

Factors associated with bone density in young women with karyotypically normal spontaneous premature ovarian failure

Paula Leite-Silva · Aloísio Bedone ·
Aarão Mendes Pinto-Neto · José Vilton Costa ·
Lúcia Costa-Paiva

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Abstract

Objective To evaluate bone density and associated factors in women with premature ovarian failure (POF) compared to age-matched women with normal ovarian function.

Methods A cross-sectional study of 50 patients with POF undergoing bone mineral densitometry was conducted, compared to 50 women paired by age who menstruated regularly.

Results In women with POF, the mean bone mineral density measured was 1.22 g/cm² at the spine and 0.92 g/cm² at the femur, values which were significantly lower than in the control group ($P < 0.0001$). Factors directly associated with bone density of the lumbar spine were age and with bone density of the femur were BMI and reproductive age.

Conclusion Young women with POF have a decrease in lumbar spine and femoral bone density. Age, reproductive age and BMI were the factors associated with BMD. These women need early investigation and treatment to prevent bone loss and minimize fracture risk in the future.

Keywords Premature ovarian failure ·
Estrogen deficiency · Bone mineral density ·
Bone mass · Osteoporosis

Introduction

Adequate hormone secretion during puberty and early adult life has an important action on bone metabolism and is fundamental for the acquisition of bone mass [1, 2]. Peak bone mass in healthy subjects is the result of an interaction between genetic factors and hormonal effects, influenced by ethnic and nutritional aspects, exposure to risk factors and mechanical forces such as physical activity [2–4]. There is no consensus about the age at which peak bone mass is achieved and it may occur between the end of the second decade of life until around 30 years of age [2, 5, 6].

Different clinical conditions that accompany changes in sex hormones may compromise the gain in bone mass in reproductive-aged women [7–9]. Sex steroids also have an important role in the maintenance of bone mass. With cessation of ovarian function, bone loss occurs as in physiological menopause [10, 11] and surgical or medical castration [12]. An association between estrogen deficiency in the postmenopause period and osteoporosis has been clearly established [13, 14].

Young women may present with premature ovarian failure (POF) which is characterized by loss of ovarian function before age 40 leading to amenorrhea with serum FSH levels above 40 UI/l [15]. It affects about 1% of women [16], corresponding to 4–18% of cases of secondary amenorrhea [17, 18]. Depending on the age at POF, it may result in osteoporosis due to less acquisition or loss of bone mass. A study comparing subgroups of women with physiological menopause to women with POF showed a significant increase in the risk of osteoporotic fractures in the early menopause [19]. Not all aspects pertaining to POF and bone mass are known. A potential cause may be due to not only low estrogen levels but also a direct effect of FSH levels on bone metabolism [9]. Furthermore, the strategies

P. Leite-Silva · A. Bedone · A. M. Pinto-Neto · J. V. Costa ·
L. Costa-Paiva (✉)
Departament of Obstetrics and Gynaecology,
School of Medicine, State University of Campinas,
Rua Alexander Fleming, 101, Cidade Universitária Zeferino Vaz,
Campinas, São Paulo CEP: 13083-881, Brazil
e-mail: paivaepaiva@uol.com.br

employed for maintenance of bone mass in women with POF are the same as those used for older women, including hormone therapy and calcium supplementation [13]. These strategies may not be sufficient for younger women with early loss of ovarian function [20, 21].

Although ovarian failure is a well-known condition, various aspects of bone metabolism that relate to this process are still not fully elucidated. The aim of this study was to evaluate bone mineral density of the lumbar spine and femur and factors associated in women with POF, which were compared to age-matched women with normal ovarian function.

Materials and methods

A cross-sectional study of 50 women diagnosed with POF was conducted. Patient follow-up was in the endocrinologic gynecology outpatient facility at the Women's Integral Healthcare Center in the Universidade Estadual de Campinas.

Criteria for the diagnosis of premature ovarian failure were below 40 years of age; two serum FSH measurements with values higher than 40 UI/l and karyotype 46, XX. Women with iatrogenic causes of ovarian failure and chromosome abnormalities were excluded from the study.

All patients were investigated by clinical history, physical examination, high-resolution karyotype and measurement of body mass index, calculated by dividing the weight in kilograms by the height in square meters.

The evaluation of bone mass was performed by measuring bone mineral density of the lumbar spine and femur by means of dual X-ray absorptiometry (DXA) using the Lunar DPX (Madison, WI, USA) scanner. The coefficient of variation was 0.71% for the lumbar spine and 2% for the femoral neck. The same equipment was used in all women to obtain comparable results. Values were expressed in grams per square centimeter (g/cm^2) [22].

Fifty young women with regular menstrual cycles served as a comparison group and were paired by age (± 1 year). These women were selected from a family planning outpatient facility. Only women who did not use any hormone methods and had no chronic disease (hyperthyroidism, hyperparathyroidism and malabsorption syndrome) or did not use any other medications (corticosteroids, thyroid hormones and anticonvulsants) that could affect bone metabolism were included in the study.

Statistical analysis

Data analysis was performed using paired Student's *t* test for comparison of the means. To evaluate the factors associated with bone mineral density, a multiple linear

regression analysis with backward variable selection was used. For these statistical procedures, the statistical analysis system (SAS) program version 9.1.3 was used. A statistical significance level of $P < 0.05$ was chosen.

Results

Table 1 shows the clinical characteristics of women with POF. In this study patient age ranged from 20–40 years in both groups. Mean age at menopause was 26 years, and 70% were HT users with a mean duration of 28 months of use. Women with POF and controls were paired by age. The mean age of these women was 29.9 years in both groups. The BMI of the patients with POF varies from 17 to 23.4 kg/m^2 and the control groups from 18.3 to 37.3 kg/m^2 . There were also no significant differences regarding age at menarche and BMI between groups. Regarding bone mineral density, it was observed that women with POF had a significantly lower mean BMD than in the both controls, lumbar spine and femur.

Table 2 shows the factors correlated with BMD of the lumbar spine and femur. In patients with POF, chronologic age, age at menopause and reproductive age (age at menopause minus age at menarche) were factors significantly and directly correlated with BMD of the lumbar spine. For the femoral neck, the factors directly correlated were age, age at which premature ovarian failure occurred, reproductive age and BMI. There was no correlation with age at menarche, time of estrogen deficiency and length of HT use. For women in the control group, there was a statistically significant and direct correlation only with BMI both in the spine and in the femur.

Taken together, using multiple regression analysis, the only factor associated with BMD of the lumbar spine was age. For the femur, the factors directly associated were BMI and reproductive age (Table 3).

Discussion

This study evaluated bone mineral density in women with POF and the results showed that these women have low BMD both of the lumbar spine and femur. The lumbar spine was the most affected site.

Two important factors that influence bone density in women with premature ovarian failure are hypoestrogenism and age. To separate the effect of both these factors, groups paired by age were compared. Many studies have shown that women with early natural or surgical menopause have a lower BMD when compared to controls paired by age [23–26]. However, the majority of these studies evaluated bone mass in women with POF after age 50. One advantage

Table 1 Clinical characteristics of women with premature ovarian failure and controls

Characteristics	POF		Controls		<i>P</i> value*
	Mean	SD	Mean	SD	
Age of POF (years)	26	7.2	–	–	–
Years since POF	4	3.5	–	–	–
Years of reproductive life	12	7.4	–	–	–
Length of estrogen deficiency (months)	28	37.3	–	–	–
Age (years)	29.2	5.9	29.9	6.3	0.855
Age at menarche (years)	13.4	1.8	14.5	1.5	0.094
Body Mass Index (kg/m ²)	23.9	3.7	25	4.7	0.114
Lumbar spine BMD (g/cm ²)	1.22	0.13	1.07	0.13	<0.001
Femoral neck BMD (g/cm ²)	0.92	0.11	1.05	0.11	<0.001
Trochanter BMD (g/cm ²)	0.85	0.11	0.72	0.10	<0.001
Ward's triangle BMD (g/cm ²)	0.99	0.14	0.84	0.13	<0.001

Paired Student's *t* test**Table 2** Correlation between clinical characteristics of women with POF and controls and bone mineral density (g/cm²)

Characteristics	Lumbar spine		Femoral neck	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
POF				
Age ^a	0.400	(0.004)	0.390	(0.0051)
Age at POF ^b	0.323	(0.0223)	0.325	(0.0212)
Age at menarche ^a	−0.079	(0.5859)	−0.231	(0.1069)
BMI ^b	0.111	(0.4427)	0.472	(0.0005)
Duration of estrogen deficiency ^a	−0.054	(0.7095)	−0.063	(0.6632)
Reproductive age ^b	0.347	(0.0137)	0.381	(0.0063)
Duration of HT use ^a (months)	−0.025	(0.8632)	−0.119	(0.411)
Controls				
Age ^a	−0.050	(0.7295)	−0.008	(0.9533)
Age at menarche ^a	0.057	(0.6944)	0.183	(0.2031)
BMI ^b	0.291	(0.0402)	0.299	(0.0349)

Linear correlation coefficient (*r*) and between parenthesis *P* value^a Spearman's coefficient^b Pearson's coefficient**Table 3** Factors associated with bone mineral density (g/cm²) of women with POF: multiple linear regression

Variable	Coefficient	ER	<i>P</i>	<i>R</i> ²
Lumbar spine				
Intercept	0.810	0.092	<0.0001	0.15
Age	0.009	0.003	0.0052	
Femoral				
Intercept	0.554	0.084	<0.0001	0.33
BMI	0.013	0.003	0.0006	
Reproductive age	0.005	0.002	0.0072	

Stepwise

of the present study was a better assessment of the effect of POF on bone mass, since measurement of bone mass and pairing of subjects by age were performed in younger women soon after diagnosis.

In the literature, the association between hypoestrogenism and decreased BMD both in the lumbar spine and femur has been well-established [11, 13]. Similar results were observed not only in women with POF but also in young women with other causes of secondary amenorrhea [27, 28] and in cases of primary amenorrhea due to gonadal dysgenesis [8]. In a study with women in which amenorrhea resulted from diverse causes, the prevalence of low bone mass was 68% [29].

Studies have shown that estrogen deficiency in young women has an important negative impact on bone mass, since it occurs during a phase of intense gain in bone mass [9, 30]. Around 90% of peak bone mass is acquired until age 18, although increases of 5–12% have been observed in the third decade of life [5].

This reduction in bone mass is a predictive factor for fracture risk, since a decrease of 1 SD for age may increase fracture risk by 2.6 times [31]. Studies that compared women experiencing menopause at a normal age to women

who had premature menopause reported relative risks for fracture of approximately 1.5 in women with premature menopause [19].

In this study, the lumbar spine was the most affected site. The literature has demonstrated that trabecular bone is present in the vertebrae and is metabolically more active in the flat bones. That is the reason why it is more susceptible to the effects of estrogen deficiency. Amenorrhea must last 5–6 years for estrogen deficiency to manifest itself in the cortical bone [32]. The annual rate of spinal bone loss measured by DXA scan is around 2.5% in the first 2 years after menopause; 1.8% between 2 and 4 years and 1–1.3% in the subsequent years. The rate of bone loss in the hip is about half of that observed in the vertebrae [33, 34].

In the current study, age, age at POF and reproductive age were the factors associated with BMD of the lumbar spine. Factors related to estrogen deficiency, such as length of amenorrhea and reproductive age are reported as causes that determine bone loss. However, age at which ovarian failure occurs, especially when amenorrhea takes place before peak bone mass is achieved, has been indicated as a more important factor than the duration of estrogen deficiency [8, 9]. Furthermore, in this study the mean age of women with POF was younger than 35, which might explain why age was a better predictor of bone mass than length of estrogen deficiency. Data of the present study may suggest that women with POF had not attained peak BMD when ovarian failure occurred, therefore a lower bone mass was observed in these patients. In contrast, in the control group with normal ovarian function, there was little variation in BMD in the 20–40 years age group, which may have resulted in the lack of correlation observed. In this study, we also observed that BMI was only associated with BMD of the femur confirming the influence of body weight on bone mass. A possible reason for the influence of BMI on femoral bone density could be an increased androgen conversion into estrogen or the mechanical effects of body weight or a combination of both factors [35, 36].

The lack of correlation between HT use and BMD was an unexpected result. This may be explained by the fact that the mean duration of estrogen deficiency was longer (4 years) than the length of HT use (2 years) in the present case study. Furthermore, since this was not a clinical trial, in which the treatment employed is strictly controlled, problems related to adherence to therapy may interfere in BMD results. However, this would still reflect the reality commonly observed in clinical practice among HT users. HT is effective at preventing the loss of bone mass and decrease the risk of fractures in postmenopausal women older than 50. This has been confirmed in recent clinical trials that show a 34% reduction in vertebral and non-vertebral fractures in users of estrogens combined with

progestins [37] or alone [38]. Nevertheless, the strategies used for the prevention and treatment of osteoporosis in older menopausal women may not be adequate for young women with POF. In agreement with our results, another study also demonstrated that a dose of 0.625 mg of conjugated estrogens was not capable of preventing vertebral bone loss in premenopausal women who used GnRh analogs [21]. It is currently recommended that HT should be used in the lowest dose for the least time possible to reduce the risks associated with these drugs, especially breast cancer. However, women with POF need to use HT for many years. There is still no consensus about the time period required for hormone use, the effective dose and types of exogenous hormones used that would be most similar to normal ovarian function [20].

It is worth mentioning that a limitation of the present study was the type of study conducted. A cross-sectional study is not the most adequate type to evaluate the relationship of causality. Despite this limitation, the presence of a control group that was paired by age and had homogeneous clinical characteristics made a comparison between results more effective.

The results in this study suggest that women with POF need early intervention and effective strategies to minimize the effects of estrogen deficiency on bone mass. Long-term prospective studies with different doses and HT regimens associated with calcium supplementation and vitamin D, improvement in adherence to treatment in addition to physical activity are necessary to reduce the risk of osteoporosis in this group of women.

Conflict of interest statement None declared.

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