Original Article

Longitudinal Study of Bone Loss in Pre- and Perimenopausal Women: Evidence for Bone Loss in Perimenopausal Women

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Abstract. Bone loss before and around the time of menopause is not well characterized by longitudinal studies. We measured bone mineral density at various skeletal sites – total body, femoral neck, trochanter, anteroposterior (AP) and lateral spine, and forearm – with dual-energy X-ray absorptiometry in a large prospective cohort of 272 untreated pre- and perimenopausal women aged 31–59 years, at 1 year intervals for 3 years. Sex steroids and the following markers of bone remodeling were measured: serum osteocalcin (OC), procollagen I carboxyterminal extension peptide, bone alkaline phosphatase (BAP) and urinary crosslinks (CTX and NTX). Seventy-six women were classified as perimenopausal and 196 as premenopausal. Over the 3 years, perimenopausal women had no significant bone loss at any site and a small but significant increase in bone mineral density at the trochanter, total hip, AP spine and radius. Perimenopausal women significantly lost bone from cancellous and cortical sites, i.e., the femoral neck, trochanter and lumbar spine. In perimenopausal women with increased follicle stimulating hormone, the rate of bone loss at the femoral neck correlated negatively with OC and BAP. In perimenopausal women, serum estradiol levels decreased during the 3 years of follow-up and bone loss from the trochanter and the AP spine was correlated with serum estradiol after 3 years. In conclusion, among premenopausal women there is no bone loss. In contrast, there is a rapid and diffuse bone loss in perimenopausal women, related to decreased estrogen secretion. Bone markers may be useful to identify these women losing bone.

Keywords: Bone loss; DXA; Markers; Perimenopause; Premenopause

Introduction

Low bone mass is the most important determinant of osteoporotic fractures. Bone mass in elderly women is related to the level of peak bone mass reached during adolescence and early adulthood, and to the amount of bone lost subsequently [1]. Most reports have focused on postmenopausal bone loss, whereas the existence of pre- and perimenopausal bone loss is still a matter of debate. Most studies are based on a cross-sectional design, some of them finding bone loss in the premenopause or perimenopause [2–4] whereas others have not [5–7]. The few longitudinal studies show either a loss [8] or no change [9]. These conflicting results are probably related to methodologic issues of cross-sectional studies and, in longitudinal studies, to inadequate number of subjects and/or to the short duration of the study. In addition, the onset and rate of bone loss may vary in different parts of the skeleton.

It is generally accepted that estrogen deficiency is the most important factor in the genesis of postmenopausal bone loss [10]. Studies performed in premenopausal women with amenorrhea resulting from intense sport training [11] or anorexia nervosa [12] have demonstrated that estrogen deficiency in premenopausal women is associated with bone loss. However, other steroid hormones play a role in skeletal metabolism. Indeed, premenopausal women with luteal deficiency may be at high risk of bone loss before menopause [13], and

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perimenopausal women with higher testosterone concentrations may have slower rates of bone loss than those with lower concentrations [14].

Markers of bone turnover are significantly increased after the menopause and return to premenopausal levels within a few months of hormone replacement therapy [15,16]. It has been shown that in untreated postmenopausal women, serum osteocalcin is negatively correlated with the rate of bone loss, so that a higher rate of bone turnover is associated with a higher rate of bone loss [14,16], but this issue is still controversial. In a large cohort of elderly healthy women, those with increased urinary type I collagen C-telopeptide and deoxypyridinoline had a 2-fold higher risk of sustaining a hip fracture [17]. In perimenopausal women, bone loss was more rapid in those with higher osteocalcin concentrations [14].

Our 3 year prospective study was designed to address the issue of the existence and magnitude of bone loss in pre- and perimenopausal women, and the relationships of hormonal status with bone mass in these women. Markers of bone turnover were measured to identify women with a high turnover.

Subjects and Methods

Subjects

The OFELY study is a cohort of 1039 women, 31–89 years of age, stratified by age groups. Subjects were recruited between February 1992 and December 1993. All women are healthy ambulatory Caucasian volunteers, randomly selected from the affiliates of a health insurance company (Mutuelle Générale de l’Education Nationale) from the Rhône district, i.e., the region around Lyon, France. Eighteen percent of the women contacted volunteered to participate in the study. Their demographics are close to those of the general French population, as the age pyramids are quite similar. However, education and professional levels are higher in our cohort than in the general French population. There was no compensation provided for participation.

A total of 355 women from this cohort were pre- and perimenopausal at the beginning of the study. Women suffering from a disease interfering with bone metabolism or who were taking medications which might affect bone metabolism were excluded. Pregnant women were also ineligible. Thus, 35 women were excluded: 23 because of disease (Paget’s disease of bone, primary hyperparathyroidism, diabetes, liver cirrhosis, hyper- or hypothyroidism, cancer, renal failure, hypercortisolism, stroke) and 12 because of their treatment (estrogens, tamoxifen, fluoride, bisphosphonate, calcitonin, thyroidine, corticosteroids, LH-RH analogs). Eight were not taken into account because their data were not available after 3 years. Forty women (11%) were lost from follow-up during the first 2 years of the study.

We followed the pre- and perimenopausal women for 3 years. Premenopausal women were defined as women cycling regularly (25–35 days per cycle), with follicle stimulating hormone (FSH) levels <16.7 UI/l (mean + 1 SD of premenopausal women). Women were classified as perimenopausal if they had FSH concentrations ≥16.7 UI/l and/or irregular menses (cycles >35 days, with previous regular menses). Women with long cycles (and previously normal cycles) were considered as perimenopausal because there is some evidence that long cycles are symptomatic of ovarian dysfunction [18] which could predispose to future fractures [19].

When women were classified differently during the follow-up, as shown by their FSH or menses status, data available after the change were not used for the analyses. A total of 76 women were classified as premenopausal (mean age 46.8 ± 6.1 years) and 196 as premenopausal (mean age 38.6 ± 5.6 years) at baseline. Among the 76 women who were perimenopausal at the beginning of the study, 20 became postmenopausal (26%); among the 196 women who were premenopausal, 27 became perimenopausal and 7 postmenopausal. The 61 women taking oral contraceptives were not excluded because the contraceptive pill is widely used and our study was aimed at describing patterns of bone changes in the normal population. There were 56 premenopausal women and 7 perimenopausal women in that case. Menopause was defined as a 1 year cessation of menses.

Measurements

Clinical assessment was made at each yearly visit. Bone mineral density (BMD) measurements were made at 1 year intervals. BMD was measured at various skeletal sites: whole body bone mineral content (BMC) and BMD; lumbar spine including the anteroposterior (AP) measurement from L1 to L4, and the lateral measurement of the total of the vertebral bodies of L2 to L4, with results expressed in grams per square centimeter and grams per cubic centimeter; hip, including femoral neck, trochanter and total area; and radius, at the mid, distal and ultradistal areas. BMD was measured by dual-energy X-ray absorptiometry (Hologic QDR 2000, Hologic, Waltham, MA). The coefficients of variation (CV) were: for whole body, 1% for BMC and 0.5% for BMD; for the spine, 0.9% for AP view, and respectively 1.5% and 1.7% for the total and the mid area of the lateral view of the total vertebral bodies expressed in g/cm² and g/cm³; for the hip, 1.2% for the neck, 1.7% for the trochanter and 1% for the total hip region; at the radius, respectively 1.2%, 0.6% and 1.2% for the mid, distal and ultradistal regions. A control phantom scan was performed every day, and the system calibrated once a week.

Blood and urine were drawn during the follicular phase (days 5–10 of the menstrual cycle) for pre- and perimenopausal women, on morning samples. Measurements were made for: serum intact osteocalcin (OC; ELSA-OSTEO, Cis bio international, Gir sur Yvette, France), serum bone alkaline phosphatase (BAP; Tandem-R Ostase, Hybritech, San Diego, CA), serum