

**1 Premenopausal women and low bone density**

2

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4

5 **OBJECTIVE** To review the evidence and  
6 provide an approach to management of low bone  
7 density among premenopausal women.

8 **QUALITY OF EVIDENCE** MEDLINE was  
9 searched from January 1990 to November 2004  
10 and articles graded by level of evidence (I to III).

11 Diagnosis and management recommendations  
12 were based on evidence from randomized  
13 controlled trials and expert consensus.

14 **MAIN MESSAGE** Bone mineral density (BMD)  
15 testing among premenopausal women should be  
16 completed only in the presence of approved  
17 indications. Current evidence does not support  
18 screening for osteoporosis among premenopausal  
19 women. Low BMD in premenopausal women  
20 might not be associated with the same increased  
21 fracture risk seen in postmenopausal women. In  
22 the absence of fragility fractures, low BMD could  
23 reflect low peak bone mass based on genetic  
24 predisposition, environment, and lifestyle factors.  
25 Clinical evaluation enables distinction between  
26 low peak bone mass and a systemic disorder  
27 resulting in low BMD and skeletal fragility.  
28 Common causes of low bone density among  
29 premenopausal women include ovulatory  
30 disturbances and low body weight.

31 **CONCLUSION** Bone mineral density alone is  
32 insufficient for diagnosis of osteoporosis among  
33 premenopausal women in the absence of fragility  
34 fractures. Antiresorptive therapy has been  
35 evaluated and shown to benefit premenopausal  
36 women using glucocorticoid therapy or those with  
37 primary hyperparathyroidism.

38

39 This article has been peer reviewed.

40 Cet article a fait l'objet d'une révision par des  
41 pairs.

42 *Can Fam Physician* 2006;52:0000-0000.

43

**44 EDITOR'S KEY POINTS**

Please check byline and postgraduate degrees

Is this what you mean? Or do you mean "is unlikely to be"?

1 ● Bone density follows a bell curve, so that  
2 among premenopausal women, low bone density  
3 can be normal and the result of low peak bone  
4 mass that is genetically determined or can be  
5 secondary to poor calcium intake, lack of exercise,  
6 smoking, excessive alcohol intake, or medical  
7 conditions.

8 ● Osteoporosis should be diagnosed in  
9 premenopausal women only if fragility fractures  
10 are present and not on the basis of low bone  
11 density measurements alone.

12 ● Low bone density should be investigated,  
13 however, for patients who have certain medical  
14 conditions (such as estrogen failure,  
15 hyperparathyroidism, and renal disease) or who  
16 use certain medications (such as lithium,  
17 corticosteroids, and long-term heparin therapy).

18 ● In this population, bisphosphonates have been  
19 evaluated only for treating patients who have  
20 received glucocorticoid therapy; they have  
21 improved bone density. Other measures to  
22 increase bone mass, depending on the cause,  
23 include estrogen replacement and lifestyle  
24 changes.

25

## 26 **POINTS DE REPÈRE DU RÉDACTEUR**

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28 *Dr Khan is Associate Clinical Professor of*  
29 *Medicine in the Divisions of Endocrinology and*  
30 *Geriatrics at McMaster University in Hamilton,*  
31 *Ont.*

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33

34 Osteoporosis is common among postmenopausal  
35 women. Younger premenopausal women who  
36 have diseases or conditions associated with  
37 progressive bone loss could be at increased risk  
38 for osteoporosis. Some asymptomatic women ask  
39 to have bone mineral density (BMD) tested.  
40 Premenopausal women can have low bone density  
41 without fragility fractures or serious risk factors  
42 for fracture. It is thus necessary for primary care  
43 physicians to know the indications for BMD  
44 testing among premenopausal women as well as

1 the appropriate interpretation of BMD tests and  
2 management of low BMD among premenopausal  
3 women.

4 Low bone density (T-score of less than 1  
5 standard deviation below the mean for young  
6 adults) affects approximately 15% of young  
7 healthy women between the ages of 30 and 40.<sup>1</sup>  
8 Bone density follows a bell curve distribution, and  
9 approximately 0.5% of young healthy women  
10 between the ages of 30 and 40 have T-scores of  
11  $-2.5$  or less.<sup>2,3</sup> Osteoporosis in premenopausal  
12 women is diagnosed when fragility fractures are  
13 present and diagnosis is not based solely on the  
14 results of a BMD test.<sup>1</sup> Premenopausal women  
15 experiencing fragility fractures should be further  
16 evaluated to determine why bones fracture despite  
17 adequate estrogen levels. A few patients require a  
18 bone biopsy to evaluate the underlying histology  
19 using histomorphometry and to identify a possible  
20 cause for bone fragility before menopause.

Is this what you meant?

21 This paper addresses managing low BMD  
22 among premenopausal women and reviews the  
23 underlying pathophysiology, diagnosis, and  
24 therapy.

25

### 26 **Quality of evidence**

27 MEDLINE was searched to identify all English-  
28 language abstracts evaluating low BMD among  
29 premenopausal women. The search was limited to  
30 articles published in peer-reviewed journals from  
31 January 1990 to November 2004. The term “low  
32 bone density” was cross-matched with  
33 “premenopausal women” and with the MeSH  
34 headings “management” and “pathophysiology.”  
35 All studies evaluating premenopausal women  
36 were included except for case reports. Current  
37 prospective evidence of BMD risk factors and  
38 their relationship to fractures among  
39 premenopausal women is extremely limited and  
40 insufficient for recommending appropriate criteria  
41 to diagnose osteoporosis among premenopausal  
42 women.

43 The 2001 National Institutes of Health  
44 Consensus Development Panel on osteoporosis

1 identified densitometric diagnosis of osteoporosis  
2 among premenopausal women to be an important  
3 area for future research. Data on the efficacy of  
4 antiresorptive therapy among premenopausal  
5 women are limited to the treatment of steroid-  
6 induced osteoporosis and to parathyroid bone  
7 disease (level I evidence).

8

## 9 **Diagnosis**

10 The World Health Organization defines  
11 osteoporosis as a progressive systemic disease  
12 characterized by low bone density and  
13 microarchitectural deterioration in bone that  
14 predisposes patients to increased bone fragility  
15 and fracture.<sup>1</sup> The WHO criteria for diagnosis of  
16 osteoporosis by T-scores applies only to  
17 postmenopausal women. These criteria were not  
18 intended to apply to premenopausal women with  
19 low BMD.<sup>1</sup>

20 Low BMD among premenopausal women  
21 can be either physiologic or pathologic. Bone  
22 mineral density among young healthy women  
23 follows a bell curve distribution; approximately  
24 15% of young healthy women have T-scores of  
25 less than -1, and 0.5% of young healthy women  
26 have T-scores of -2.5 or less.<sup>2</sup> In the normal  
27 population, people at the upper or the lower end of  
28 the normal bell curve could represent the normal  
29 variation in BMD. This might not reflect  
30 underlying disease and might not be associated  
31 with increased fracture risk before menopause.<sup>1</sup> In  
32 premenopausal women without fragility fractures  
33 or height loss, low BMD could simply reflect an  
34 underlying low peak bone mass. Low peak bone  
35 mass is genetically determined and also affected  
36 by environmental factors, such as inadequate  
37 exercise and dietary calcium intake, as well as  
38 smoking and excess alcohol consumption during  
39 patients' years as teenagers and young adults.<sup>1</sup>

40 Low BMD among young women is not  
41 associated with the same increased risk of fracture  
42 as low BMD among older women. Premenopausal  
43 women, being younger, have a substantially lower  
44 risk of fracture even with falls. Premenopausal

1 women have relatively increased muscle mass.  
2 They are estrogen replete and have lower rates of  
3 bone turnover than postmenopausal women have.  
4 Therefore, the risk of fracture in young women  
5 with low BMD is much less than that in  
6 postmenopausal women.<sup>4-6</sup> Age is an independent  
7 risk factor for fracture,<sup>1</sup> and low BMD among  
8 postmenopausal older women is associated with  
9 higher risk of fracture.<sup>1</sup>

10 Bone density testing should be completed  
11 among women with identifiable causes of bone  
12 loss (**Table 1**).<sup>1</sup> The decision to complete BMD  
13 testing is made on clinical grounds. Secondary  
14 causes of bone loss (**Table 2**<sup>1</sup>) can be important  
15 indications for BMD testing.

16

### 17 **Clinical evaluation**

18 It is necessary to evaluate premenopausal women  
19 with low BMD to ensure that no secondary causes  
20 of bone loss have contributed to the low BMD.  
21 Clinical assessment includes taking a complete  
22 history, performing a physical examination of the  
23 patient, and requesting appropriate laboratory tests  
24 to exclude common conditions associated with  
25 bone loss.<sup>7</sup> Patients with low BMD in the absence  
26 of fragility fractures need to be evaluated, as do  
27 those with a history of fracture and those who  
28 have a secondary cause of bone loss likely to have  
29 contributed to development of low BMD levels.

30 Evaluation should include assessment of  
31 thyroid, liver, and renal function (**Table 3**). Serum  
32 calcium (corrected for albumin) is elevated in  
33 hyperparathyroidism or malignancy. Low serum  
34 calcium levels are seen among people with  
35 vitamin D deficiency or malabsorption.  
36 Malabsorption of calcium and vitamin D can  
37 result in low BMD as well as osteomalacia. A low  
38 measurement for calcium in 24-hour urine  
39 assessment is an early indicator of inadequate  
40 calcium intake or malabsorption. If results from  
41 24-hour urine assessment for calcium do not  
42 return to normal when calcium supplementation is  
43 increased, the possibility of malabsorption or  
44 occult celiac disease should be considered. A

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1 celiac panel with assessment of antiendomysial  
2 and antigliadin antibodies can help to diagnose  
3 celiac disease. History taking and physical  
4 examination will guide physicians considering  
5 additional investigations. It is also important to  
6 ensure that young women truly are estrogen  
7 replete. Subclinical deficiency in estrogen has  
8 been associated with low BMD among young  
9 women.<sup>8-10</sup>

10 Amenorrhea, as a result of estrogen  
11 deficiency, causes accelerated bone loss.  
12 Menstrual status is an important factor in  
13 achieving peak bone mass and in maintaining  
14 BMD among women before menopause.<sup>1,8-11</sup> It is  
15 necessary to ensure that women with low bone  
16 mass are not experiencing estrogen deficiency  
17 either clinically or subclinically.<sup>1</sup> Elevations in  
18 follicle-stimulating hormone of more than 20  
19 miu/L have been associated with increased bone  
20 turnover and progressive bone loss in the  
21 perimenopausal period.<sup>10,12</sup> Therefore, a detailed  
22 assessment of menstrual status is necessary, as  
23 ovulatory disturbances are frequently observed  
24 among premenopausal women with low BMD.<sup>8-10</sup>

25 A premenopausal woman with fragility  
26 fractures or progressive bone loss should be  
27 referred to a metabolic bone clinic for further  
28 assessment. A bone biopsy using  
29 histomorphometry might be necessary for further  
30 evaluation. A bone biopsy is completed using a  
31 technique similar to that of a bone marrow biopsy;  
32 however, the bone biopsy needle removes a core  
33 of bone tissue with both cortical and cancellous  
34 bone intact. This removal is completed while the  
35 patient receives local anesthetic, and risks are  
36 essentially limited in experienced hands to local  
37 bleeding.

38

### 39 **Intervention**

40 Few data examine the usefulness of  
41 bisphosphonates among premenopausal women  
42 with low BMD in the absence of glucocorticoid  
43 therapy. Bisphosphonates have been evaluated  
44 only among premenopausal women who have

**Isn't FSH usually measured in IU/L? Please use SI units**

**Is this what you meant?**

1 received glucocorticoid therapy. Glucocorticoid  
2 therapy is associated with an increase in the rate  
3 of bone turnover. Bisphosphonates lower bone  
4 turnover and, therefore, are effective among  
5 premenopausal women who have been treated  
6 with glucocorticoid therapy.<sup>13-16</sup> Women who have  
7 not received glucocorticoid therapy and who are  
8 estrogen replete could have normal bone turnover  
9 rates. Suppressing these rates with a  
10 bisphosphonate might not be safe or effective for  
11 improving bone density or reducing fracture risk.  
12 This patient population is thus best served by a  
13 specialized metabolic bone clinic before  
14 antiresorptive therapy is implemented.

15  
16 ***Antiresorptive therapies.*** Antiresorptive therapy  
17 benefits premenopausal women with secondary  
18 causes of bone loss, such as glucocorticoid use or  
19 primary hyperparathyroidism (level I evidence).<sup>17</sup>  
20 Cyclic etidronate, a less potent bisphosphonate,  
21 has not been evaluated among premenopausal  
22 women with osteoporosis. Bisphosphonates have  
23 long-term skeletal retention, and these agents can  
24 be released from the skeleton several years later,  
25 potentially in a subsequent pregnancy. The effects  
26 of bisphosphonates on the developing fetal  
27 skeleton are unknown. Alendronate has been  
28 evaluated among premenopausal women with  
29 primary hyperparathyroidism and has been shown  
30 to be effective in improving BMD in this  
31 population.<sup>17</sup> Alendronate and risedronate are  
32 effective in improving BMD in glucocorticoid-  
33 induced bone loss (level I evidence).  
34 Antiresorptive therapy has not been evaluated  
35 among premenopausal women with low BMD in  
36 the absence of secondary causes of osteoporosis.

37  
38 ***Lifestyle modification.*** Lifestyle modification  
39 should be encouraged among premenopausal  
40 women in order to improve BMD. This would  
41 include weight-bearing exercises, adequate dietary  
42 calcium intake, smoking cessation, limiting  
43 caffeine, and reducing excessive alcohol  
44 consumption (level II evidence).<sup>18</sup>

1           After identifying estrogen deficiency and  
2 excluding secondary causes of bone loss, it is  
3 important to ensure adequate calcium and vitamin  
4 D intake and to make additional lifestyle changes.  
5 Maintenance of normal body weight, with a body  
6 mass index of 20 to 25, and a daily exercise  
7 program are of value in maintaining BMD (level  
8 II evidence).<sup>18</sup> Smoking cessation and limitation  
9 of alcohol, coffee, and phosphorus-containing soft  
10 drinks should be strongly emphasized (level III  
11 evidence).<sup>18</sup>

12  
13 ***Estrogen supplementation.*** Women who are  
14 estrogen deficient, either clinically or  
15 subclinically, could benefit from estrogen  
16 supplements. Estrogen supplementation, in the  
17 form of either oral contraceptive pills or 17beta-  
18 estradiol in combination with a progestin, should  
19 be considered in order to prevent progressive bone  
20 loss (level III evidence). Estrogen  
21 supplementation is associated with improvements  
22 in BMD among estrogen-deficient women (level  
23 I evidence).<sup>19</sup> Cyclic medroxyprogesterone in  
24 women with ovulatory disturbance has been  
25 shown in a randomized placebo-controlled  
26 prospective study over 1 year to result in gains in  
27 BMD (level I evidence).<sup>20</sup> Prospective data are  
28 needed to evaluate further the effect of short  
29 luteal-phase cycles on BMD. Further evaluation of  
30 intervention with estrogen or progesterone  
31 supplements is also warranted. The role of  
32 estrogen supplementation for women who are not  
33 estrogen deficient is controversial (level III  
34 evidence).

35           While oral contraceptive pills can exhibit  
36 a protective effect on premenopausal and  
37 postmenopausal women, other trials have  
38 demonstrated a negative effect (level II  
39 evidence).<sup>21,22</sup> Data from the Canadian Multicentre  
40 Osteoporosis Study indicated that oral  
41 contraceptive users had lower BMD at the  
42 trochanter and spine than non-users had.<sup>23</sup>  
43 Evaluation of this patient population indicated,  
44 however, that these women also had higher rates

1 of smoking and alcohol use and had a higher  
2 prevalence of menstrual irregularity before  
3 initiating oral contraceptive use than non-users  
4 had (level II evidence).<sup>23</sup> Thus, prospective data  
5 are required to assess the effects of oral  
6 contraceptive use on BMD among premenopausal  
7 women. Depot medroxyprogesterone acetate, an  
8 injectable contraceptive, inhibits release of  
9 luteinizing hormone and follicle-stimulating  
10 hormone and results in suppression of ovarian  
11 synthesis of estradiol and progesterone (level II  
12 evidence).<sup>24,25</sup> Depot medroxyprogesterone use has  
13 been associated with decreased BMD at the  
14 lumbar spine (level II evidence).<sup>26,27</sup>

Please check our expansion of MPA

15

## 16 **Conclusion**

17 Low BMD among premenopausal women should  
18 be further evaluated. Low BMD can be due to  
19 genetically predetermined low peak bone mass.  
20 Environmental factors, such as inadequate  
21 calcium intake, alcohol and tobacco excess, low  
22 body weight, and estrogen deficiency, can  
23 contribute to development of lower peak bone  
24 mass or to bone loss in the premenopausal years.  
25 Osteoporosis among premenopausal women is  
26 diagnosed in the presence of fragility fractures and  
27 diagnosis is not based solely on the results of a  
28 BMD test. Secondary causes of bone loss should  
29 be excluded, and any underlying condition  
30 contributing to low BMD should be corrected.  
31 Referral to a metabolic bone clinic is appropriate  
32 for patients with fragility fractures or progressive  
33 bone loss. Antiresorptive therapy has been  
34 evaluated only for premenopausal women  
35 receiving glucocorticoid therapy or those with  
36 primary hyperparathyroidism. Only in these  
37 conditions has antiresorptive therapy been shown  
38 to improve BMD measurements. Screening for  
39 osteoporosis among premenopausal women is not  
40 justified based on available evidence.

41

## 42 **Acknowledgment**

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#### 6 **Competing interests**

7 *None declared*

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address**

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**Table 1. Indications for BMD testing in premenopausal women**

- Glucocorticoid therapy
- Premature ovarian failure (first-degree or second-degree)
- Diseases and conditions associated with bone loss (**Table 2**)
- Fragility fractures

**Note: Tables 1-3 will be formatted properly at the page proof stage. Please ensure all information is accurate**

**Table 2. Important secondary causes of bone loss**

- Diseases and conditions
  - Hypogonadism (primary and secondary)
  - Primary hyperparathyroidism
  - Thyrotoxicosis
  - Hypercortisolism
  - Growth hormone deficiency
  - Osteomalacia
  - Myeloproliferative disorders
  - Connective tissue disorders
  - Malabsorptive states (ie, celiac disease)
  - Hepatic disorders (ie, primary biliary cirrhosis)
  - Inflammatory bowel disease
  - Renal disease
  - Hypercalciuria
  - Osteogenesis imperfecta
- Medications
  - Glucocorticoids
  - Thyroxine (excessive)
  - Anticonvulsants (eg, phenytoin, phenobarbital)
  - Heparin (long-term)
  - Lithium
  - Cytotoxic chemotherapy
  - Gonadotropin-releasing hormone agonists
  - Depot medroxyprogesterone acetate

**Are these explanations or just examples?**

**Please check our correction**

Data from Khan et al.<sup>1</sup>

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**Table 3. Workup for low bone mineral density in premenopausal women**

Laboratory investigations

- Serum calcium (corrected for albumin)
- Complete blood count
- Erythrocyte sedimentation rate
- Phosphate
- Magnesium

● Liver function tests

- Thyrotropin-stimulating hormone

- Creatinine

● Alkaline phosphatase

- Follicle-stimulating hormone

- Estradiol

24-hour urine collection

- Calcium

- Creatinine

Additional investigations

- 25-hydroxy vitamin D

● Parathyroid hormone

- Antigliadin antibodies

- Antiendomysial antibodies

**Please check our expansion of your abbreviations**

**25-hydroxy vitamin D: Please check this term**

**Antigliadin antibodies, Antiendomysial antibodies: Please check these terms**

**Please note our addition of additional investigations from text**