporosis have been described. Rather, pediatric osteoporosis is increasingly recognized in the setting of chronic illness related to the disease itself or its treatment. Table 3 is a comprehensive list of pediatric disorders associated with osteoporosis. Several disorders with a high prevalence of osteoporosis are discussed in detail.

QUS = qualitative ultrasound

Idiopathic juvenile osteoporosis

Idiopathic juvenile osteoporosis is a rare type of osteoporosis in children characterized by the occurrence of vertebral and metaphyseal fractures, bone pain and gait disturbances. The disorder is self-limiting and shows a marked improvement during adolescence. The pathogenesis of this disorder is not entirely clear but seems to involve deficient bone formation as a result of impaired osteoblast/osteoclast team performance [22].

Rheumatoid arthritis

Bone loss is common in chronic rheumatoid disorders, including juvenile rheumatoid arthritis, systemic lupus erythematosus and juvenile dermatomyositis, occurring early in the disease course even in children not taking corticosteroids. Children with JRA have

skeletal abnormalities demonstrated by the presence of periarticular bone destruction and the occurrence of generalized osteopenia. Generalized osteoporosis and pathologic long bone and vertebral fractures have been reported in 15–30% of JRA patients [23].

Local produced pro-inflammatory cytokines (TNF-α, IL-1, IL-6), resulting from the rheumatoid process within the synovium, are presumed to be responsible for the juxta-articular bone loss. The pathogenesis of generalized osteoporosis and osteopenia is undoubtedly multifactorial and includes disease activity and duration, reduced physical activity, limited sunlight exposure, inadequate intake of calcium and vitamin D, low body mass, delayed puberty, and the use of various anti-inflammatory medications such as steroids and methotrexate [24]. The presence of osteoporosis should be suspected in all children with chronic rheumatoid disorders, in order to avoid the complications associated with both local and generalized osteoporosis – namely, functional impairment associated with periarticular osteoporosis and increased risk of fractures with generalized osteoporosis.

There is a paucity of interventional studies for treatment of osteoporosis in children with JRA. In the meantime, optimizing calcium and vitamin D intake and physical activity, along with corticosteroid avoidance and control of disease activity is advocated for children with JRA. Encouraging results have been reported from a study in children with connective tissue disorders treated with bisphosphonates, which found this treatment to be safe and efficient [25].

Inflammatory bowel disease

The prevalence of osteoporosis and osteopenia in adult patients with IBD ranges from 31% to 59% and is reported to be more frequent and more severe in patients with Crohn's disease as compared with ulcerative colitis. Malnutrition and miscellaneous nutritional deficiencies, calcium and vitamin D malabsorption, bowel resection and various medications (corticosteroids, methotrexate, 6-mercaptopurine) were reported to correlate with bone loss [26]. Although the cause of IBD is not clearly known, the interplay of cytokines with immunoregulatory and pro-inflammatory activities (IL-1, IL-6, TNF-α) with anti-inflammatory cytokines (IL-1 receptor antagonist) may contribute to the pathogenesis of ongoing inflammation. Osteoporosis and osteopenia were also reported in children with IBD and correlated with nutritional status and corticosteroid therapy [27,28]. In addition to increased bone loss, children and adolescents with growth failure and delayed puberty may have diminished bone mass acquisition (lower peak bone mass), which further compromises bone status. Therefore, for patients with IBD, it was recommended that their bone status be monitored and preventive measures implemented already at their initial evaluation [29].

Celiac disease

Celiac disease, a common cause of malabsorption in childhood, is frequently associated with skeletal disorders (osteoporosis, rickets and osteomalacia). Several studies demonstrated the presence of low bone mineral density in up to 75% of adults and children with untreated celiac disease [30]. The abnormality of bone mineral density seems to be mainly the result of altered calcium metabolism related to calcium and vitamin D malabsorption and secondary hyperparathyroidism, in addition to pro-inflammatory and anti-inflammatory cytokines (IL-1β, IL-6, IL-1 receptor antagonist). Strict adherence to a gluten-free diet leads to complete recovery of the intestinal mucosa and correction of malabsorption. However, the effects of a gluten-free diet on bone are still controversial in adults, with studies reporting either a scarce effect or a remarkable improvement in BMD. By contrast, short and long-term longitudinal studies in children showed a complete recovery after a gluten-free diet for less than one year of [31,32].

Cystic fibrosis

Osteoporosis is highly prevalent in adult patients with cystic fibrosis and represents a heavy infirmity for patients surviving into adulthood. Its pathophysiology is complex and involves malnutrition, vitamin D deficiency, calcium malabsorption, chronic inflammation, delayed puberty and hypogonadism, physical inactivity, and medication. Therefore, bone disease in cystic fibrosis is a mixture of osteoporosis and rickets [33]. Although the extent of the problem is well documented in adults, the results of studies in children are less conclusive [34]. Since inadequate bone mineral accretion as well as increased bone loss contributes to the deficits in bone mineral, treatment of osteoporosis addresses both aspects and begins with preventive measures that should be instituted from childhood.

Drug-induced osteoporosis

The list of drugs that may cause osteoporosis, in the absence of other predisposing genetic or environmental factors, include: glucocorticoids, excessive thyroid hormones, alcohol, medroxyprogesterone acetate, luteinizing hormone-releasing hormone agonists, anticonvulsants, cyclosporine A, methotrexate, 6-mercaptopurine, aluminium, lithium and exchange resins.

Osteoporosis and glucocorticoids

Glucocorticoid therapy is life-saving for various disorders frequently encountered in pediatrics. However, steroid therapy is associated with a number of significant side effects, of which glucocorticoid-induced osteoporosis is one of the most serious. The time course of glucocorticoid-induced bone loss has not been well documented, but there is evidence that the rate of loss is most rapid in the first 6 to 12 months of treatment (as much as 27%) and decreases thereafter [35]. The average dose and duration of therapy are both related to the extent of bone loss: higher doses are more likely associated with greater bone loss as well as extended periods of treatment (more than 3 months). There is uncertainty regarding the maximum "safe" dose, yet there is some evidence that daily prednisone doses lower than 7.5 mg do not cause adverse bone effects. Whether alternate-day prednisone therapy has any advantage over daily dosage in terms of bone-sparing effects is also controversial. It seems that bone loss associated with glucocorti-

JRA = juvenile rheumatoid arthritis
IBD = inflammatory bowel disease

coid excess is at least partially reversible, as shown by studies in patients with Cushing's syndrome, although the recovery is slow [36].

The alterations of bone remodeling induced by the glucocorticoid excess involve inhibition of osteoblast differentiation and proliferation, and stimulation of osteoblast apoptosis. Other factors include reduced expression of type I collagen, osteocalcin, IGF-1 and IGF-1 binding proteins, which have direct suppressive effects on bone formation. Furthermore, bone resorption is increased by predominantly indirect effects including hyperparathyroidism secondary to reduced intestinal calcium absorption, and hypogonadism resulting from glucocorticoid effects on the hypothalamic-pituitary-adrenal axis and gonads. High dose glucocorticoids also decrease renal tubular phosphate reabsorption and increase 1,25 $(OH)^2$ D synthesis [36].

Recently, the American College of Rheumatology published its guidelines regarding recommendations for diagnosis, prevention and treatment of glucocorticoid-induced osteoporosis [37]. The Committee recommends baseline measurement of BMD in all patients when initiating long-term (> 6 months) glucocorticoid therapy, with yearly follow-up as indicated. Intervention in patients taking glucocorticoids should include primary prevention in which prophylaxis is administered at the start of glucocorticoid therapy, and secondary prevention in which a bone active agent is given to glucocorticoid-treated patients with low BMD or fractures. Two therapies have proven effective and were approved for the treatment of glucocorticoid-induced osteoporosis in adults: sex hormone replacement therapy and bisphosphonates, but none in children [38]. The therapies aimed to prevent or treat glucocorticoid-induced bone loss should be continued as long as the patient is receiving glucocorticoids, and modification of osteoporosis lifestyle risk factors should be stressed.

Management of osteoporosis

Primary prevention

Pediatricians should supervise the implementation of primary prevention programs, such as vitamin D administration in infants, regular weight-bearing exercise and a healthy diet. Anticipatory guidance regarding healthy lifestyle habits, including avoidance of smoking and alcohol use, should be an essential component of routine pediatric health supervision.

Secondary prevention

Secondary prevention involves the recognition of disorders associated with increased risk of osteoporosis and prevention of its development. Usually, optimal management of these disorders together with the provision of satisfactory nutrition and adequate replacement of minerals and vitamins may prevent bone loss and even improve bone mineral density.

Therapy for osteoporosis

Several therapeutic options have been developed for the treatment of involutional osteoporosis and secondary osteoporosis in adults: estrogen replacement therapy, selective estrogen receptor modulators, bisphosphonates, calcitonin and parathormone therapy. None of these agents has been approved for the treatment of osteoporosis in children. However, biphosphonates have been used in isolated cases in several pediatric disorders, such as idiopathic juvenile osteoporosis, osteogenesis imperfecta, osteoporosis secondary to immobilization, steroid treatment in juvenile rheumatoid arthritis, leukemia, and after bone marrow and liver transplantation [39].

Conclusions

Impressive advances have been made lately in the understanding of bone physiology and pathophysiology, together with tremendous progress in the diagnosis and treatment of osteoporosis. The pediatrician should be aware that osteoporosis is not only a disorder of adults but may also concern children afflicted by several disorders with onset in childhood. Improvement and adaptation of techniques for the determination of bone mass and strength (DXA, ultrasound) in the pediatric population will increase our diagnostic accuracy and provide invaluable tools for assessing different therapies. Further studies in children should address the topic of osteoporosis in childhood, including its epidemiology, pathophysiology, diagnosis and treatment.

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