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Original Article

Bone Densitometry in Premenopausal Women

Synthesis and Review

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Abstract

Bone loss prior to menopause is being increasingly identified in women. Clearly, low bone mineral density (BMD) is a significant risk factor for fracture in the estrogen-deficient female postmenopause. The significance of low bone density prior to menopause needs to be addressed. Low bone density in the premenopausal female may reflect attainment of a lower peak bone mass. It may also be secondary to progressive bone loss following achievement of peak bone density. The etiology of low bone density in the premenopausal female needs to be clarified with meticulous exclusion of secondary causes of bone loss.

Menstrual status is an important determinant of peak bone mass as well as the development of bone loss in women prior to the onset of menopause. Subclinical decreases in circulating gonadal steroids may be associated with a lower peak bone mass as well as progressive bone loss in otherwise reproductively normal women. Elevations of follicle-stimulating hormone (FSH) of greater than 20 miu/L are associated with evidence of increased bone turnover marker activity and correlate with progressive bone loss in perimenopausal women. This transitional period requires further study with respect to the magnitude of bone loss experienced and the potential benefits of antiresorptive therapy. Detailed assessment of menstrual status is necessary in the evaluation of low bone density in premenopausal women.

The majority of the cross-sectional and longitudinal studies completed evaluating BMD in the premenopausal years suggest that minimal bone loss does occur prior to menopause after attainment of peak bone mass. The magnitude of premenopausal bone loss, however, is controversial and may be site-dependent. More rapid rates of bone loss are seen in the transitional period beginning 2–3 yr prior to the onset of menopause. Prospective data are needed to understand further the relationship between BMD and fracture in the premenopausal period.

Women with steroid-induced bone loss as well as other secondary causes of osteoporosis respond to antiresorptive therapy with documented improvements in BMD. Biomarkers can identify perimenopausal women with increased bone turnover. Lifestyle modification can improve BMD in the pre- and the perimenopausal period. Antiresorptive therapy has not been evaluated in pre- or perimenopausal women with low BMD in the absence of secondary causes of osteoporosis. As new treatment options are evaluated and become available, biomarker assessment may be of value in identifying women at risk of fracture. This paper provides a review of the literature and recommendations with respect to management of low bone density in the premenopausal female.

Key Words: Bone density; premenopausal women; fracture risk; biomarkers; management.

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Introduction

Low bone mineral density (BMD) is a major risk factor for osteoporosis and fragility fractures *(1)*. Low bone density in the adult population may be secondary to either low peak bone mass attained in the second to third decade and/or subsequent bone loss after achieving peak bone mass *(1)*. Bone loss prior to menopause may contribute to fracture risk later in life. The precise relationship between BMD and fracture risk in younger patients is currently not well defined, as fracture data have been obtained predominantly in the elderly over the age of 65. The World Health Organization (WHO) definition of osteoporosis based on the relationship between bone density and fracture risk was developed on a population basis for postmenopausal Caucasian women *(2)*. Different criteria, however, need to be established for women younger than the age of 50; however, there is insufficient data to do so at this time.

There are a number of issues that need to be addressed in evaluating BMD in the premenopausal years:

1. Does BMD fall after attainment of peak bone mass and prior to menopause?
2. If BMD is low in a patient, why is it low?
3. Is low BMD in the premenopausal years associated with an increased risk of fracture?
4. Should low BMD be treated, and if so, how?

This paper provides a review of the literature as well as recommendations for the management of low bone density in the premenopausal female.

Bone Mineral Density and Bone Turnover in the Premenopausal Years

Bone mineral density in the young healthy population is approximately Gaussian in distribution regardless of the technique used *(2)*. In the young healthy population, 15% of women have a T-score of less than –1 and thus have low bone mass *(3)*. Approximately 0.5% of women have a T-score of –2.5 or less *(3)*. The proportion of women affected by osteoporosis at any site increases with age, as does the fracture risk *(3)*.

The majority of studies completed evaluating BMD prior to the onset of menopause suggest that minimal bone loss does occur in the premenopausal years. The magnitude of premenopausal bone loss, however, is controversial and may be site-dependent *(4–11)*. The differences in the cross-sectional data may be explained by methodological issues. Rates of bone loss are difficult to determine from cross-sectional studies. BMD may be affected by age-related changes in size *(12)*. Areal dual X-ray absorptiometry (DXA) does not completely correct for size. As wider bones are also deeper, they appear to have a greater BMD when evaluated by areal DXA technology. With age, increases in the width of bone may result in artificial increases in BMD and may affect the results of cross-sectional studies. Age is associated with increased periosteal bone formation, and this can help to offset endosteal bone loss *(13)*. Periosteal bone formation is greater in males than in females *(13)*. This results in less cortical bone loss with ageing in men than in women, as the degree of endocortical bone resorption is similar *(14)*.

As areal DXA does not adjust for differences in height cross-sectional studies may falsely estimate the rate of bone loss. Height differences between older and younger individuals may not necessarily be a result of height loss in the older population, but may instead reflect a cohort effect if the individuals born more recently are in fact reaching a greater adult height than previous generations. These differences in adult heights may falsely affect BMD as measured by areal DXA. Some of these methodological issues are overcome by longitudinal studies.

Longitudinal assessment of BMD was evaluated in premenopausal women *(15)*. BMD at the forearm, hip, spine, and total body in 199 premenopausal women, 199 postmenopausal women, and 222 men was studied prospectively over 2 yr. DXA assessments were completed at baseline and at 2 yr. Women aged 20–49 demonstrated stable BMD at the radius and total body. A slight but significant fall of 0.4% yr was noted at the hip and the lumbar spine. Bone loss accelerated by threefold in the immediate postmenopausal period and loss was seen at all sites during the ages of 50–59, after which time period the rate of bone loss returned to the low rate seen in the premenopausal years *(15)*. Similar findings were noted by Sowers and colleagues in the Michigan Bone Health Study *(16)*. This longitudinal population-based study evaluated women between the ages of 25 and 45 over 3 yr. A total of 481 premenopausal

women (follicle-stimulating hormone [FSH] < 20 miu/L) were followed, as were 45 perimenopausal women (FSH > than 20 miu/L) and 57 women defined as "fluctuating" (FSH not consistently more or less than 20 miu/L). Stable BMD at the femoral neck with slight increments in total body BMD was observed in the premenopausal women. However, significant bone loss was noted at the femoral neck in perimenopausal women and in those women defined as "fluctuating." Total body BMD was stable *(16).*

Bone turnover has been evaluated in the perimenopausal period. A cohort of 272 pre- and perimenopausal women between the ages of 31 and 59 were followed for 3 yr *(17).* Biomarkers and BMD at various skeletal sites were evaluated by DXA at 1-yr intervals for 3 yr. In perimenopausal women with increased FSH, higher levels of alkaline phosphatase and osteocalcin are associated with greater rates of bone loss at the femoral neck. Decreases in serum estradiol during the 3 yr of follow-up were closely associated with bone loss at the trochanter and anterior-posterior (AP) spine after 3 yr *(17).* In the premenopausal women, there was no evidence of bone loss. A small but statistically significant increase in BMD was noted at the total hip, trochanter, AP lumbar spine, and radius.

Bone loss of significance occurring the later perimenopausal years has also been reported by other investigators *(18–20).* A prospective assessment of 75 women over the age of 46 for 9.5 yr of follow-up demonstrated menopause-related bone loss beginning with rises in FSH and occurring approx 2–3 yr prior to the last menses *(21).* This accelerated rate of bone loss ended approx 3–4 yr after the last menses *(21).* Current data support the concept of bone loss beginning prior to the menopause and continuing for the immediate 3–4 yr following the last menstrual period. It is known that FSH levels rise prior to menopause *(22–24).* Bone turnover marker activity has been shown to correspond closely to increases in FSH *(25),* and data indicate that the perimenopausal period is associated with increased rates of bone loss. The perimenopausal transitional period consisting of irregular menstrual bleeding 2–3 yr prior to menopause and the 1 yr following the last menstrual period require further assessment. The potential role of antiresorptive therapy during this transitional period needs to be evaluated.

Bone Mineral Density and Fracture Risk

Limited data are available with regard to the relationship between BMD and fracture risk in the premenopausal period. Assessment of the relationship between BMD and fracture in the perimenopausal period has been reported prospectively in 3222 perimenopausal women aged 47–59. Individuals in the lowest quartile of spinal BMD were at a 2.9-fold greater fracture risk than those in the highest quartile. Those in the lowest quartile of hip BMD were at a 2.2-fold greater fracture risk than those in the highest quartile. BMD thus appears to be of value in fracture risk prediction in perimenopausal women *(26).* It is not known if antiresorptive therapy will be of value in increasing BMD.

Women with a history of a premenopausal fracture are at an increased risk of subsequent fracture. Data from the study of osteoporotic fracture in 9086 ambulatory Caucasian women over the age of 65 followed prospectively for 12 yr demonstrated a higher fracture risk in women with a history of premenopausal fracture. The hazard ratio was 1.33 (CI 1.14–1.56, $p < 0.001$). Adjustment for differences in age, BMD, and maternal fracture history did not explain this strong relationship. Premenopausal fractures are a strong predictor for fracture postmenopause independent of BMD *(27).*

Other investigators have reported a similar relationship between premenopausal fracture history and subsequent fracture. A 74% increased risk of fracture after the age of 50 was noted in women who reported a history of fracture premenopausal, as seen in a cross-sectional retrospective study of postmenopausal women *(28).* Premenopausal fracture was an independent predictor of future fracture risk after adjusting for age, bone density, weight, alcohol, smoking, and maternal history of a hip fracture *(28).*

Genetic and Environmental Effects on BMD

Peak bone mass is affected by genetic and environmental factors. Genetic factors account for up to 46–62% of the variance in BMD *(29).* Environmental factors can modify genetic potential; notably, nutrition, calcium, and exercise can affect BMD.

Menstrual status is also an important determinant of peak bone mass.

Agreement has been reached that BMD has strong genetic components and this has been supported by twin and family studies *(29–34).* Part of the mechanism for this genetic effect has been ascribed to polymorphism of the vitamin D receptor gene locus, which accounts for as much as 75% of the variance in BMD *(35).* The interplay of genetic and lifestyle factors on BMD at the lumbar spine and proximal femur was evaluated in 470 healthy premenopausal women between the ages of 44 and 50 *(36).* DXA assessments of the lumbar spine and hip were completed as well, as genotyping for vitamin D receptor polymorphism. The presence of a restriction site within the vitamin D receptor was associated with reduced spinal bone density. Absence of this site conferred a greater spinal BMD *(36).* The vitamin D receptor genotype, weight, exercise, and calcium intake were all significant determinants of BMD. The association of the vitamin D receptor genotype with femoral neck BMD was modified by calcium intake as well as physical activity *(36).* This suggests that dietary modification and exercise may be important in maximizing BMD. Higher calcium intake was associated with a greater femoral neck BMD in comparison to a lower calcium intake for the same vitamin D receptor genotype *(36).* The association between physical activity and BMD was modified by the vitamin D receptor genotype at the femoral neck, with higher physical activity associated with significantly higher femoral neck BMD. Body weight of greater than 160 lb was associated with increases in BMD irrespective of the vitamin D receptor genotype *(36).* These data support the hypothesis that genetic predisposition for BMD may be modified by environmental factors. There is a need for prospective data to further determine the extent to which BMD responds to lifestyle changes across the vitamin D receptor genotypes.

Calcium intake in addition to physical activity has been shown to have an additive positive benefit on BMD in the order of 3–7% in comparison to low calcium intakes in sedentary women *(37).* This is supported by other investigators *(38–40).* Vitamin D supplements, caffeine, smoking, and reproductive history have not been consistently found to influence BMD or bone turnover *(37).* This is supported by other investigators *(41,42).*

Oral contraceptives have been evaluated with respect to effect on BMD in premenopausal women. This has been a subject of debate. Most studies have documented no effect on bone mass *(43–47)* or a negative effect *(64).* Other studies have demonstrated a positive effect of oral contraceptives on BMD *(48–50).* Conflicting findings relate to differences in dose, direction of use, and study populations. Prospective long-term studies are necessary to determine the effects of oral contraceptives on bone in estrogen-replete premenopausal healthy women. Depot medroxy progesterone acetate (DMPA) inhibits FSH and luteinizing hormone (LH) release and ovarian estrogen production. DMPA use has been associated with decreased BMD at the lumbar spine *(51–54).* Further prospective data regarding long-term skeletal effects of DMPA are needed.

Smoking has been evaluated with respect to effects on BMD in premenopausal women. A negative effect of smoking on premenopausal BMD has been noted by investigators at the lumbar spine *(44,45).* No effect of smoking on premenopausal BMD was found in a recent meta-analysis *(55).*

Effect of Menstrual Status on BMD

Bone loss is accelerated following cessation of menses. Amenorrhea, both primary and secondary, is accompanied by estrogen deficiency and associated with bone loss. Anovulatory cycles as well as cycles with a short luteal phase of less than 10 d are associated with bone loss documented at the lumbar spine by quantitative computed tomography (QCT), with approx 4.2% loss noted prospectively over 1 yr *(56).* This degree of bone loss was noted despite only minimal changes noted in cycles by patients *(56).*

The relationship between sex steroids and low BMD was evaluated in a nested case with control study *(57).* Thirty-one premenopausal women with a BMD of the lumbar spine, femoral neck, or total body of less than the 10th percentile were compared to 34 premenopausal women with a BMD at two of these three skeletal sites between the 50th and the 75th percentile. BMD was measured by DXA. These women were healthy and were experiencing regular menses. Age of menarche, number of periods per

year, parity, smoking history, calcium and caloric intake, and family history were all comparable between the two groups, with no significant differences. The women with lower BMD had significantly lower urinary estrogen and progesterone metabolites in comparison to women with normal BMD *(57)*. A less pronounced luteinizing hormone (LH) response was noted in the women with the lower BMD. These data suggest that subclinical decreases in circulating gonadal steroids may impair the attainment and/or maintenance of bone mass in otherwise reproductively normal women *(57)*.

Ovulatory disturbances are more common in premenopausal women with low BMD. A detailed menstrual history is necessary in the evaluation of premenopausal women with low BMD. Slight irregularities in menstrual cycles may be associated with ovulatory disturbances and subclinical decreases in sex steroids.

Hypogonadism in young women may be primary or secondary to a number of conditions. These include anorexia nervosa, excessive exercise, hyperprolactinemia, GnRH agonists, chronic diseases with sufficient stress to cause pituitary ovarian dysfunction such as rheumatoid arthritis, as well as premature menopause either spontaneous or secondary to surgery, chemotherapy, or radiotherapy. All of these conditions are associated with an increased rate of bone loss.

Cyclic medroxy progesterone intervention in women with ovulatory disturbances has been shown to result in significant gains in BMD in a randomized placebo-controlled prospective study over 1 yr *(58)*. Prospective data are needed to evaluate further the effect of short luteal phase cycles on BMD. Further evaluations of intervention with estrogen or progesterone supplementation are also warranted.

Etiology of Low BMD

In the assessment of premenopausal individuals with decreased BMD, it is necessary to exclude secondary causes of osteoporosis (Table 1). Glucocorticoids are an important cause of bone loss in the premenopausal period. Bone loss is believed to be most rapid within the first few months and affects both the axial and the appendicular skeleton. It is most pronounced at the spine. Skeletal response to glucocorticoids varies. High doses are associated with a greater adverse effect. Doses of prednisone above 2.5 mg/d may be associated with greater fracture risk *(59)*. Doses of less than 7.5 mg/d are less likely to result in rapid bone loss and fractures *(59)*.

Table 1
Secondary Causes of Bone Loss

Conditions	Drugs
Hypogonadism (primary and secondary)	Glucocorticoids
Primary hyperparathyroidism	Thyroxine
Thyrotoxicosis	Anticonvulsants
Hypercortisolism	Heparin
Growth hormone deficiency	Lithium
Osteomalacia	Cytotoxic chemotherapy
Hypophosphatasia	GnRH agonists
Mastocytosis	Depot medroxyprogesterone acetate
Myeloproliferative disorders	
Connective tissue disorders	
Malabsorptive states	
Hepatic disorders (primary biliary cirrhosis)	
Inflammatory bowel disease	
Renal disease	
Hypercalciuria	
Osteogenesis imperfecta	

Primary hyperparathyroidism is also an important cause of bone loss in the premenopausal years. Previously, primary hyperparathyroidism would present with significant symptoms including osteitis fibrosa cystica, seen in approx 25% of individuals. This is now rare at the time of presentation *(60)*. Similarly, severe hypercalcemia or nephrolithiasis and nephrocalcinosis, previously seen in 57% of individuals at the time of presentation, are no longer common presenting features, currently being seen in only 17% of individuals. The majority of patients detected with primary hyperparathyroidism are indeed asymptomatic (80%), resulting from the widespread use of the auto-analyzer and the detection of mild hypercalcemia prior to the development of significant bone or renal disease. Primary hyperparathyroidism is a result of emergence of clones of abnormal parathyroid cells with an increased set point to calcium *(61)*. Individuals with primary

hyperparathyroidism meeting the revised guidelines for parathyroidectomy should proceed to surgery *(62).* Those individuals with asymptomatic disease who do not wish to proceed to surgery or cannot proceed to surgery may be considered for antiresorptive therapy. Antiresponse agents may be effective in preventing bone loss in premenopausal women with primary hyperparathyroidism. Alendronate has recently been evaluated in both pre- and postmenopausal women with asymptomatic primary hyperparathyroidism and was associated with significant increases in BMD and reductions in markers of bone turnover were also noted *(63).*

The assessment of a premenopausal female with low BMD requires a detailed evaluation in order to ensure that secondary causes of osteoporosis are not present and contributing factors to the decreased bone density. Effective treatment of the secondary cause of bone loss may be associated with improvement in BMD and a reduction in fracture risk.

Summary

In premenopausal women, BMD should be restricted to those individuals who have an identifiable cause of bone loss. This includes the following important indications:

1. Glucocorticoid therapy
2. Premenopausal ovarian failure, both primary and secondary
3. Presence of diseases or conditions associated with bone loss
4. Presence of low-trauma fractures
5. Endocrinopathies known to be associated with secondary osteoporosis

The assessment of an individual with low BMD in the premenopausal years requires a detailed history and physical exam. The assessment should include a detailed evaluation of menstrual history. Risk factors for fracture also require assessment. It is necessary to exclude secondary causes of bone loss. Assessment of thyroid, parathyroid, renal, and adrenal function is necessary. Evaluation of vitamin D status and exclusion of malabsorption states are also necessary. Assessment of gonadal status and bone turnover are of value in the assessment of a premenopausal female with low BMD. Individuals who are experiencing unexplained low-trauma fracture may require a bone biopsy in order to determine the cause of fractures in the estrogen-replete female as well as to guide therapy in individual patients.

There are currently no established BMD criteria for the diagnosis of osteoporosis in premenopausal females. It is necessary to ensure that such women are estrogen-replete and that other causes of bone loss are not present. BMD cannot be used in isolation to make the diagnosis of osteoporosis in premenopausal women. Diagnosis can be made in the presence of fragility fractures.

Biomarkers may be of value in identifying perimenopausal women with increased bone turnover. These women may benefit from antiresorptive therapy, and placebo-controlled trials are needed. This period of transition from premenopausal to postmenopausal state does require further evaluation. It is also important to address nutrition and lifestyle modification. It is necessary to treat the underlying cause of bone loss if a cause is identified.

It is anticipated that prevention of bone loss in perimenopausal women may decrease current lifetime fracture risk. Prospective data, however, are required to understand further the relationship between BMD and fracture in the premenopausal period.

References

1. Kanis JA. 1997 Diagnosis of osteoporosis. Osteoporos Int 7(suppl 3):S108–S116.
2. Kanis JA. 2002 Diagnosis of osteoporosis and assessment of fracture risk. Lancet 359:1929–1936.
3. Kanis JA, Melton LJ, Christiansen C, Johnston CC, Khaltaev N. 1994 The diagnosis of osteoporosis. J Bone Miner Res 9:1137–1141.
4. Sowers MFR, Kshirsagar A, Crutchfield M. 1991 Body composition, age and femoral bone of young adult women. Ann Epidemiol 1:35–42.
5. Hedlund LR, Gallagher JC. 1989 The effect of age and menopause on bone mineral density of the proximal femur. J Bone Miner Res 4:639–642.
6. Ravn P, Hetland ML, Overgaard K, Christiansen C. 1994 Premenopausal and postmenopausal changes in bone mineral density of the proximal femur measured by dual-energy X-ray absorptiometry. J Bone Miner Res 9:1975–1980.
7. Rosenthal DI, Mayo-Smith W, Hayes CW. 1989 Age and bone mass in premenopausal women. J Bone Miner Res 4:533–538.
8. Mazess RB, Bardden HS. 1991 Bone density in premenopausal women: effects of age, dietary intake, physical

activity, smoking and birth-control pills. Am J Clin Nutr 53:132–142.
9. Hansen MA. 1994 Assessment of age ad risks factors on bone density and bone turnover in healthy premenopausal women. Osteoporos Int 4:123–128.
10. Recker RR, Lappe JM, Davies MK, Kimmel DB. 1992 Changes in bone mass immediately before menopause. J Bone Miner Res 7:857–862.
11. Slemenda C, Longcope C, Peacock M, Hui L, Johnston CC. 1996 Sex steroids, bone mass and bone loss: a prospective study of pre-, peri- and postmenopausal women. J Clin Invest 97:14–21.
12. Jergas M, Breitenseher M, Gluer CC, Yu W, Genant HK. 1995 Estimates of volumetric bone density from projectional measurements improve the discriminatory capability of dual X-ray absorptiometry. J Bone Miner Res 10:1101–1110.
13. Duan Y, Turner CH, Kim BT, et al. 2001 Sexual dimorphism in vertebral fragility is more the result of gender differences in age-related bone gain than bone loss. J Bone Miner Res 16:2267–2275.
14. Kalender WA, Felsenberg D, Loius O, et al. 1989 Reference values for trabecular and cortical vertebral bone density in single and dual-energy quantitative computed tomography. Eur J Radiol 9:75–80.
15. Warming L, Hassager C, Christiansen C. 2002 Changes in bone mineral density with age in men and women: a longitudinal study. Osteoporos Int 13:105–112.
16. Sowers M, Crutchfield M, Bandekar R, et al. 1998 Bone mineral density and its change in pre- and perimenopausal white women: the Michigan Bone Health Study. J Bone Miner Res 13:1134–1140.
17. Chapurlat RD, Garnero P, Sornay-Rendu E, Arlot ME, Claustrat B, Delmas PD. 2000 Longitudinal study of bone loss in pre- and perimenopausal women: evidence for bone loss in perimenopausal women. Osteoporos Int 11:493–498.
18. Slemenda CW, Hui SL, Loncope CL, Johnston CC. 1987 Sex steroids and bone mass: a study of the changes about the time of menopause. J Clin Invest 80:1261–1269.
19. Nilas L, Christiansen C. 1989 The pathophysiology of peri- and postmenopuausal bone loss. Br J Obstet Gynaecol 96:580–587.
20. Pouilles JM, Tremollieres F, Ribot C. 1993 The effects of menopause on longitudinal bone loss from the spine. Calcif Tissue Int 52:340–343.
21. Recker B, Lappe J, Davies K, Heaney R. 2000 Characterization of perimenopausal bone loss: a prospective study. J Bone Miner Res 15:1965–1973.
22. Sherman BM, Halmi KA, Zamudio R. 1975 LH and FSH response to gonadotropin-releasing hormone in anorexia nervosa: effect of nutritional rehabilitation. J Clin Endocrinol Metab 41(1):135–142.
23. Melcalfe MG, Donald RA, Livesey JH. 1981 Pituitary-ovarian function in normal women during the menopausal transition. Clin Endocrinol 124:125–155.
24. Li TC, Dockery P, Thomas P, Rogers AW, Lenton EA, Cooke ID. 1988 The effects of progesterone receptor blockage in the luteal phase of normal fertile women. Fertil Steril 50(5):732–742.
25. Garton M, Martin J, New S, et al. 1996 Bone mass and metabolism in women aged 45–55. Clin Endocrinol (Oxf) 44(5):563–570.
26. Kroger H, Huopio J, Honkanen R, et al. 1995 Prediction of fracture risk using axial bone mineral density in a perimenopausal population: a prospective study. J Bone Miner Res 10:302–306.
27. Hosmer WD, Genant HK, Browner WS. 2002 Fractures before menopause: a red flag for physicians. Osteopor Int 13:337–341.
28. Wu F, Mason B, Horne A, et al. 2002 Fractures between the ages of 20 and 50 years increase women's risk of subsequent fractures. Arch Intern Med 162:33–36.
29. Krall EA, Dawon-Hughes B. 1993 Heritable and life-style determinants of bone mineral density. J Bone Miner Res 8:1–8.
30. Pocock NA, Eisman JA, Hopper J, Yeates M, Sambrook PN, Eberl S. 1987 Genetic determinants of bone mass in adults. J Clin Invest 80:706–710.
31. Dequeker J, Nijs J, Verstaeten A, Geusen P, Gevers G. 1987 Genetic determinants of bone mineral content at the spine and radius: a twin study. Bone 8:207–209.
32. Seeman E, Hopper JL, Bach LA, et al. 1989 Reduced bone mass in daughters of women with osteoporosis. N Engl J Med 320:554–558.
33. Lutz J. 1986 Bone mineral, serum calcium and dietary intakes of mother/daughter pairs. Am J Clin Nutr 44:99–106.
34. Tylavsky PA, Bortz AD, Hancock RL, Andersen JJB. 1989 Familial resemblance of radial bone mass between premenopausal mothers and the college-age daughters. Calcif Tissue Int 45:265–272.
35. Garnero P, Arder NK, Griffith G, Delmas PD, Spector TD. 1996 Genetic influence on bone turnover in postmenopausal twins. J Clin Endocrinol Metab 81:140–146.
36. Salamone LM, Glynn NW, Black DM, et al. 1996 Determinants of premenopausal bone density: the interplay of genetic and lifestyle factors. J Bone Miner Res 12(10):1557–1565.
37. Hansen MA. 1994 Assessment of age and risk factors on bone density and bone turnover in healthy premenopausal women. Osteoporos Int 4:123–128.
38. Rico H, Revilla M, Villa LF, et al. 1994 Longitudinal study of the effect of calcium pidolate on bone mass in eugonadal women. Calcif Tissue Int 54:477–480.
39. Elders PJM, Lips P, Netelenbos JC, et al. 1994 Long-term effect of calcium supplementation on bone loss in perimenopausal women. J Bone Miner Res 9:963–970.
40. Recker RR, Davies M, Hinders SM, et al. 1992 Bone gain in young adult women. JAMA 268:2403–2408.
41. Kanders B, Dempster DW, Lindsay R. 1988 Interaction of calcium nutrition and physical activity on bone mass in young women. J Bone Miner Res 3:145–149.
42. Chapuy M-C, Preziosi P, Maamer M, et al. 1997 Prevalence of vitamin D insufficiency in an adult normal population. Osteoporos Int 7:439–443.
43. Hreshchyshyn MM, Hopkins A, Zylstra S, Anbar M. 1988 Associations of parity, breast-feeding and birth control pills with lumbar spine and femoral neck bone densities. Am J Obstet Gynecol 159:318–322.

44. Stevenson JC, Lees B, Devenport M, Cust MP, Ganger KF. 1989 Determinants of bone density in normal women: risk factors for future osteoporosis? BJ 298:924–928.
45. Mazess RB, Barden HS. 1991 Bone density in premenopausal women: effects of age, dietary intake, physical activity, smoking and birth-control pills. Am J Clin Nutr 53:132–142.
46. Lloyd T, Buchanan JR, Ursino GR, Myers C, Woodward G, Halbert DR. 1989 Long-term oral contraceptive use does not affect trabecular bone density. Am J Obstet Gynecol 160:402–404.
47. Melton LJ III, Bryant SC, Wahner HW, et al. 1993 Influence of breastfeeding and other reproductive factors on bone mass later in life. Osteoporos Int 3:76–83.
48. Lindsay R, Tohme J, Kanders B. 1986 The effect of oral contraceptive use on vertebral bone mass in pre- and postmenopausal women. Contraception 34:333–340.
49. Goldsmith NF, Johnston JO. 1975 Bone mineral: effects of oral contraceptives, pregnancy, and lactation. J Bone Joint Surg 57:657–668.
50. Sowers M, Clark MK, Hollis B, et al. 1992 Radial bone mineral density in pre- and perimenopausal women: a prospective study of rates and risk factors of loss. J Bone Miner Res 7:647–657.
51. Wanichsetakul P, Kamudhamas A, Watanaruangkovit P, Siripakarn Y, Visutakul P. 2002 Bone mineral density at various anatomic bone sites in women receiving combined oral contraceptives and depot-medroxyprogesterone acetate for contraception. Contraception 65:407–410.
52. Paiva LC, Pinto-Neto AM, Faundes A. 1998 Bone density among long-term users of medroxyprogesterone acetate as a contraceptive. Contraception 58:351–355.
53. Gbolade B, Ellis S, Murby B, Randall S, Kirkman R. 1998 Bone density in long term users of depot medroxyprogesterone acetate. Br J Obstet Gynaecol 105:790–794.
54. Berenson AB, Rickert VIVI, Grady JJ. 2000 A prospective study of the effects of oral and injectable contraception on bone mineral density. Obstet Gynecol 95(4 suppl 1):S6.
55. Law MR, Cheng R, Hackshaw AK, Allaway S, Hale AK. 1997 Cigarette smoking, sex hormones and bone density in women. Eur J Epidemiol 13(5):553–558.
56. Prior JC, Vigna YM, Schechter MT, Burgess AE. 1990 Spinal bone loss and ovulatory disturbances. N Engl J Med 323:1221–1227.
57. Sowers M, Randolph JF Jr, Crutchfield M, et al. 1998 Urinary ovarian and gonadotropin hormone levels in premenopausal women with low bone mass. J Bone Miner Res 13:1191–1202.
58. Prior JC, Vigna YM, Barr SI,, Rexworth C, Lentle BC. 1994 Cyclic medroxyprogesterone treatment increases bone density: a controlled trial in active women with menstrual cycle disturbances. Am J Med 96:521–530.
59. Van Staa TP, Leufkens HGM, Abenhaim L, et al. 2001 Use of oral corticosteroids and risk of fractures. J Bone Miner Res 15:993–1000.
60. Khan A, Bilezikian J. 2000 Primary hyperparathyroidism: pathophysiology and impact on bone. Can Med Assoc J 63(2):184–187.
61. Potts JT Jr, Fradkin JE, Aurbach GD, et al. 1991 Proceedings of the NIH Consensus Development Conference on Diagnosis and Management of Asymptomatic Primary Hyperparathyroidism. J Bone Miner Res 6(suppl 2):S1–S165.
62. Bilezikian JP, Potts JT Jr, Fuleihan GE, et al. 2002 Summary statement from a Workshop on Asymptomatic Primary Hyperparathyroidism: a perspective for the 21st century. J Bone Miner Res 17(suppl 2):N2–N11.
63. Khan AA, Bilezikian JP, Kung AWC, et al. 2002 A double-blind randomized placebo-controlled trial of alendronate in primary hyperparathyroidism. J Bone Miner Res 17(suppl 1):S165.
64. Prior JC, Kirkland SA, Joseph N, et al. and for Group 2001. Oral Contraceptive use and bone mineral density in premenopausal women: cross-sectional, population-based data from the Canadian Multicentre Osteoporosis Study. Can Med Assoc J 165(8).