Editorial

Premature Ovarian Insufficiency and Bone Health Care: A Concern of the Gynecologist

Insuficiência ovariana prematura e os cuidados com a saúde óssea: uma preocupação do ginecologista

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The greatest increase in bone mass occurs during puberty, and the amount of bone gained during adolescence is the major contribution to the peak bone mass (PBM) that occurs around the age of 30–35 years old. Studies conducted by the National Osteoporosis Foundation have shown the importance of the timing of the PBM, as it determines the phase of the life cycle in which the bone mass is optimized.[1] In healthy girls, the earlier the onset of puberty, the greater the body mass and the bone mineral density (BMD) at the completion of skeletal maturity.[2–5]

The PBM varies according to the location in the skeleton. Estimates based on longitudinal studies performed by the Canadian Multicentre Osteoporosis Study showed the PBM for the lumbar region occurs between 33 and 40 years of age, and that the PBM for the hip occurs between 16 and 19 years of age.[6]

PBM is influenced by genetic factors, nutritional status, adequate endocrine function, and physical activity, and is the major determinant of the future risk of fractures in elderly women.[7] Among the endocrine factors are gonadal, adrenal and pituitary hormones; and, in women, estradiol plays a key role. Estradiol acts on the bones through several mechanisms and exerts an antiresorptive action.[8] According to some authors, estrogens also act on the bones by indirect mechanisms through an action in the muscles by evidencing an interrelationship between mechanical forces and the action of steroids and growth factors on the tissue masses of both the bones and the muscles.[9]

Several clinical situations that lead to hypoestrogenism are associated with BMD loss by leading to osteopenia and osteoporosis. The most typical known situation is the menopausal period. However, when hypoestrogenism occurs in the pubertal period and in adolescence, it may result in a PBM reduction in these young women. Amenorrheic adolescents have a lower BMD compared to those who menstruate regularly. The earlier the hypoestrogenic condition is established and the longer it is extended, the greater the repercussions on bone mass, with an increased risk of fractures. Several conditions can lead to hypoestrogenism in young women, such as hypothalamic amenorrhea, hyperprolactinemia, and premature ovarian insufficiency (POI), among others.[8,10,11]

Premature ovarian insufficiency is a clinical syndrome defined by the depletion of the follicular activity before the age of 40 years old. It is characterized by amenorrhea, increased gonadotrophins (follicle-stimulating hormone [FSH] $>$ 25 mIU/mL) and low levels of estradiol.[11] The incidence of POI in the general population is 1%, and it represents 6% to 10% of the causes of amenorrhea in general, and 10% to 15% of the causes of primary amenorrhea. There is a family history of the disease in 4% of the patients.[11] Patients with POI have a pattern in bone turnover markers similar to the one found in the menopausal state.[12–18] This is an important concern for the health of young women with POI, particularly if they have not yet reached PBM.

Compared to women who experience menopause at normal ages, patients with POI have a 1.5-fold greater risk of fracture.[19] Some studies have shown a lower BMD in women with POI or in the menopause before the age of 45 years old by any etiology. Compared to women who menstruate regularly, women with POI, karyotype 46, XX (mean age: 32 years; range: 20–39 years) had significantly lower BMD Z-scores. About 20% of these women had a BMD Z-score $<$ 2.0, which indicates a low BMD for their age and a fracture risk factor.[20]

A delay in the diagnosis greatly contributes to worsening the BMD.[21] It is very common to find patients with amenorrhea who have already lost precious time in doctors' offices and basic health units without the doctor investigating for a diagnosis of POF. In cases of amenorrhea, the possibility of

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POI should always be considered, and an effective search should be performed regarding the clinical picture (the climacteric symptoms of women) and high dosage of serum FSH. After the POI diagnosis, bone vitality should always be addressed because a loss in bone mass may have already occurred, and this should be a primary concern with the health of young women with POI.[22–24]

The treatment for osteopenia and osteoporosis caused by hypoestrogenism is essential and fundamentally based on the administration of estrogen replacement, which is indicated as a mandatory procedure as long as formal contraindications and patient acceptance are respected.[11,25]

Densitometry is directly related to estradiol levels.[26] Bone mineral density correlates positively with body fat (%), fat distribution and estradiol levels, and estradiol and age were among the factors associated with L2–L4 BMD.[27] Levels below 20 pg/mL may have protective effects on the bone mass. Women with undetectable levels of estradiol ($<$ 5 pg/mL) were at a 2.5-fold higher risk of fracture compared to women with estradiol levels between 5 pg/mL and 25 pg/mL.[28,29]

Thus, smaller estrogen dosages are required to meet bone maintenance needs. Low doses of estrogen, especially when associated with calcium, have a positive effect on bone mass, and its action appears to be predominantly on reabsorption, but not on bone formation after the age of 70 years old.[30]

We must always remember that there are several other goals of hormone replacement therapy (HRT) besides prevention and treatment of secondary bone loss due to ovarian failure. Therefore, the needs of each patient should be taken into account in order to define the estrogen dose to be administered. Further studies are needed to prove the efficacy of lower estrogen doses for cardiovascular protection, vasomotor phenomena, etc.

A three-year prospective randomized clinical trial was conducted by the United States National Institutes of Health (NIH) in young women with POI, karyotype 46, XX, in order to investigate the efficacy of a standardized HRT regime for BMD treatment. The study used transdermal E2 replacement (100 µg/day) with cyclic oral progestogen (10 mg oral medroxyprogesterone acetate daily for 12 days per month). This replacement therapy improved the BMD of the lumbar spine and of the femoral neck, so that at the end of the three-year intervention, the BMD did not differ between women with POI and the control group.[31]

The treatment of POI can have different doses and dosages according to the life period of onset of the disease. There is no evidence of which is the best route, oral or transdermal, and what is the best therapeutic regimen.[11,32–35] In patients diagnosed in the pubertal period and without adequate development of secondary sexual characteristics, puberty should be induced with a low dose of 17β-estradiol and a gradual increase over a period of 2 to 3 years. Progestogens should be used two years after the onset of puberty induction with estradiol or as soon as the first menstrual bleeding occurs. In cases of later diagnosis, and with no remaining concern about growth, the initial estrogen dose may be higher and more rapidly progressive with increases every three to six months until the adult dose is reached. The recommendation is that the hormonal therapy simulates as close as possible the regular levels of ovarian estrogen production and its continuity until the natural menopause age.[11,21]

The use of combined oral contraceptives (COCs) is an alternative to the conventional treatment with natural estrogens. In cases of adolescents, who are still in the development phase of the PBM, some studies have shown that COCs may have a less positive impact on the BMD.[36] However, further studies are needed to prove this effect..

A point to consider is the inclusion or not of BMD in the propaedeutic routine of patients with POI, especially those affected by the disease during adolescence and/or those with additional risk factors. Although BMD measurement is the gold standard for bone mass evaluation, and despite the large number of publications clearly pointing to bone loss, there is no consensus regarding the need to routinely indicate BMD measurement in the evaluation and follow-up of patients with POI.

According to Cox and Liu,[35] "as a consequence of decreased estrogen levels, women with POI often do not achieve peak bone density and may experience loss of bone mass. If hormone therapy is initiated and the woman has not experienced fractures, it is not necessary to do bone mineral density testing."

On the other hand, other authors indicate BMD examination after the diagnosis of POI.[37,38] Torrealday et al[39] suggest that BMD measurement may be useful and should be considered for women with POI already at the beginning of the approach. It should be repeated in those who decide to continue hormone therapy until the equivalent time of menopause for that population. In turn, the European Society for Human Reproduction and Embryology (ESHRE)[11] recommends the initial BMD measurement. If the results are normal and the patient undergoes hormonal therapy immediately upon diagnosis, there is no need to repeat the measurement. If the BMD measurement indicates osteoporosis, once the HRT is initiated, the BMD measurement should be repeated after five years. If the BMD continues to decline even with estrogen therapy, the conduct should be reviewed, and other factors that trigger osteoporosis should be sought.

The cost-benefit of measuring BMD in osteoporosis screening to assess its benefit as a prevention method for fractures in women is questioned. Most cohort studies to assess the use of BMD for this purpose included patients older than 65 years of age.[40] For these patients, by considering the cut-off point of 2 standard deviations, the sensitivity is 9%, the specificity is 99%, and the positive predictive value is 56%. Therefore, the BMD can predict the risk of fracture, but has low accuracy to identify individuals who will (or will not) have fractures.[41]

However, there are currently no alternatives to BMD for this evaluation, since bone turnover markers do not have well-established reference standards yet, given the variations observed among the various studies.[12–18]

In the Brazilian Unified Health System (SUS, in the Portuguese acronym), BMD measurement is authorized in some special situations,[42] including cases of hypogonadism in men and women, postmenopausal women with risk factors, and

to monitor changes in bone mass due to the course of osteoporosis and the different treatments available for this disease. Therefore, there is a possibility of access to the measurement of BMD, even if using public services, but also practical difficulties to perform the exam because it has a high cost and, in Brazil, few public services are available to the population.

Many questions remain unanswered given the lack of scientific evidence:

Are there differences in the behavior of bone mass over time when comparing women with POI and those who experienced menopause at the natural time?

Can we extrapolate to women with POI the sensitivity, specificity and predictive values for predicting fractures obtained with the BMD measurement performed in postmenopausal women?

Is it justified to perform a BMD measurement in young women with POI?

The evidence of the association of hypoestrogenism and low bone density and its association with the increased risk of fractures could be a justification for dispensing patients from undergoing a BMD measurement before starting hormone therapy?

It is known that estrogen therapy may fail in some patients, since other factors may interfere with the maintenance or loss of bone mass. How can we be sure that the patient undergoing hormone therapy will be protected from bone loss if she is not monitored through BMD measurements?

Are there alternative ways to confirm that patients with POI are already losing bone mass without BMD measurements?

Conclusion

In the literature, there are no evidence-based guidelines on criteria to maintain bone health in women with POI. It has not been definitively demonstrated that a reduced BMD in POI is indicative of an association of the disease with an increased fracture risk because the evidence is based on short-term observations and expert opinion. In fact, studies with the clear aim to clarify this cause-effect relationship are difficult to perform because they would involve ethical issues (for example, failure to treat patients on estrogen therapy as a control group), or the high cost and long duration of the follow-up, since the patients should be observed for long periods.

Moreover, the results of BMD studies performed in postmenopausal women cannot be extrapolated to a population of young women with estrogen deficiency before the age of 40 years old in order to predict fractures that will occur 20 to 30 years later, when other risk factors for fractures may be involved.

Despite the lack of such evidence with long-term randomized clinical trials, common sense suggests that the physician should rely on existing data in the literature, especially the guidelines of specialty societies.

The review of the literature shows that the consulted studies are practically consensual about these aspects of the POI approach. Estrogen replacement therapy should begin immediately after diagnosis, obviously respecting the contraindications to its use. The BMD measurement for an initial evaluation before starting hormone therapy would be a good practice. However, if the patient's access to this test is difficult, she can be dispensed by considering the unquestionable benefits of estrogens on bone mass, even in very small doses. The risks of treatment failure should be carefully ascertained in view of the possibility of associated comorbidities or other factors interfering with bone mass.

More than half of the women with POI have inadequate vitamin D levels and low calcium intake. Many are not adherent to hormone therapy, do not exercise regularly, and may be smokers. Therefore, to ensure good bone mass, in addition to hormone therapy, women with POI should maintain a healthy lifestyle that involves physical exercise, abstinence from smoking, a balanced diet with good intake of foods rich in calcium and vitamin D, and weight control.

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