Bone mineral density assessment in premenopausal women

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In the absence of fragility fractures, low bone mineral density may reflect attainment of a lower peak bone mass in comparison with the young adult mean value. It is necessary to distinguish between low peak bone mass and a systemic disorder resulting in low bone mineral density and skeletal fragility. Low peak bone mass in the absence of fragility fracture or progressive bone loss may not require pharmacological intervention. However, systemic disorders contributing to bone loss do require diagnosis and intervention. Common causes of low bone density in premenopausal women include ovulatory disturbances and low body weight. Other diseases, conditions or medications may also contribute to bone loss and these should be identified and treated if present. Fracture risk is reduced by lifestyle changes and pharmacological intervention in those with glucocorticoid-induced bone loss. Discontinuing depot medroxyprogesterone acetate use has been associated with improvements in bone mineral density. Bone mineral density alone is insufficient for the diagnosis of osteoporosis in premenopausal women in the absence of fragility fractures. Bone mineral density testing should only be performed in premenopausal women in the presence of approved indications.

Keywords: antiresorptive therapies, depot medroxyprogesterone acetate, fracture risk, glucocorticoid therapy, low bone mineral density, oral contraceptives, osteoporosis, premenopausal, prevention, therapy

future medicine

Osteoporosis is a common condition associated with an increased fracture risk in postmenopausal women. In the presence of diseases or conditions associated with progressive bone loss, younger premenopausal women may also be at an increased risk for osteoporosis. With increased public awareness of skeletal health, many young women are requesting bone mineral density (BMD) testing, and low BMD is being identified in the absence of fragility fractures or important risk factors for fracture in premenopausal women. This article addresses appropriate utilization and interpretation of BMD testing in premenopausal women and recommendations for the management of low BMD in this population are provided in light of current evidence and guidelines.

Bone density follows a bell-curve distribution and low bone density with the number of standard deviations below average bone density (T-score) of less than 1 standard deviation below the young adult mean is present in approximately 15% of young, healthy women aged between 30 and 40 years [1]. Approximately 0.5% of young healthy women aged 30–40 years have a T-score of -2.5 or less [2,3]. Osteoporosis can be diagnosed in the premenopausal female population in the presence of fragility fractures. This diagnosis cannot be based solely on the results of a BMD test [1]. Premenopausal women experiencing fragility fractures should be further evaluated in order to determine why fractures are occurring in an estrogen-replete woman. In certain individuals, a bone biopsy may be necessary to evaluate the underlying histology and histomorphometry and to elucidate the possible cause for decreased bone strength and skeletal fragility in an estrogen-replete woman.

At the present time there is insufficient prospective data regarding the relationship between BMD and fracture risk in the premenopausal female population. Therefore it is not possible to make recommendations regarding the appropriate BMD criteria for a diagnosis of osteoporosis in premenopausal women in the absence of secondary causes of bone loss such as the use of glucocorticoid (GC) therapy. The WHO definition of osteoporosis based on a T-score cut-off point of -2.5 is applicable to the postmenopausal female and cannot be applied to the premenopausal female in the absence of secondary causes of bone loss. Prospective evidence regarding the BMD-fracture risk relationship in the premenopausal female is extremely limited and is currently insufficient for recommendations to be made regarding the appropriate BMD criteria for the diagnosis of osteoporosis in the premenopausal female. The 2001 National Institutes of Health (NIH) Consensus Development Panel on osteoporosis identified the densitometric diagnosis of osteoporosis in the premenopausal woman to be an important area of future

research. Data regarding the efficacy of antiresorptive therapy in premenopausal women is also limited to the treatment of steroid-induced osteoporosis and parathyroid bone disease, which is level-1 evidence.

Diagnosis

Osteoporosis is a progressive systemic disease characterized by low bone density and microarchitectural deterioration in bone that predisposes patients to increased bone fragility and fracture as defined by the WHO [1]. It is necessary to ensure that low peak bone mass is not misdiagnosed as an osteoporotic process in the premenopausal woman. Low peak bone mass in the absence of fragility fractures or height loss may be reflective of the normal variation in BMD. This may not reflect underlying pathology and may in fact not be associated with increased fracture risk in the premenopausal period [1]. Low peak bone mass is genetically determined and also affected by environmental factors such as inadequate exercise and dietary calcium intake, as well as smoking and excess alcohol consumption during the teenage and young adult years [1].

The risk of fragility fracture in a premenopausal woman is significantly less than that of an older postmenopausal female with the same reduction in BMD. Multiple factors contribute to these differences in fracture risk including age and bone turnover, as well as differences in muscle mass and neuromuscular function. Thus, premenopausal women have a significantly lower risk of fracture even with falls than older postmenopausal women [4,5,6].

Bone density testing should be completed in those premenopausal women with identifiable causes of bone loss [1]. These include the use of GC therapy in doses of 7.5 mg/day for 3 months or greater, premature ovarian failure (primary or secondary) or the presence of diseases, conditions or medications associated with bone loss (**Box 1**). Individuals receiving depot medroxyprogesterone acetate (DMPA) for longer than 24 months should be considered for BMD testing if other risk factors for fracture are present.

Assessment

Clinical assessment excludes common conditions associated with bone loss [7]. Individuals presenting with low BMD with or without fragility fractures should be evaluated with exclusion of secondary causes of bone loss that may have contributed to the development of low BMD.

The evaluation includes assessment of thyroid, liver and renal function. Serum calcium (corrected for albumin) is most commonly elevated in primary hyperparathyroidism or malignancy. Low serum calcium may be reflective of vitamin D inadequacy or malabsorption states, which may also result in low BMD and/or osteomalacia. The 24-h urinary calcium level can be an early indicator of inadequate calcium or vitamin D intake or malabsorption. If the 24-h urine calcium level does not normalize with increased calcium supplementation, occult celiac disease should be excluded with appropriate antibody testing and a small bowel biopsy if indicated. Additional investigations will be guided by the clinical presentation. As subclinical estrogen deficiency has been associated with low bone density in young women [8–10], it is necessary to ensure that the young woman truly is estrogen replete.

Normal gonadal function is necessary for the achievement of peak bone mass and for the maintenance of BMD in women in the premenopausal period [1,8–11]. Elevations in follicle-stimulating hormone (FSH) of more than 20 mIU/l have been associated with increased bone turnover activity and progressive bone loss in the perimenopausal period [10,12]. A detailed assessment of menstrual status with exclusion of ovulatory disturbances is important, as subclinical and clinical estrogen deficiency is more frequently observed in premenopausal women with low BMD [8–10].

Drugs can contribute to progressive bone loss, requiring a careful evaluation of the use of medications such as GCs, anticonvulsants, cytotoxic chemotherapy and DMPA use. GC use is the leading cause of drug-induced osteoporosis and is associated with rapid reductions in BMD by as much as 6.4% within the first 6 months of treatment [13,14]. Losses are greatest at skeletal sites rich in cancellous bone, reflecting areas of increased bone turnover such as the spine. GC therapy is associated with an increase in the rate of bone turnover as well as changes in gonadal function, impaired absorption of calcium from the bowel and increased renal calcium losses. In addition, GC therapy may affect the lifespan and function of the osteocytes, resulting in an impaired ability to ensure maintenance of skeletal integrity. The increased risk of fracture in patients receiving GC therapy is attributed to the use of the GC as well as the underlying disease process for which the GC is initiated and other coexisting risk factors for fracture such as the presence of rheumatoid arthritis [15,16].

Box 1. Important secondary causes of bone loss.

Diseases/conditions

- Hypogonadism (primary and secondary)
- Primary hyperparathyroidism
- Thyrotoxicosis
- Hypercortisolism
- Growth hormone deficiency
- Osteomalacia
- Myeloproliferative disorders
- Connective tissue disorders

Malabsorptive states (e.g., Celiac disease)

- Hepatic disorders (e.g., primary biliary cirrhosis)
- Inflammatory bowel disease
- Renal disease
- Hypercalciuria
- Osteogenesis imperfecta

Medications

- Glucocorticoids
- Thyroxine (excessive)
- Anticonvulsants (e.g., phenytoin, phenobarbital)
- Heparin (long term)
- Lithium
- Cytotoxic chemotherapy
- Gonadotropin-releasing hormone agonists
- Depo medroxyprogesterone acetate

Adapted from [1].

Doses of the GC prednisone as low as 2.5–7.5 mg/day can increase the risk of fracture and the relative risk (RR) of hip fracture increases to 1.77 and of vertebral fracture increases to 2.59 with GC use [15]. GCs in doses of greater than 7.5 mg/day increase the risk of fracture further (RR: 2.27 for hip fractures and 5.18 for vertebral fractures). This increased risk of fracture can be realized as early as 3 months after initiating GC therapy. Discontinuation of GC therapy is associated with a reduction in fracture risk [15]. Both current and prior use of GCs is associated with a significantly increased risk of fractures [16].

Fracture risk in premenopausal women receiving GCs appears to be lower than that seen in postmenopausal women receiving GCs, as demonstrated in three randomized, controlled trials evaluating the protective skeletal effects of bisphosphonates in patients receiving GCs [34–36]. Vertebral fractures occurred in 7.6–21.9% of the postmenopausal study population treated with calcium and vitamin D alone, while no new fractures were seen in the 97 premenopausal women enrolled in the placebo arms [34–36].

However, it is necessary to further evaluate the effects of GCs on fracture risk in premenopausal women and also to further evaluate the protective skeletal effects of bisphosphonates on BMD and fracture risk in the premenopausal female.

Data from studies evaluating risedronate in women receiving GC therapy demonstrated that women receiving GCs had more fractures than the placebo group of postmenopausal osteoporotic women not receiving GC therapy. This higher fracture risk with GC use was seen even though the women receiving GC therapy were younger (mean age 64.7 vs 74.1 years) and had a higher baseline BMD (T-score -1.8 vs -2.6) and a lower percentage of baseline fractures (42.9 vs 58.3%) than nonusers of GCs [37]. Fracture risk was increased at any given level of BMD in the GC users compared with the postmenopausal osteoporotic women in the placebo group.

A large retrospective cohort study (n: 280,645) reported that the rate of vertebral and nonvertebral fractures in women exposed to GCs was greater than that of men exposed to GCs in any age group. Among women in all age groups over 30 years, vertebral and nonvertebral fracture rates were higher among those receiving GCs than among those not exposed to GCs [17].

A recent large meta-analysis of seven cohorts followed prospectively found that the risk of all fractures was greater in GC-induced osteoporosis (GIOP) than in postmenopausal osteoporosis for the same level of BMD [16]. These findings suggest that there may be changes other than BMD losses that are contributing to the increased fracture risk with GC therapy, such as changes in bone microarchitecture and osteocyte lifespan and function. There is a significant correlation between fracture risk and baseline BMD in individuals receiving GC therapy. However, a normal baseline BMD is not necessarily protective against incident fractures in the presence of GC therapy. In certain situations such as transplantation, the risk of fracture is markedly enhanced despite normal baseline BMD.

The literature is not clear as to the relationship between GC dose and fracture risk with inhaled GC therapy. Although premenopausal women have a lower fracture risk with GC therapy than that seen in postmenopausal women, it may still be significant.

The lowest effective dose of GC should be used and for the shortest possible duration. Inhaled GCs are preferable to oral GCs. When medically indicated, alternative therapies that may minimize GC exposure should be

considered. It is also important to address lifestyle changes to ensure maintenance of skeletal health (i.e., smoking cessation, adequate calcium and vitamin D, active lifestyle) and these should be emphasized in the management of the premenopausal woman receiving GC therapy.

Progestational agents used for contraception in young women potentially cause bone loss due to the associated estrogen deficiency. DMPA inhibits luteinizing hormone (LH) and FSH release and results in suppression of ovarian synthesis of estradiol and progesterone [30,31]. DMPA use has been associated with decreased BMD at the lumbar spine [32,33]. This effect may be of particular concern in the young adolescent female in the process of achieving peak bone mass. Significant gains in BMD were seen in adolescent women aged 14–18 years discontinuing DMPA therapy in a prospective cohort study, demonstrating that the loss of bone seen with the use of DMPA can be reversed [18].

Prospective use of DMPA in the adolescent population demonstrated that DMPA use in doses of 150 mg every 3 months resulted in decreases in BMD at the lumbar spine and the hip in comparison with nonusers [18]. The annual mean percentage change in BMD with DMPA use was -1.81% at the hip and -0.97% at the spine ($p < 0.001$) compared with nonusers of DMPA [18].This study demonstrated rapid and quick recovery of BMD at the spine and whole body with discontinuation of DMPA use. It is not possible to know if the DMPA users would have achieved a higher peak bone mass if they had not used DMPA; however, the gains in BMD following cessation of therapy were significant. The adjusted mean BMD for women 12 months or more after stopping DMPA were comparable to the nonusers at all sites.

A premenopausal woman who continues to experience fragility fractures or progressive bone loss should be referred to a metabolic bone clinic for further assessment. This may include obtaining a bone biopsy to further evaluate the underlying bone histomorphometry with appropriate tetracycline labeling in order to better appreciate the underlying pathophysiology contributing to the impaired skeletal strength.

Intervention

If a secondary cause for the low BMD is identified, it should be corrected and this may be associated with significant improvement in the BMD with reductions in fracture risk. Increases in BMD have been documented in women diagnosed with celiac disease with the introduction of a gluten-free diet. Correction of vitamin D inadequacy is also associated with improvements in BMD and reductions in bone turnover. Bisphosphonates have been evaluated in premenopausal women who have received GC therapy. Antiresorptive therapy, in addition to adequate calcium and vitamin D initiated with long-term GC therapy, is effective in preserving bone mass and reducing the risk of fragility fracture with GC therapy. Pharmacological intervention is recommended in women requiring long-term GC therapy, particularly in the presence of progressive bone loss or fragility fracture. Bisphosphonates lower bone turnover and are therefore effective treatment options in premenopausal women receiving long-term GC therapy [19–22]. Both alendronate and risedronate are effective in improving BMD in GC-induced bone loss. The lowest effective dose of GC should be used for the shortest possible duration. Inhaled GCs are preferable to oral GCs. When medically indicated, alternative therapies that may minimize GC exposure should be considered. It is also important to address lifestyle changes to ensure maintenance of skeletal health (i.e., smoking cessation, adequate calcium and vitamin D, active lifestyle, etc.) and these should be emphasized in the management of the premenopausal woman receiving GC therapy.

Antiresorptive therapy has been evaluated in the management of premenopausal women with secondary causes of bone loss such as primary hyperparathyroidism [23]. Alendronate was demonstrated to be effective in improving BMD and reducing bone turnover in this population [23].

In the absence of a documented secondary cause for the osteoporosis such as the presence of GC therapy, bisphosphonates should not be routinely initiated. There are no data regarding the efficacy of bisphosphonates in premenopausal women with low BMD in the absence of such secondary causes of osteoporosis. In the estrogen-replete woman with normal bone turnover, bisphosphonates may not be safe or helpful as suppressing bone turnover below normal values with bisphosphonates has not been evaluated with respect to safety or efficacy. This patient population is thus best served by a specialized metabolic bone clinic prior to implementing antiresorptive therapy.

Bisphosphonates have long-term skeletal retention and these agents may be released from the skeleton several years later; potentially in a

Executive summary

Diagnosis

- Osteoporosis in premenopausal women is diagnosed in the presence of fragility fractures and is not based solely on the results of a bone mineral density (BMD) test.
- BMD alone cannot be used to diagnose osteoporosis in the absence of fragility fractures in the premenopausal woman in the absence of secondary causes of osteoporosis.
- Low BMD with the number of standard deviations below average bone density (T-score) of less than -1 is seen in 15% of healthy young women and may reflect acquisition of low peak bone mass and may not be associated with increased skeletal fragility.

Assessment

- Low BMD in premenopausal women should be further evaluated.
- Environmental factors such as inadequate calcium intake, alcohol and tobacco excess, and low body weight can contribute to low peak bone mass.
- Clinical or subclinical estrogen deficiency can contribute to achieving a lower peak bone mass or to the development of bone loss in the premenopausal years.
- Secondary causes of bone loss should be excluded and any underlying condition or medication contributing to low bone density should be addressed.
- Referral to a metabolic bone clinic is appropriate for patients experiencing fragility fractures or progressive bone loss.

Intervention

- Antiresorptive therapy has only been evaluated in premenopausal women receiving glucocorticoid therapy or in secondary causes of bone loss such as primary hyperparathyroidism.
- Secondary causes of bone loss should be corrected.
- Improvements in BMD occur with correction of estrogen deficiency, inadequate calcium and vitamin D intake or malabsorptive states.
- Lifestyle modification is of value in preventing progressive bone loss in premenopausal women.
- Bone densitometry data should be carefully interpreted in the premenopausal female within the context of our limited current knowledge regarding the BMD-fracture risk relationship in this population.
- BMD as measured by dual-energy x-ray absorptiometry can result in overestimation of BMD in individuals who are taller than the average female and underestimate BMD in petite individuals. This size artifact should be borne in mind when evaluating BMD in those at extremes of height.

subsequent pregnancy. The effects of bisphosphonates on the developing fetal skeleton are not known.

Lifestyle modification should be encouraged in premenopausal women with low BMD in order to improve BMD. This would include weight-bearing exercises, adequate dietary calcium intake, smoking cessation, and limiting caffeine and excessive alcohol consumption [24]. Maintenance of normal body weight with a body mass index (20–25 kg/m^2 [2]) and a daily exercise program are of value in maintaining BMD [24].

Women under the age of 50 years with clinical or subclinical estrogen deficiency may benefit from estrogen supplementation

Estrogen supplementation, either in the form of oral contraceptive pills or 17-β estradiol in combination with a progestin, should be considered in order to prevent progressive bone loss. Estrogen supplementation is associated with improvements in BMD in estrogen-deficient women [25]. In women with ovulatory disturbance, cyclic medroxyprogesterone has been shown to result in significant gains in BMD in a randomized, placebo-controlled, prospective study over 1 year [26]. Prospective data are needed to further evaluate the effect of short luteal-phase cycles on BMD. Further evaluations of intervention with estrogen or progesterone supplementation are also warranted. In the absence of estrogen deficiency, the role of estrogen supplementation is controversial.

Data regarding the use of oral contraceptive pills and effects on BMD have been conflicting, with some studies demonstrating improvements in BMD in premenopausal and postmenopausal women, while other studies have shown a negative effect [27,28]. Data from the Canadian Multicenter Osteoporosis Study (CaMos) indicated that oral contraceptive pill users had decreased BMD at the trochanter and spine in comparison with nonusers [29]. However, these women also had increased rates of smoking and alcohol use and had a higher prevalence of menstrual irregularity prior to initiating oral contraceptive pill use compared with nonusers [29]. Thus, prospective data are required to assess the effects of oral contraceptive pills on BMD in premenopausal

women [33]. Improvements in BMD with cessation of DMPA use have been documented and are reassuring.

Future perspective

As BMD testing becomes financially and physically more accessible, it is expected that BMD testing will be utilized to a greater degree in evaluating skeletal health with the aim of more aggressive strategies in preventing bone loss in younger women. Greater compliance with preventive strategies is expected if women are aware of their skeletal health and risk factors for fracture. In addition, knowledge of a patient's peak bone mass would be of value in those who subsequently present with fragility fractures. At the present time, it is not financially feasible to recommend screening for bone loss; however, this may not be true in the next decade. Anabolic therapies are also becoming available, enabling reversal of microarchitectural deterioration seen in those with severe osteoporosis. Experience with anabolic agents such as teriparatide, as well as strontium, may increase in the younger premenopausal population and these agents may be of value in improving bone microarchitecture in those with severe osteoporosis, complementing the use of antiresorptive therapies. Intervention in the receptor activator of NF-κB (RANKL)–osteoprotegrin signaling system with potent new agents may also revolutionize our ability to safely and effectively treat osteoporosis in young, premenopausal women. Advances in skeletal assessment with the availability and improved reliability of biomarkers will enable more targeted intervention of therapy.

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