Original Article

Longitudinal Evaluation of Perimenopausal Femoral Bone Loss: Effects of a Low-Dose Oral Contraceptive Preparation on Bone Mineral Density and Metabolism

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Abstract. To characterize the pattern of biochemical markers of bone metabolism and femoral bone mineral density in eumenorrheic and oligomenorrheic perimenopausal women, and assess the effects of a low-dose oral contraceptive (OC) on bone metabolism and femoral bone density, bone biochemical markers and femoral bone density (measured at the neck, Ward’s triangle and trochanter regions) were evaluated in a longitudinal 2-year follow-up study. The study was conducted in healthy, normally menstruating perimenopausal women ($n = 18$), perimenopausal oligomenorrheic women ($n = 18$), and perimenopausal oligomenorrheic women treated with an OC containing 20 μg ethinylestradiol plus 0.15 mg desogestrel ($n = 19$). The results were analyzed by factorial or repeated measures analysis of variance, as appropriate. During the observation period, in normally menstruating women there were no changes in the menstrual cycle, plasma FSH and estradiol levels, biochemical markers of bone turnover or femoral bone density. In oligomenorrheic untreated women an increase in cycle length with a concomitant decrease in plasma estradiol and an increase in plasma FSH levels were found ($p < 0.05$). In this group a significant increase in urinary excretion of hydroxyproline and in plasma osteocalcin levels with a concomitant significant decrease in femoral bone density ($p < 0.05$) occurred. In OC-treated women, osteocalcin plasma levels and urinary excretion of hydroxyproline significantly ($p < 0.05$) decreased, leading to a significant ($p < 0.05$) increase in femoral bone density. It is concluded that perimenopausal OC administration can avoid the increase in bone turnover and the decrease in femoral bone density due to the perimenopausal impairment of ovarian function.

Keywords: HRT; Menopause; Oral contraceptive; Osteoporosis

Introduction

Osteoporosis is a major health care problem leading to a high incidence of spine, radial and, in particular, hip fractures that are causes of morbidity and mortality in an aging population. Bone mineral density is an important determinant of fracture risk. It is now well recognized that the chronic hypoestrogenism in the first postmenopausal years can cause a critical decrease in bone density [1–4]. Hormone replacement therapy prevents the reduction in bone density related to the postmenopausal hypoestrogenism [5,6]. However, in premenopausal oligomenorrheic women, the progressive ovarian failure is associated with a decrease in estradiol production. Previous studies have shown that during the menopausal transition a progressive impairment in bone metabolism and a significant bone loss can occur, particularly in women suffering from hypoestrogenic oligomenorrhea [7–11]. We have recently reported that low-dose oral contraceptive (OC) administration is able to prevent the perimenopausal decrease in radial [10] and vertebral [11] bone density. The aim of the present study was to determine the possible effects of perimenopausal hypoestrogenism on femoral bone density and the effects of OC administration on femoral bone loss.

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Materials and Methods

In the present study we enrolled women, aged 40–49 years, attending the Menopause Clinic of our Department. Bone density was measured as a part of the screening program for premenopausal women. Twenty women reported regular menstrual cycles, while 40 women experienced oligomenorrhea in the 3–6 months before they entered the study. Oligomenorrhea was defined as episodes of menstrual bleeding occurring at intervals of more than 35 and less than 90 days. Regardless of their menstrual pattern and basal bone metabolism and density, these patients were randomly assigned to two treatment groups, by using a list of random numbers: 20 subjects received oral calcium supplementation (500 mg/day) with the evening meal, while 20 women received monophasic OC containing 20 μg of ethinylestradiol plus desogestrel 0.15 mg. The three groups (eumenorrheic, oligomenorrheic, and oligomenorrheic OC-treated subjects) were matched for age, weight, parity, diet and lifestyle habits. All women were free from diseases known to influence calcium metabolism, and had a basal femoral bone density in the normal range for our reference population aged 40–50 years. None had a history of glucocorticoid treatment. Inclusion criteria included normal thyroid, adrenal and renal function, as assessed by clinical, biochemical and hormonal evaluations. None had received hormones or drugs known to interfere with bone metabolism in the 6 months before observation. No other drugs able to affect calcium metabolism were allowed during the study.

At the end of the study period we evaluated the data of 18 eumenorrheic women, 18 oligomenorrheic women and 19 oligomenorrheic women treated with OC. The remaining women dropped out of the study for personal reasons or because they needed other pharmacological or surgical interventions.

Methods

The bone mineral density (BMD; g/cm²) of the femoral neck, Ward’s triangle and trochanter were measured in the supine position by dual-energy X-ray absorptiometry (DXA) using a Lunar DPX machine (Lunar, Madison, WI). The foot of the leg to be scanned was strapped into a brace to rotate the entire leg until the femoral shaft was parallel to the center line of the body. The precision of the instrument used in this study was tested. In 15 healthy premenopausal women BMD was measured six times with repositioning, and the coefficients of variation (CV) were 1.8%, 3.9% and 1.6% for the femoral neck, Ward’s triangle and trochanter measurements, respectively. The long-term stability of the instrument was assessed as previously reported [4], by measuring a phantom every other day for a 2-year period, resulting in a CV of 0.5%.

Fasting urinary excretion of hydroxyproline was measured by a spectrophotometric method [12,13]. The results are reported as the urinary hydroxyproline/creatinine ratio, expressed in milligrams per liter, multiplied by 100 (OHP/Cr). The intra- and inter-assay CV of this analysis were 3.6% and 4.5%, respectively. Plasma osteocalcin (BGP) was measured in duplicate by radioimmunoassay, using a commercially available kit (Osteocalcin Kit, Technogenetics, Trezzano sul Naviglio, Italy). The sensitivity is 0.59 ng/ml, and intra- and inter-assay CV are 3.5% and 5.5%, respectively. Plasma estradiol and FSH levels were measured as previously described [14]. In all women the above biochemical and biophysical determinations were performed at the start of the study and after 12 and 24 months of observation.

All the results are reported as the mean ± SE of absolute values or percent variation over the basal values. Baseline values were compared by one-way analysis of variance. Two-way analysis of variance for repeated measures and factorial analysis of variance were used to test the differences within and between the groups, respectively. The post-hoc comparison was made using the Scheffé F-test.

Results

There were no significant differences (by one-way analysis of variance) in age, body mass index (Table 1), hormone values (Table 2), bone metabolism markers and femoral bone density in the three groups before the study (Figs. 1, 2). During the 24-month observation period, no modification in the menstrual pattern or in plasma hormone levels was observed in the eumenorrheic women (Table 2). Conversely, in the oligomenorrheic subjects an increase in cycle length was evident, with a significant (p < 0.05) increase in circulating plasma FSH that paralleled a significant (p < 0.05) decrease in plasma estradiol levels (Table 2). Hormonal evaluation was not performed during OC administration.

In the eumenorrheic women, BGP did not show any significant modification from basal values of 7.5 ± 0.1 to 7.4 ± 0.2 (–1.6 ± 3.0%) and 7.6 ± 0.2 ng/ml (2.4 ± 3.4%) after 12 and 24 months, respectively (Fig. 1). OHP/Cr was 3.0 ± 0.1, 2.9 ± 0.2 (–1.4 ± 2.4%) and 2.9 ± 0.1 (–0.518 ± 2.62%) at the beginning of the study and after 12 and 24 months, respectively. After 24 months of observation, in eumenorrheic women OHP/Cr was significantly (p < 0.01) different from the value in the oligomenorrheic group (Fig. 1). Femoral neck BMD did not show any modification from the basal value of 0.879 ± 0.023 to 0.878 ± 0.024 (–0.1 ± 1.0%) and 0.868 ± 0.024 to 0.870 ± 0.022 (–1.0 ± 1.0%).

Table 1. Basal characteristics of eumenorrheic (n = 18), oligomenorrheic (n = 18) and oligomenorrheic, oral contraceptive (OC)-treated (n = 19) perimenopausal women

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Body mass index (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eumenorrheic</td>
<td>46.0 ± 0.7</td>
<td>24.5 ± 0.6</td>
</tr>
<tr>
<td>Oligomenorrheic</td>
<td>46.0 ± 0.6</td>
<td>24.5 ± 0.5</td>
</tr>
<tr>
<td>Oligomenorrheic + OC</td>
<td>45.7 ± 0.7</td>
<td>23.6 ± 0.7</td>
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Values are the mean ± SE.