Osteoporosis in young individuals

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ABSTRACT

Although there are some differential aspects related to peak bone mass acquisition and later bone loss throughout life between genders, the frequency of osteoporosis in young individuals is similar for both genders. In addition, in this population group, the development of osteoporosis is frequently associated with secondary causes. Indeed, nearly 50% of young individuals with osteoporosis have diseases or therapies related to the development of this disorder, with glucocorticoid therapy being one of the most frequently associated conditions. There are several other processes, which have also been associated with such a disorder in these individuals, but the causes differ between genders. In addition, idiopathic osteoporosis is also a frequent condition in these patients. In this subgroup of patients, a family history of osteoporosis or hypercalciuria is also a frequently associated finding. Because of that, in order to rule out secondary causes of osteoporosis, the laboratory studies performed to these patients should be extensive. Although there is few data on the treatment of these patients, basic rules such as exercise, correct calcium and vitamin D consumption, and avoiding alcohol and tobacco consumption should be advised. Drug therapy will depend on the cause of osteoporosis. However, it should be taken into account that most young women are of childbearing age, so drug therapy in these patients should be evaluated cautiously.

Osteoporosis en individuos jóvenes

RESUMEN

Aunque existen aspectos diferenciales relacionados con la adquisición del pico de masa ósea y la pérdida ósea que se produce a lo largo de la vida entre ambos sexos, la frecuencia de osteoporosis en individuos jóvenes es similar en ambos sexos. Sin embargo, en este grupo de población el desarrollo de osteoporosis suele asociarse a causas secundarias; de hecho, se ha descrito que alrededor del 50% de los individuos jóvenes con osteoporosis, tanto hombres como mujeres, presentan enfermedades o fármacos relacionados con su desarrollo, siendo el tratamiento prolongado con glucocorticoides una de las causas más frecuentes. Existen otros procesos que también han sido implicados en su desarrollo y que varían según el sexo del individuo. Por otro lado, la osteoporosis idiopática es otra causa frecuente de disminución de la masa ósea en estos pacientes, en donde la historia familiar de osteoporosis y la presencia de hipercaleuciria son hallazgos habituales. Por esto, la valoración de estos pacientes precisa de un estudio minucioso para descartar causas secundarias de osteoporosis. Aunque existen pocos estudios sobre el tratamiento de este proceso en este grupo de población, son aconsejables una serie de normas básicas que incluyan ejercicio físico, ingesta adecuada de calcio y vitamina D, y evitar el consumo de tabaco y alcohol. El tratamiento farmacológico dependerá de la etiología de la osteoporosis y del sexo del paciente. Debe recordarse que la mayoría de las mujeres jóvenes se encuentran en edad fértil, por lo que el tratamiento farmacológico en este grupo de población siempre deberá valorarse con cautela.

Introduction and incidence

There are distinguishing aspects related to the acquisition of peak bone mass and bone loss that occurs throughout life between genders. Thus, men have a later-onset puberty and are taller than women, so they have larger bones and a higher peak bone mass.\textsuperscript{12} This fact, coupled with increased periosteal apposition and lower endosteal resorption of male bones contributes to the biomechanical advantages that lead to greater bone strength and reduced fracture incidence in this gender in adulthood.\textsuperscript{3} However, although the incidence of osteoporosis in the adult population is higher in women, in young population the frequency of this process is similar for both sexes.
Studies examining the incidence of osteoporosis in young population are scarce. However, if we assume a Gaussian distribution of bone mineral density (BMD) in the general population, about 0.5% of young adults may have a decrease in BMD according to WHO criteria. Thus, a prevalence of densitometric osteoporosis in young women (aged between 20-44 years) of 0.34% to 0.17% in the lumbar spine and femoral neck respectively has been seen in our population. The prevalence of osteoporosis in men for the same age group is 1.39% to 0.17%, respectively, the prevalence increases to 4.3% to 3.45% when including women and men over 45 years. In other populations, like the United States, the prevalence of osteoporosis in young women is lower and although there is little data on the incidence of this process in the young population an incidence of 4.1 per 100,000 person-years has been estimated for this disease, with a women:men ratio of 1.2/1.

Although studies examining the incidence of fractures in this population are scarce, an incidence of vertebral fractures in young (<35 years) of 3 per 100,000 persons per year, amounting to 21 per 100,000 person years in the population aged 35-44 years is estimated. In these individuals, especially the younger ones, vertebral fractures are often of a traumatic origin. Despite this, it is important to note that the presence of fractures in this population, especially the distal radius, are associated with decreased bone mass and also as a risk factor for future fractures suffered in adulthood.

Determinants of bone mass

Several factors influence the acquisition of "peak" bone mass and its progression throughout life. Thus, genetic factors along with environmental factors such as exercise and diet and hormonal factors are the main determinants in the acquisition of peak bone mass. Although the genetic factor contributes to a greater extent in its acquisition, environmental factors, such as exercise and calcium intake may also play a role. Thus the practice of exercise that involves mechanical load, especially when performed during early life may be associated with a marked increase in bone mass that appears to be long-term. In addition, exercise produces positive structural geometry changes that influence increased cortical bone thickness with a consequent further increase in bone strength. Typically, the peak bone mass is usually reached between 25-35 years of age, being very similar in both sexes until the age of 40. From this age, evolution is different, because estrogen deficiency significantly influence bone loss in women, this gap occurs gradually, so that a few years before menopause (about 3 years) women usually start to present increased bone loss that is often associated with increased values of serum gonadotropins and reduced estradiol. In fact, increased serum gonadotropin values above 20mU/l are associated with an increased bone turnover and bone loss in perimenopause.

Several factors have been associated with decreased bone mass in adult premenopausal women. Thus, a low body mass index at menarche has been associated with decreased bone mass in adult women 40-45 years, while low weight, age at menarche over 15 years and physical inactivity during adolescence are factors that have been associated with decreased bone mass in young women under 35 years. In addition, late menarche is not only associated with a lower bone mass, but also deleterious structural changes of bone tissue. It must be remembered that adolescence is a critical period in the growth and the acquisition of bone mass, and approximately 86% peak bone mass is attained before age 14 or two years after menarche. Therefore, exposure to deleterious factors or diseases that may affect bone metabolism during this period will greatly influence bone mass in adulthood. In this sense, it is estimated that the "peak" bone mass has a greater relative influence in the development of osteoporosis in adulthood than the bone loss that occurs at a later age.

Causes of osteoporosis in young people

In young people the presence of one or more factors related to osteoporosis is common. It has been reported that about 50% of patients present diseases or take drugs related to the development of this bone disease, being Glucocorticoids (GCC) one of the most common causes. Most studies examining the impact of the GCC on skeletal tissue include patients of both genders and are consistent in showing that all patients, young and old, male and female, are susceptible to the effects of GCC on bone mass. Thus, although postmenopausal women are at an increased risk for fracture, young individuals may also lose bone mass rapidly. In fact, between 18%-22% of young premenopausal women develop osteoporosis following prolonged treatment with high doses of prednisone.

It is interesting to note that although the presence of a cause associated with loss of bone mass in young individuals with osteoporosis is common, the origin of this often differs with sex. Thus, while in men alcohol, hypogonadism and treatment with GCC are the most common causes of secondary osteoporosis, in young women Cushing's disease, osteoporosis associated with pregnancy and osteogenesis imperfecta are some of the most frequent causes. However, other processes have also been implicated in the development of osteoporosis in these patients, among which intestinal malabsorption (especially that associated with celiac disease), hemochromatosis, endocrine disease (hyperthyroidism, hyperparathyroidism, hypopituitarism), anorexianervoosa, rheumatoid arthritis, systemic mastocytosis, certain drugs (anticonvulsants or hepati) and even some anovulatory medications, such as medroxyprogesterone acetate (Table 1) stand out. Young women who follow treatment for breast cancer, patients undergoing organ transplantation and those with HIV infection can also present this complication.

There are few studies analyzing idiopathic osteoporosis in these patients. In general, idiopathic osteoporosis can be seen in up to 50% of young individuals with osteoporosis and is considered that this disease has a similar incidence in both genders. The exact cause of this entity is likely to be a heterogeneous process in its pathogenic mechanisms. Thus, some patients have a family history of osteoporosis, while others described the existence of associated hypercalciuria. The latter hovers around 36%-50% of cases and quite often is associated with kidney stones.

The exact cause of the bone loss associated with this entity is not fully elucidated, it is assumed that the negative calcium balance, and possibly the increasing values of 1 to 25-dihydroxyvitamin D observed in some patients could promote bone loss through increased bone resorption. Other findings have been reported in isolation in patients with idiopathic osteoporosis, such as an alteration in the dynamics of parathyroid hormone secretion, decreased values of growth hormone (IGF-I) or serum estradiol values in some of these patients and alterations in α-estrogen receptor expression of osteoblasts. Other findings include an increased production of interleukin-1, which stimulates bone resorption, and decreased bone formation associated with an impaired proliferative ability by osteoblasts.

The existence of a family history of osteoporosis in these patients confirms the relevance of genetic factors in the acquisition of "peak" bone mass. In fact, a family history of fragility fracture is a known risk factor related to the presence of osteoporosis. In this regard, a previous study showed that about 50% of adult daughters of women with osteoporosis had a decrease in BMD. These findings are consistent with those provided by Cohen-Solal et al in men with idiopathic osteoporosis, observing a decrease in bone mass in first-degree relatives.
Although no specific characteristics identify patients with idiopathic osteoporosis, they often have a lower BMI and higher Z score in the femur when compared with those with secondary osteoporosis. Some authors attribute this finding to a predominance in involvement of trabecular bone in idiopathic osteoporosis.

Diagnosis

The diagnosis of osteoporosis in young people should be made with caution and should not rely solely on the determination of BMD. Thus, there must be additional factors, such as the presence of processes associated with development of osteoporosis, or a history of fragility fractures. We all know that in 1994 the WHO established diagnostic criteria. However, such criteria were established for postmenopausal women and should not be applied to young people. Recently, the International Society for Clinical Densitometry recommended the use of the Z score for the youth population. Thus, a Z score < –2 at the lumbar spine and/or proximal femur (femoral neck or total) in young (LH-RH : luteinizing hormone releasing hormone, <50 years) would indicate that there is a BMD below the normal value for the age and gender of the individual and, although the diagnosis of osteoporosis in this population should not be set solely on the basis of densitometric determinations, this criterion and the additional presence of other risk factors, such as treatment with GCC, hypogonadism, fragility fractures or diseases associated with bone loss, would confirm this diagnosis. This is because the decrease in BMD in a young individual can not be related to an increased risk of fracture and reflects only a poor acquisition of the “peak” bone mass, so that quantification of BMD in young individuals should only be done in certain risk situations, such as GCC use, gonadal deficiency, fragility fractures or the presence of diseases associated with bone loss.

In these patients family history of osteoporosis, weight, height and exclude the existence of osteogenesis imperfecta should be assessed; also, a detailed study to rule out secondary osteoporosis which initially include: blood count, serum iron, electrolytes, protein, function liver and kidney, and urine calcium 24 should be carried out. It is also advisable to study the gonadal axis in all cases and serum 25-hydroxyvitamin D. Other hormones, such as parathyroid hormone, thyroid hormones, prolactin, IGF-1 or cortisol, should be made according to the degree of clinical suspicion. The determination of serum tryptase and endomyosal antibodies, transglutaminase or antigliadin should be performed when there is suspicion of mastocytosis or celiac disease, respectively (Table 2). The diagnosis of idiopathic osteoporosis is established only when other secondary causes have been excluded.

In patients with idiopathic osteoporosis and hypercalculia the clinician should rule out other conditions that induce an increase in urinary excretion of calcium, especially Cushing’s disease, hyperthyroidism and hyperparathyroidism. The determination of biochemical markers of bone remodeling, while not obligatory, may provide additional information on bone turnover and the therapeutic response in these patients. It may occasionally be necessary to practice a bone biopsy for the study of bone metabolism, especially to exclude osteomalacia.

Treatment

A series of basic rules in all patients are recommended, including both lifestyle changes entailing physical exercise and adequate calcium intake, as well as avoiding the consumption of tobacco and alcohol. In fact, a recent observational study shows that this therapeutic approach may be effective in treating young women with idiopathic osteoporosis. Similarly, alcohol addiction has also been associated with increased BMD in individuals with osteoporosis associated with alcoholism.

There are very few studies on drug therapy in this population. The treatment depends on the etiology of osteoporosis. Thus, hormone replacement therapy should be evaluated in those patients where there are associated menstrual disorders or amenorrhea, provided there are no contraindications. This is especially common in anorexia nervosa, where in addition to estrogen therapy, other treatments such as dehydroepiandrosterone and bisphosphonates such as alendronate and risedronate, which also proved effective in preventing bone loss in this process, have been tried. However, in this entity, the recovery of weight and gonadal function are the most important factors related to increased BMD, and therefore constitutes the main type of therapeutic approach in these patients. Selective estrogen receptor modulators, such as raloxifene should not be used in premenopausal women for the treatment of osteoporosis; they should only be indicated in younger women if they are menopausal. A study in young women with amenorrhea secondary to treatment with gonadotropin analogs showed that treatment with raloxifene prevented bone loss in this population, the same way, treatment with PTH has also shown a protective effect after six months of treatment in this latter group of patients.

In young men with hypogonadism hormone replacement therapy with testosterone should be assessed if there are no contraindications. Thus, in children with delayed puberty, the administration of this hormone increases bone mass, however, efficacy of this treatment in the acquisition of peak bone mass in adulthood is unknown. In fact, in patients with osteoporosis and Klinefelter syndrome, testosterone treatment fails to normalize bone mass values and in patients with hypogonadism of different causes, hormonal treatment is usually associated with an increase in BMD during the first year of treatment, while we later see stabilization. Patients in whom it is contraindicated or do not wish to continue hormone treatment or those at high risk of fracture, antiresorptive bisphosphonates, treatment with PTH or osteotransforming therapy can be used and/or associated. Thus, treatment with alendronate in patients with osteoporosis and low levels of testosterone is associated with

### Table 1

<table>
<thead>
<tr>
<th>Causes of osteoporosis in young individuals</th>
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<tbody>
<tr>
<td>Hypogonadism (primary or secondary)</td>
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<tr>
<td>Malabsorption (celiac disease, inflammatory intestinal disease, intestinal resection)</td>
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<tr>
<td>Hyperthyroidism</td>
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<tr>
<td>Cushing’s disease</td>
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<td>Osteoporosis related to pregnancy</td>
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<tr>
<td>Growth hormone deficit</td>
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<td>Primary hyperparathyroidism</td>
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<tr>
<td>Panhypopituitarism</td>
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<tr>
<td>Anorexia nervosa</td>
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<tr>
<td>Liver disease (primary biliary cirrhosis)</td>
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<tr>
<td>Hemochromatosis</td>
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<tr>
<td>Idiopathic osteoporosis</td>
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<td>Hypercalcia</td>
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<tr>
<td>Osteogenesis imperfecta</td>
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<tr>
<td>HIV infection</td>
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<td>Marfan’s syndrome</td>
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<td>Organ transplant</td>
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<tr>
<td>Systemic mastocytosis</td>
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<tr>
<td>Drug treatments</td>
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<tr>
<td>○ Glucocorticosteroids</td>
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<tr>
<td>○ Antiepileptic drugs</td>
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<tr>
<td>○ Heparin</td>
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<tr>
<td>○ Aromatase inhibitors</td>
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<tr>
<td>○ LH-RH analogues</td>
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<tr>
<td>○ Medroxyprogesterone acetate</td>
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</tbody>
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HIV indicates human immunodeficiency virus; LH-RH, lutenizing hormone releasing hormone.
a progressive increase in bone mass,\textsuperscript{65} and treatment with nasal calcitonin in patients undergoing castration produces a decrease in biochemical markers of bone turnover.\textsuperscript{66}

In patients with osteoporosis associated with idiopathic hypercalciumia restriction of dietary sodium to reduce the excretion of calcium in the urine is recommended. These patients should avoid reducing the intake of calcium in the diet to avoid negative calcium balance (405). In fact, it has been reported that low calcium intake (<500 mg/d) may increase the risk of kidney stones in individuals with no history of\textsuperscript{67} stones, whereas intake of 1,200 mg of calcium daily through diet together with a restriction of sodium and animal protein, decreases calcium and prevents new episodes of lithiasis in patients with hypercalciumic lithiasis.\textsuperscript{68}

Thiazide diuretics, chlorthalidone, indapamide and amiloride are anticalciuric drugs. Thus, thiazides can reduce urinary calcium excretion by about 50%, increasing tubular reabsorption of calcium\textsuperscript{69} in absorptive hypercalciumia but its effect diminishes over time.\textsuperscript{70} Its use in patients with osteoporosis associated with hypercalciumia is associated to increased BMD and decreased calcium.\textsuperscript{71,72} In addition, prolonged use of this drug has been associated with increased BMD and reduced risk of hip fracture in the elderly population.\textsuperscript{73,74}

Bisphosphonates such as alendronate and risedronate, have proven effective in the treatment of men with idiopathic osteoporosis, as have teriparatide (PTH 1-34) and PTH 1-84.\textsuperscript{75} However, there is little safety and efficacy data of these types of treatments in young women with this disease.

Treatment with GH or IGF-I has also been proposed, albeit with controversial results, since some authors show an increase in bone mass,\textsuperscript{76} while others do not confirm these results.\textsuperscript{77} In fact, a multicenter study in adult patients with impaired GH showed no changes in BMD after 1 year of treatment.\textsuperscript{78} While these discrepancies may be related to the duration and the doses used, the response to this type of treatment may also depend on age and the patient’s gender, with younger patients and men obtaining the best response to this therapy.\textsuperscript{79,80}

Treatment of osteoporosis secondary to other diseases and/or drugs must be addressed depending on the associated cause. Thus, treatment of the disease itself may be associated with a marked increase in bone mass in some patients. This is especially common in patients with Cushing’s disease, which described an increase in bone mass of more than 15% per year after surgery\textsuperscript{81} and also in patients with primary hyperparathyroidism and hyperthyroidism.\textsuperscript{82,83}

Similarly, women with pregnancy-associated osteoporosis have a spontaneous and progressive increase in bone mass after pregnancy.\textsuperscript{84} However, despite this increase, these patients usually have a normalization of bone mass values after pregnancy, suggesting that it is likely that many of them have low bone mass before pregnancy.\textsuperscript{85} In these patients breastfeeding is not recommended due to bone loss that occurs during this period, although new pregnancies are not contraindicated.\textsuperscript{86}

There are several options in the treatment of corticosteroid osteoporosis. Thus, treatment with bisphosphonates, and\textsuperscript{87} etidronate, alendronate\textsuperscript{88} and risedronate,\textsuperscript{89} are effective in preventing bone loss and the development of vertebral fractures in this patient group. However, it should be noted that the number of premenopausal women included in this series is very small, so that information on treatment and prevention of GCC osteoporosis with bisphosphonates in this group of patients is scarce. Despite this, antiresorptive therapy is recommended in patients at risk, advising a 5 mg/day dose of alendronate or 5 mg/day of risedronate.\textsuperscript{90} A recent study in patients with osteoporosis induced by GCC, which also included premenopausal women, has shown that treatment with PTH (teriparadise [20 mcg/d]) is effective in preventing bone loss and the development of vertebral fractures, with better results than treatment with alendronate.\textsuperscript{91} Calcitonin is considered a second line agent in this condition and can be used in patients who have contraindications or who can not tolerate bisphosphonates or PTH.\textsuperscript{92,93}

In young women with breast cancer undergoing chemotherapy and/or anti-hormone therapy, treatment with bisphosphonates, specifically through IV zolendronate prevents bone loss.\textsuperscript{94,95}

In other processes, such as osteogenesis imperfecta, especially those associated with severe forms of multiple fractures, treatment with bisphosphonates, particularly IV pamidronate, has shown an increase in bone mass and decrease fractures\textsuperscript{96} and recent data indicate similar efficacy with oral preparations such as alendronate.\textsuperscript{97} In adult patients with osteogenesis imperfecta there has also been an increase in bone mass and reduced fractures after treatment with bisphosphonates, in this case with IV neridronate.\textsuperscript{98} However, it should be noted that bisphosphonates are incorporated into bone tissue where they remain for several years and are slowly released by bone resorption. In fact, a recent study has detected the presence of pamidronate in urine up to seven years after administration in children who had received IV treatment.\textsuperscript{99} The main issues to consider when using this type of treatment in younger people are its effect on fracture healing and teratogenicity. The finding of delayed healing of osteotomy in patients with osteogenesis imperfecta undergoing this treatment has caused some surgeons, in an empirical way, to discontinue treatment before 6 months and not reintroduce it until a bone callus has formed.\textsuperscript{100,101} In addition, bisphosphonates are teratogenic in experimental animal studies,\textsuperscript{102} so that the deposit of bisphosphonates in bone tissue of young women could theoretically cause teratogenic effects after marrow mobilization. Although to date no congenital abnormalities have been reported in children in the isolated cases of women who have...
been treated with oral bisphosphonates, preventive contraception should be advised in premenopausal women who follow this kind of treatment.

Therefore, the Canadian Society of Mineral Metabolism indicates that the treatment of osteoporosis in premenopausal women should be approached with caution and the use of bisphosphonates encouraged only for secondary causes of osteoporosis, such as corticosteroid osteoporosis and in isolated cases of osteoporosis (probably those in which patients have decrease in BMD associated with the development of fractures). The use of this preparation during pregnancy is contraindicated.

Dieu. They suggest that calcitonin may be useful due to its safety, but indicate the lack of studies confirming the usefulness of this drug in this population. In fact, treatment with calcitonin nasally in doses of 100 IU/day has been insufficient in preventing bone loss in young women. Finally, the use of intermittent PTH may be a promising therapeutic option in these patients, although more studies to confirm this hypothesis are recommended. Is should also be noted that the use of this preparation is contraindicated in growing young individuals and those who have undergone prior treatment with radiotherapy.

Disclosures

The author has no disclosures to make.

References

222


