Osteoporosis in Pediatric Patients and Its Clinical Management

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1. Introduction

The increase in longevity achieved at present, the population has determined a striking increase in the prevalence of certain diseases and in other cases, the emergence of new forms of illness and during different life stages (1).

Osteoporosis is defined as a decrease in bone mass associated with the deterioration of bone tissue architecture and increased fracture risk, has become a serious public health problem in our society that affects a wide strata of the population age variable, though increasingly common among younger (2). There are two types of osteoporosis, primary and secondary. Primary osteoporosis is rare affecting one case per 100,000 subjects. For high school, its frequency is higher, being secondary to diseases or drug therapies. Table 1 shows the main causes that can lead to a primary or secondary osteoporosis.

The bone will undergo changes during growth reaching its peak during the second decade. After the fourth decade, there is progressive increase in bone loss that mainly affects trabecular tissue at both the peripheral and axial. Accordingly, it is during childhood when determining events occur in the development of adequate bone mineralization and bone mass final (3).

It is now accepted that osteoporosis in the adult subject has its origins in childhood. Accordingly, the prevention of it would begin with the empowerment of those factors that promote the acquisition of optimal bone mass development. Now if we take into account the dietary habits and sedentary marking between the current youth population, we can glimpse the high risk of developing the disorder to an increasingly early age (3).

During the first decade of life, the appendicular skeleton is growing faster than the axial. Also, the bone mineralization process starts in utero found strongly influenced by calcium intake during growth. However, calcium requirements vary throughout life, being greatest during the first years of life and in times such as puberty, pregnancy and lactation. Moreover, the loss of bone mass increases with age and accelerates with menopause. In this sense, it is advisable to increase the intake of calcium from the perimenopause.

For pediatric patients, there is a relationship between bone mass and size. However, in periods like puberty and after the pubertal growth spurt can be established called an imbalance between the rate of bone growth rate and increased bone mass resulting from this transient increase in bone fragility (4).
### Primary Osteoporosis
- Idiopathic juvenile osteoporosis
- Osteogenesis imperfecta
- Ehler Danlos syndrome
- Bruck syndrome

### Secondary Osteoporosis

#### Neuromuscular Disease
- Cerebral Palsy
- Duchenne Muscular Dystrophy
- Prolonged Immobilization

#### Endocrine Diseases
- Hypogonadism
- Turner Syndrome
- Growth hormone deficiency
- Hyperthyroidism
- Hyperprolactinemia
- Cushing Syndrome
- Congenital Metabolic Disorders
- Gaucher Disease

#### Procesos Crónicos
- Leucemia
- Fibrosis Quística
- Malabsorción intestinal
- Talasemia
- Cirrosis Biliar Primaria
- Anorexia Nerviosa
- Trasplantes
- Infección por VIH
- Yatrogenia
- Corticosteroids
- Metotrexate
- Cyclosporine
- Heparin
- Anticonvulsivants
- Radiotherapy

Table 1. Causes of primary and secondary osteoporosis in children

On the other hand, it is normal that there is a correlation between the stage of pubertal development and BMD at both the peripheral and axial. Among girls after menarche has been a significant increase in BMD. BMD in boys increases after puberty, with a more extended in time because their pubertal development is slower (5).

Genetic factors in turn, are equally important in the development of an adequate peak bone mass. Thus, a correlation in BMD between twins. For their part, black women have greater BMD and thus a lower incidence of osteoporosis when compared to white women. Also found lower BMD among women whose mothers had a post-menopausal status with osteoporosis compared to those other women the same age but without such a history. Accordingly, it should raise the transmission of genetic information is carried out mainly through the mother (6).

Analyzing the etiology of osteoporosis in children are significantly different from those in adulthood. Accordingly, the diagnostic approach would be completely different in children compared to adults. Among the risk factors associated with the occurrence of bone metabolism during childhood are processes that interfere with proper bone mineralization, the absence of positive stimulus of calcium and vitamin D from diet or exercise to obtain adequate bone mass. Other causes are disorders that cause interference in pubertal
development as well as any conditions that cause increased bone loss. Finally, prolonged exposure to certain drugs that induce the development of osteoporosis. Given the above should be considered the early diagnosis of osteoporosis in pediatric patients who have had one or more fractures are not preceded by trauma or as a result of minor trauma. Moreover, the development of significant angular deformities in the extremities and the presence of a marked kyphosis should guide the clinician to the presence of impaired bone quality.

This review aims to provide guidance on the characteristics of the process of normal and abnormal bone mineralization in the pediatric patient, the main factors involved and the existing prevention strategies.

2. Bone mass concept and assessment of their status

Bone mass is defined as the total amount of bone tissue in the organism including the extracellular matrix ossified. At present, it is accepted that the acquisition of appropriate peak bone mass is essential to prevent osteoporosis later in life. Since this formation and accumulation of bone mass occurs during the first decades of life, control of bone mineralization during childhood is a significant aspect to assess interest. This monitoring should aim to identify children at risk of developing osteopenia. Also, in the general population should implement measures to prevent the onset of the disease promoting lifestyles and measures to increase bone mass (7).

The development of an adequate level of bone mass is partly dependent on nutritional factors, so it is necessary to maintain an adequate nutrient supply during the growing season. Another aspect to consider genetic factors, accounting for 60% of total factors. In adulthood decreases the neo-bone formation after a period in which bone mass remains stable (8).

Puberty brings the largest increase in bone mineral density in both sexes, however, as in any period may generate changes to diet and exercise as much as 20% (9). Bone mass is increased from birth to be reduced by calcium deposition significantly as we approach the third decade or so. To three years increases to 30% after 20% and reach puberty about 40%. From the end of growth and to reach adulthood is increasing by 15%. Even 10 years ago mineralization at the same rate in both sexes. From this age is accelerated significantly in the girls (10).

The diagnosis and even prevention evaluation and therapy of osteoporosis may be jeopardized in a special way in the child all because of the need to use techniques which, although sensitive, reproducible and precise, resulting quick, painless, safe and non invasive.

Of all the methods proposed by the National Osteoporosis Foundation to assess the quality of bone, the most used technique is dual x-ray absorptiometry (DEXA). The basis of this technique in the study of attenuation is subjected to a dual X-ray beam through bone tissue (11). Although it can be done at different levels, the benchmarks for determining the criteria of normality, osteopenia or osteoporosis referred to data obtained at the height of the femoral neck or lumbar vertebrae (L2-L4) of the reference population. The interpretation of this technique has some difficulties in the child (12). There are already benchmarks (13-15), although obtained in cross-sectional studies.

The measures are available in axial regions (hip, spine) or peripheral (calcaneus, tibia, knee, radio and phalanges), but it has shown that measurements in predicting spinal fracture risk at that level, but not others, and so does the rest of the locations where BMD is measured.
In children, the area selection is further complicated because the timing and rate of mineralization depends on the biological age (13). Should be selected sufficiently vascularized bone, with good motility and under some pressure. In this regard, the determination in the calcaneus could induce excessive bias to withstand pressure, although some authors is the preferred (14).

Other recent application techniques are ultrasound imaging and computed tomography. It is noninvasive, excellent acceptance of any age which have been effective as bone assessment procedures in both the adult and the child (15). However, in the case of computed tomography to excessive cost limits their use as a technique for the prevention of osteoporosis.

3. Bone mineralization process

Bone mineralization is a complex process regulated by both genetic and hormonal factors, environmental and nutritional (16). From a genetic standpoint, the mineralization is controlled by a large group of genes. Among the most studied is the gene that controls vitamin D receptor, which depends on calcium absorption in the intestine. Hormonal level, there are several hormones involved in bone mineralization. These include parathyroid hormone which balances the mechanisms of formation and resorption of bone at the same time enhances the action of vitamin D. Calcitonin, which inhibits the action of osteoclasts, and growth hormone, HGH and IGF-1 that acts in the formation of cartilage and promotes the synthesis of the active metabolite of vitamin D (17).

Other molecules with activity on bone mass are the corticosteroids. They only act on bone mineralization when increased above normal levels, decreasing bone mass and bone growth. This is an important consideration in those children treated with corticosteroids. Thyroid hormones, in turn, are also involved in mineralization diminishing with increasing concentration. But all of these factors may also act on the environmental factors that can intervene by modifying diet and lifestyle (18).

4. Concept of osteopenia and osteoporosis

Osteopenia is defined by decreased bone mineral density between -1 and -2.5 SD for age, sex, height and pubertal stage. In cases where the decrease in bone mineral density is below 2 SD is considered osteoporosis (19).

Osteoporosis was defined in 1991 as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, which leads to increased bone fragility with a consequent increase in fracture risk. This definition implies a qualitative concept of altered bone architecture and a quantity related to bone density (20). Both osteoporosis and osteopenia may be primary as in aging or menopause but may also result from inadequate nutrition, and hormonal disorders or diseases of the bone.

However, there are childhood diseases that may present with osteopenia thereby increasing the risk of osteoporosis in adulthood. Among the mechanisms of production of osteopenia could cite many, though, could be divided into three main groups. Those processes that occur with an inadequate intake of nutrients such as anorexia nervosa, bulimia, protein-calorie malnutrition or poorly controlled diets (21). A second group would be composed of those disorders with intestinal malabsorption boxes. Within this section as possible symptoms of osteopenia generators could include celiac disease, cystic fibrosis, intolerance.
to cow’s milk proteins and inflammatory bowel disease. Other processes potentially involved in the development of osteopenia will neuropathy and liver disease that present with an impairment of the synthesis of active metabolites of vitamin D. Other processes involved will be the states of metabolic acidosis, prolonged administration of certain drugs such as anticonvulsants or corticosteroids and pictures of hypogonadism (22).

5. Nutritional factors

Proper nutrition is a key factor in maintaining adequate skeletal mineralization. In this process of bone mineralization energy and nutrients intervene in various ways, either by encouraging the development of cell mitosis, participating as visual elements, to be a source of vitamins which will involve regulating the synthesis of bone matrix and promoting the absorption level intestinal calcium or contributing to the synthesis of various hormones and factors crecimiento (23).

By feeding the body receives visual elements, vitamins intervene by regulating the synthesis of bone matrix and intestinal absorption of calcium and other minerals whose primary function is to act in the formation and consolidation of mineralized bone. Another essential aspect of bone remodeling in the child will be energy intake. This is an essential as the volume decreases in energy intake induce delays in growth, maturation and hence bone mineralization (24). Then in children with malnutrition by default is necessary to control the state of bone mineralization.

The bone mineralization process will necessarily regulated by protein intake through the diet. Its role essentially plastic makes these elements are essential for the synthesis of bone matrix. In this sense, the child, situations of inadequate intake may induce default to the emergence of problems of mineralization. On the contrary, when its contribution in the diet is excessive can cause hypercalciuric boxes, this is due to increased excretion of acid produced during protein catabolism. At present it is possible that the protein diet consumed in most developed countries it is closely linked with the increase in osteoporosis in the population (25).

Another aspect to consider is the ratio of sodium ingested with the level of calcium excretion by the kidney. Sodium and calcium share the same carrier at the proximal renal tubule. Although and yet there is no need to adjust the contribution of calcium to sodium intake through the diet in children (26). Calcium is an essential pillar in the prevention of osteoporosis. In our body and especially in the bones is deposited as hydroxyapatite crystals. Your deposit varies throughout life from 30 grams at birth to about 1.300 grams in adulthood (27).

Given the above will be necessary to modulate calcium intake during periods of increased growth and, especially during adolescence. During adolescence tends to accumulate 40% of total bone mass produced throughout life. Several studies have shown that calcium supplementation during adolescence increases bone mineral density (28). After administering 500 ml of milk per day during childhood will ensure intake of about 400mg of calcium, equivalent to 60% of the recommended daily amount.

Moreover, we have to take into account the bioavailability of calcium in food. The presence of phytates inhibit absorption and therefore vegetables, legumes and cereals despite containing high levels of calcium, it is not as comparable as that of milk. Similarly oxalates, alcohol, caffeine and phosphates hinder calcium absorption even when present in the diet (29, 30). Finally, pictures of obesity and overweight in children have been associated with
increased bone density. However there is evidence linking these situations with a higher incidence of fractures (31).

Vitamin D is another factor regulating the homeostasis calcium / phosphorus. Its main sources are dairy products. Exposure to sunlight or UV light promotes the metabolism of it. However, alterations in intestinal absorption mechanism and factors affecting their metabolism at the level of the skin should be considered as processes that alter bone formation and thus risk factors for developing osteoporosis (32).

6. Idiopathic juvenile osteoporosis

In some pediatric patients (usually young) are not able to establish any risk factors for osteoporosis. In these cases must be considered the possibility of presenting idiopathic juvenile osteoporosis. Its etiology is unknown, manifesting itself in some cases for an accidental radiological finding which may also require a significant osteopenia, short stature and kyphosis (secondary to vertebral crush fractures) (32). Generally do not exhibit any endocrine abnormality nor metabolism of calcium/ phosphorus. The levels of vitamin D and calcitonin are variable in these patients. For bone biopsy, this is not conclusive proof but often shows an increase of osteocytes in trabecular bone as well as signs of increased bone resorption. In general, treatment consists of substitution of calcium and calcitriol, tending to improve spontaneously in the post pubertal period by several authors due to the effect of gonadal hormones (33).

7. Osteogenesis imperfecta

Osteogenesis imperfecta is a genetic disease, autosomal dominant, in which there is an abnormality in the formation of collagen type 1 (34). This disorder causes weakness and bone fragility of varying degrees of severity and subsequent pathological fractures, as well as affecting other tissues. The etiology of this disease lies in the mutation of genes that encode both qualitative and quantitative production of collagen fibers. In terms of prevalence in the world, this ranges from about 1 case per 30,000 live births (34). The continuous advances in diagnosis have created new expectations for subjects with the disease, greatly improving their quality of life. At present there is no effective treatment, healing, since it can not act directly on the formation of collagen type I (34). Throughout history have used various medical treatments (calcitonin, anabolic steroids, etc.) to try to increase bone mass, to no avail. Currently, treatment is symptomatic and should be approached in a multidisciplinary manner. The best results were achieved with growth hormone (GH) and bisphosphonates (34).

8. Osteopathy associated with use of drugs

Another group of pediatric patients at high risk for osteoporosis are those subjects taking medications which interfere with the normal process of bone mineralization. The drugs most commonly associated with the development of bone disease or iatrogenic demineralizantes include steroids, anticonvulsants, cyclosporine, anthracyclines, methotrexate, warfarin and agonists of gonadotropin-releasing hormone (35).

In the case of steroids, these lead to the development of osteoporosis secondary to increased bone resorption. In addition, they inhibit intestinal absorption of calcium, decreased tubular
reabsorption of calcium and induce a secondary hyperparathyroidism. They also inhibit pituitary gonadotropin secretion and decrease the response of estrogen/testosterone to the follicle stimulating hormone (FSH). A level of osteoblasts caused a decrease in their ability to replicate, in turn stimulating the expression of collagenase by the osteoblast and thereby inducing the increase in bone matrix degradation with a decrease in the synthesis of growth factors (IGF1, IGF-2) (36).

Appropriate strategies to prevent osteoporosis from childhood: The prevention of osteoporosis to necessarily an assessment of bone mineralization status since early infancy, particularly in subjects at risk. In this sense, preterm infants, patients with malabsorption syndromes and corticosteroid therapy patients constitute the population most at risk of poor bone mineralization (37, 38).

The bioavailability of calcium in milk is far superior to commercial formulas, making it the leading source for calcium during breastfeeding. Only in the case of infants it should increase their calcium intake to the recommended supplementary with commercial formulas that have a higher calcium content (39).

In children aged 1 to 8 years there is no explicit consensus on the specific requirements of calcium. In any case, we recommend an intake of 500 mg per day for ages 1 and 3 years (40). This figure should be increased as they age and approach puberty. Thus, for ages 4 to 8 years the requirements will amount up to 800mg calcium per day. But have found no overt health benefits by increasing the daily amount (41). And at puberty, it is estimated that for every inch of growth are required calcio 20g (41).

Given the above, eating disorders, inflammatory bowel disease or the use of corticosteroids and prolonged rest in the minors are situations that require an attitude of monitoring and supervision by health staff (41).

It is estimated that the highest positive balance is achieved with an average daily intake of 1300mg. By contrast, those exposed to lower levels will have a negative impact on bone mineralization process (42). This corresponds to measurements made on white teens. In the case of blacks and adolescents have shown a better efficiency for the absorption of dietary calcium, can reach the same peak bone mass even with lower contributions of calcium (43).

Excess calcium in the diet, in turn, can cause a deficiency of iron and zinc, while favoring the formation of kidney stones (44). Similarly as phosphates present in carbonated drinks can also act by inhibiting the absorption of calcium in the intestine (45).

In cases of subjects with lactose intolerance, the simple addition of commercial lactase or ingestion of fermented dairy products like yogurt can remedy this situation (46).

The existence of toxic habits such as snuff or alcohol consumption can also interfere with the process of bone mineralization (47). But if there is a successful strategy to prevent osteoporosis from childhood this is the regular practice of exercise (48). The physical exercise from an early age not only ensure optimal weight status but also a formidable mineralization of our skeleton, reason is of great importance when the subject population are children and adolescents (49, 50). The continued practice of physical activity helps to acquire peak bone mass genetically determined (51). Although, to achieve these benefits, the current recommendations set out the need to practice a minimum of three days a week (52). Moreover, at present it is unknown whether calcium intake through diet may or may not alter the beneficial effect of exercise (52).

With regard to drug-induced osteoporosis, the most important preventive factor is the wise use and dosage of the same (53).
In summary, we conclude that the onset osteoporosis in children differs in its clinical management of osteoporosis in adults. In this sense, the early identification of risk groups be a priority. Therefore it should be emphasized that during the first and second decade of life, events occur which are essential for the proper development of bone metabolism. On this basis, the prevention of osteoporosis in adults should begin as early as the early childhood.

9. References


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Osteoporosis is a public health issue worldwide. During the last few years, progress has been made concerning the knowledge of the pathophysiological mechanism of the disease. Sophisticated technologies have added important information in bone mineral density measurements and, additionally, geometrical and mechanical properties of bone. New bone indices have been developed from biochemical and hormonal measurements in order to investigate bone metabolism. Although it is clear that drugs are an essential element of the therapy, beyond medication there are other interventions in the management of the disease. Prevention of osteoporosis starts in young ages and continues during aging in order to prevent fractures associated with impaired quality of life, physical decline, mortality, and high cost for the health system. A number of different specialties are holding the scientific knowledge in osteoporosis. For this reason, we have collected papers from scientific departments all over the world for this book. The book includes up-to-date information about basics of bones, epidemiological data, diagnosis and assessment of osteoporosis, secondary osteoporosis, pediatric issues, prevention and treatment strategies, and research papers from osteoporotic fields.

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