

Management of Low Bone Mineral Density in Premenopausal Women

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Abstract

Objective: To review evidence for management of low bone density in premenopausal women and to establish practical guidelines for management of low bone density in this population by family physicians.

Method: A search of MEDLINE for relevant articles published between January 1990 and May 2004 was conducted. Articles retrieved were graded by level of evidence. Recommendations for diagnosis and therapy were based on evidence from randomized controlled trials and expert consensus.

Results: Low bone density in premenopausal women is not associated with the same increased risk of fracture seen in older women. In the absence of fragility fractures and loss of height, it may be a reflection of low peak bone mass and may represent the normal variation in bone mineral density (BMD). Women may have low bone density secondary to an underlying skeletal or systemic disorder. Common causes of low bone density in premenopausal women include ovulatory disturbances and low body weight.

Conclusion: Osteoporosis is diagnosed in the premenopausal female population in the presence of fragility fractures and is not based solely on the results of BMD testing. Secondary causes of bone loss should be excluded, and any underlying condition contributing to low bone density should be corrected. Antiresorptive therapy has been evaluated only in those premenopausal women who are on glucocorticoid therapy and in those with primary hyperparathyroidism. Only in these conditions has antiresorptive therapy been shown to improve BMD.

Résumé

Objectif : Analyser les résultats en ce qui concerne la prise en charge de la faible densité osseuse chez les femmes préménopausées et établir, à l'intention des médecins de famille, des lignes directrices pratiques pour la prise en charge de la faible densité osseuse.

Méthode : Nous avons mené une recherche dans MEDLINE en vue d'en tirer les articles pertinents publiés entre janvier 1990 et mai 2004. Les articles ainsi sélectionnés ont par la suite été classés selon leur niveau de résultat. Les recommandations en matière de diagnostic et de traitement ont été fondées sur des résultats issus d'essais comparatifs randomisés et de consensus de spécialistes.

Résultats : La faible densité osseuse chez les femmes préménopausées n'est pas associée à la même hausse du risque de fracture que celle que connaissent les femmes d'âge avancé. En l'absence de fractures de fragilisation et d'une diminution de la

taille, il est possible que la présence d'une faible densité osseuse soit le reflet d'un faible pic de la masse osseuse et qu'elle s'inscrive dans le cours normal de la variation de la densité minérale osseuse (DMO). Il est également possible que les femmes présentent une faible densité osseuse en raison d'un trouble squelettique ou systémique sous-jacent. Parmi les causes courantes de la faible densité osseuse chez les femmes préménopausées, on trouve les troubles ovulatoires et la présence d'un faible poids corporel.

Conclusion : Chez les femmes préménopausées, on rend un diagnostic d'ostéoporose en présence de fractures de fragilisation et non pas seulement en fonction des résultats de l'ostéodensitométrie. Les causes secondaires de perte osseuse devraient d'abord être écartées et l'on devrait procéder à la correction de tout état sous-jacent contribuant à la présence d'une faible densité osseuse. Le recours à un traitement aux inhibiteurs de la résorption osseuse n'a été évalué que chez les femmes préménopausées qui bénéficient d'un traitement aux glucocorticoïdes et chez celles qui présentent une hyperparathyroïdie primaire. Le traitement aux inhibiteurs de la résorption osseuse ne s'est avéré efficace, pour l'amélioration de la DMO, que dans ces situations.

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INTRODUCTION

Low bone mineral density (BMD) is present in approximately 15% of healthy women between the ages of 30 and 40 years.¹ Bone density follows a bell curve distribution and is usually expressed as the number of standard deviations (SD) a bone density figure is above or below the mean value for young healthy adults (the "T score"). Approximately 0.5% of healthy women between the ages of 30 and 40 years have a T score of -2.5 or less.^{2,3} Low bone density has been identified in the young healthy population at increasing rates because bone density assessments are being performed at the request of patients. Osteoporosis is diagnosed in the premenopausal female population in the presence of fragility fractures and is not based solely on the results of a BMD test.¹ Premenopausal women experiencing fragility fractures should be further evaluated to determine why fractures are occurring in an estrogen-replete woman. This assessment may require a bone biopsy to understand the underlying process contributing to bone fragility in the premenopausal period.

Key Words: Premenopausal women, low bone density, osteoporosis, therapy

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Table 1. Secondary causes of bone loss¹

Diseases or conditions
• Hypogonadism (primary and secondary)
• Primary hyperparathyroidism
• Thyrotoxicosis
• Hypercortisolism
• Growth hormone deficiency
• Osteomalacia
• Hypophosphatasia
• Mastocytosis
• Myeloproliferative disorders
• Connective tissue disorders
• Malabsorptive states
• Hepatic disorders (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 (GnRH) agonists
• Depo medroxyprogesterone acetate (DMPA)

This review focuses on low bone density in premenopausal women and reviews the underlying pathophysiology, advances in diagnosis, and therapy. Low bone density in premenopausal women is being identified more commonly, and it is essential for family physicians to be able to manage this condition appropriately.

METHODS

An advanced MEDLINE search was conducted to identify all published randomized controlled trials (RCTs) evaluating low bone density in premenopausal women. The search was limited to English-language articles published from January 1990 to May 2004. The term "low bone density" was cross-matched with "premenopausal women" with the MeSH headings "management" and "pathophysiology." Articles reporting RCTs with appropriate randomization were selected.

Diagnosis

The World Health Organization (WHO) defines osteoporosis as a progressive systemic disease characterized by low bone density and microarchitectural deterioration in bone that predisposes patients to increased bone fragility and fracture.¹ The WHO criteria for diagnosis of osteoporosis,

using T scores, are applicable only to postmenopausal women. These criteria were not intended to apply to premenopausal women with low bone density.¹ Low bone density in premenopausal women may be either physiologic or pathologic. Measured BMD in the young healthy population follows a bell curve distribution, and approximately 15% of young healthy women have a T score of less than -1.0. Approximately 0.5% of young healthy women have a T score of -2.5 or less.² Thus there are variations in bone mineral densities similar to variations in height. In the normal population, those individuals at the upper or the lower end of the normal bell curve may represent the normal variation in BMD. This may not be reflective of underlying pathology and may not be associated with increased fracture risk in the premenopausal period.¹ In premenopausal women not experiencing fragility fractures or height loss, it is important to consider that low bone density may therefore simply reflect an underlying low peak bone mass. Low peak bone mass results from genetically determined peak bone density, possibly influenced by such environmental factors as exercise, dietary calcium intake, smoking, and alcohol consumption during the teenage and young adult years.¹

Low bone density in young women is not associated with the same increased risk of fracture seen in older women. Premenopausal women, being younger, have a significantly lower risk of fracture than do typical postmenopausal women, even with falls. Premenopausal women have a relatively greater muscle mass. They are estrogen replete and do not have the increased rates of bone turnover seen in postmenopausal women. Therefore, the risk of fracture in a young woman with low bone density is significantly less than that in a postmenopausal woman.⁴⁻⁶ Age is an independent risk factor for fracture, and low BMD in a postmenopausal, older woman is associated with a significantly higher fracture rate.¹

Bone density testing should be completed in those women with identifiable causes of bone loss.¹ Indications for BMD testing in premenopausal women include glucocorticoid therapy, premature ovarian failure (primary or secondary), diseases and conditions associated with bone loss (Table 1), and fragility fractures.

Clinical Evaluation

Premenopausal women with low bone density must be evaluated to ensure there are no secondary causes of bone loss present that might have contributed to the low BMD. Clinical assessment includes a complete history and physical examination with appropriate laboratory investigations to exclude common conditions associated with bone loss.⁷

It is advisable to evaluate thyroid, liver, and renal function. Serum calcium levels (corrected for albumin) are elevated in hyperthyroidism and in the presence of malignancy. Low

Table 2. Investigations in premenopausal women with low bone mineral density

Laboratory investigations

- Serum calcium (albumin corrected)
- CBC
- ESR
- Serum phosphate
- Serum magnesium
- Liver function tests (including alkaline phosphatase)
- Serum TSH
- Serum creatinine
- Serum FSH and estradiol

24 hour urinary excretion of calcium, creatinine

Optional additional investigations

- Serum 25-hydroxy vitamin D
- Serum parathyroid hormone
- Antigliadin antibodies
- Antiendomysial antibodies

CBC: complete blood count; ESR: erythrocyte sedimentation rate; TSH: thyroid-stimulating hormone; FSH: follicle-stimulating hormone.

serum calcium is seen in individuals with vitamin D deficiency or malabsorption. Malabsorption of calcium and vitamin D can result in low BMD as well as osteomalacia. Reduced 24-hour urinary excretion of calcium is an early indicator of inadequate calcium intake or malabsorption. If the 24-hour urinary excretion of calcium does not normalize with increased supplementation of calcium, the possibility of malabsorption or celiac disease should be considered. Assessment of antiendomysial and antigliadin antibodies can assist in the diagnosis of celiac disease.

It is important to ensure that young women with low BMD are estrogen-replete. Subclinical estrogen deficiency has been associated with low bone density in young women.⁸⁻¹⁰

Amenorrhea associated with estrogen deficiency causes accelerated bone loss. Menstrual regularity is an important factor in the achievement of peak bone mass and for the maintenance of BMD in women in the premenopausal period.^{1,8-11} It is important to ensure that women with low bone mass do not have estrogen deficiency, either clinical or subclinical.¹ Elevations in serum 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} Therefore, a detailed assessment of menstrual status is important because ovulatory disturbances are more frequent in premenopausal women with low BMD.⁸⁻¹⁰

Intervention

The usefulness of bisphosphonates in premenopausal women with low BMD, in the absence of glucocorticoid therapy, is unknown. Bisphosphonate therapy has been evaluated only in premenopausal women who have been on glucocorticoid therapy. Glucocorticoid therapy is associated with an increase in the rate of bone turnover. Bisphosphonates reduce bone turnover and therefore constitute an effective treatment option in premenopausal women who have been treated with glucocorticoids.¹³⁻¹⁶ Women who have not been treated with glucocorticoids and who are estrogen replete may have normal bone turnover rates. Suppressing bone turnover further with a bisphosphonate may not be safe or effective in improving bone density or reducing fracture risk. This patient population should be assessed in a specialized metabolic bone clinic before antiresorptive therapy is implemented.

Antiresorptive therapy is of proven benefit in premenopausal women with secondary causes of bone loss, such as glucocorticoid use or primary hyperparathyroidism.¹³ Bisphosphonates are retained in the skeleton for a long time, and they may be released from the skeleton several years after treatment, possibly in a subsequent pregnancy. The effects of bisphosphonates on the developing fetal skeleton are not known. Alendronate use has been evaluated in premenopausal women with primary hyperparathyroidism and has been shown to be effective in improving BMD in this population.¹⁷ Alendronate and risedronate are both effective in improving BMD in glucocorticoid-induced bone loss.¹³⁻¹⁶ Antiresorptive therapy

has not been evaluated in premenopausal women with low BMD in the absence of secondary causes of osteoporosis.

Lifestyle modification should always be encouraged in premenopausal women to improve BMD. Modifications include weight-bearing exercise, adequate dietary calcium intake, cessation of smoking, limited caffeine, and avoidance of excessive alcohol consumption.¹⁸

Women who are estrogen-deficient, either clinically or subclinically, may benefit from estrogen supplementation. After excluding secondary causes of bone loss, it is important to ensure adequate calcium and vitamin D supplementation, in addition to recommending lifestyle changes. Maintenance of normal body weight (a body mass index of 20–25 kg/m²) and a daily exercise program are of value in maintaining BMD.¹⁸ Women should be strongly advised to stop smoking and to limit their intake of alcohol, coffee, and phosphorus-containing soft drinks.¹⁸ Estrogen supplementation, either in the form of oral contraceptives or 17- β estradiol in combination with a progestin, may be considered to prevent progressive bone loss. Estrogen supplementation is associated with improvements in BMD in estrogen-deficient women.¹⁹ Cyclic medroxyprogesterone in women with ovulatory disturbance has been shown to result in significant gains in BMD in a randomized, placebo-controlled prospective study over 1 year.²⁰ Prospective data are needed to evaluate further the effect of menstrual cycles with a short luteal phase on BMD. Further evaluation of interventions with estrogen or progesterone supplementation is also warranted. In women who are not estrogen deficient, the role of estrogen supplementation is controversial.

Combined oral contraceptives (OCs) may exhibit a protective effect on bone density in premenopausal and postmenopausal women; however, some studies have demonstrated a negative effect.^{21,22} Data from the Canadian Multicentre Osteoporosis Study indicated that OC users had decreased BMD at the trochanter and spine, compared with nonusers.²³ However, OC users also had increased rates of smoking and alcohol use and had a higher prevalence of menstrual irregularity before OC use, compared with nonusers.²³ Thus prospective data are required to assess the effects of OCs on BMD in premenopausal women. Depot medroxyprogesterone acetate (DMPA) inhibits LH and FSH release and results in suppression of ovarian synthesis of estradiol and progesterone.^{24,25} DMPA use has been associated with decreased BMD at the lumbar spine.^{26,27}

CONCLUSION

Low BMD in any premenopausal woman may be due to a genetically determined low peak bone mass. Environmental factors such as an inadequate calcium intake, excessive

alcohol intake, use of tobacco, low body weight, and estrogen deficiency can contribute to a lower peak bone mass or to bone loss in the premenopausal years. Osteoporosis in premenopausal women is diagnosed in the presence of fragility fractures and is not based solely on the results of a BMD test. Secondary causes of bone loss should be excluded, and any underlying condition contributing to low bone density should be corrected. Antiresorptive therapy has been evaluated only in those premenopausal women who are on glucocorticoid therapy and in those with primary hyperparathyroidism. Only in these conditions has antiresorptive therapy been shown to improve BMD.

The issue of low bone density in premenopausal women warrants further study.

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