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What is really responsible for bone loss in spontaneous premature ovarian failure? A new enigma

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Abstract

Objective. To determine if there is a relation between the follicle-stimulating hormone (FSH) and oestradiol levels with values found in bone mineral density, at lumbar spinal and femoral neck levels, in patients with spontaneous premature ovarian failure (POF) as at the time of diagnosis.

Method. Cross-sectional study. Eighty-five patients were selected with a diagnosis of POF.

Inclusion criteria. Forty women with bone mineral density (BMD) in any of the regions, that is, lumbar spine column or femoral neck. Forty-two age-matched healthy women were included as controls.

Results. The average FSH value found was 80.11 mUI/ml, while the oestradiol average value was 37.2 pg/ml. The FSH values were correlated with the BMD values at the lumbar spinal column ($p < 0.002$) and the femoral neck ($p < 0.002$). The oestradiol values did not bear any relation with the BMD values in L2-L4 ($p = 0.420$) nor with the femoral neck ($p = 0.868$).

Conclusions. High FSH concentrations, but not oestradiol, are positively associated with bone mass loss in both skeletal regions, in patients with spontaneous POF.

Keywords: *Premature ovarian failure, osteoporosis, stimulating hormone follicle, oestradiol, hormonal therapy, SWAN*

Introduction

The premature ovarian failure (POF) is a condition that affects 1–3% of the women under 40 years old, causing amenorrhoea, hypoestrogenaemia, hypoandrogenism and high gonadotropins [1]. Some patients may develop acute amenorrhoea or experience a prolonged oligomenorrhoea prodrome or dysfunctional uterine bleeding.

POF is one of the highest risk factors associated with the development of osteoporosis [2] and in previous studies it has been observed that patients who develop this condition due to its diverse causes, present bone mass reduction [3–5].

There is evidence that women with POF present a bone mineral density (BMD) of 1.0 T-score below the average for their chronological age [6].

BMD reduction in women with non-iatrogenic POF starts with a decline in ovarian function previous to the installation of amenorrhoea [7]. Almost 50% of the affected women have a significant BMD reduction within 18 months as from the diagnosis and two-thirds have a BMD level exposing them to a high risk of hip fracture [8].

In hypergonadotropic amenorrhoea only the follicle-stimulating hormone (FSH) has a negative correlation over the BMD ($p = 0.05$), and for this reason bone loss may be caused by a direct effect of FSH on bone metabolism [9].

Data of the SWAN Study (Study of Women's Health across the Nation) showed that high FSH levels are more predictive of low bone mass. Women with oestrogen deficiency and with FSH levels exceeding 40 UI/l have a significantly higher bone mass loss than with FSH values below 40 UI/l. Likewise, bone mass increase after oestrogen replacement therapy correlates with a decrease in FSH serum levels [10].

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FSH is, but not oestradiol, testosterone and SHBG are not perceptibly associated with a decrease in BMD [11]. High FSH levels, although not of any other hormones, were positively associated with a higher bone turnover [12].

High FSH concentrations are associated with low BMD at spinal and hip level. The subsequent FSH levels are predictive of bone loss for both regions in the following years. Oestradiol levels and their variation in the follow-up years are poor predictors of changes in BMD [13].

In a recent document [14] it is shown that FSH acts on osteoclasts activating bone resorption. *Ex-vivo* studies indicated that osteoclastogenesis and bone resorption diminished notably in the absence of an FSH receptor. Osteoclasts express FSHR on the surface and are directly stimulated by FSH, through MEK Gi2a/Erk, NfkB and Akt, a well-known activation pattern. Importantly, and in contrast with oestrogen, no receptors for FSH were found in osteoblasts.

So far we have summarised the latest investigations as regards the FSH role on bone metabolism, bearing in mind the findings of the SWAN study that addresses transition to physiological menopause. No references/papers have been found on studies on the effects of this variable in patients with POF and that is why this is the object of our study/work.

The objective of this article is to determine if there is a relation between the FSH and oestradiol levels with values found in BMD, at lumbar spinal and femoral neck levels, in patients with spontaneous POF as at the time of diagnosis.

Methods

Cross-sectional study

Eighty-five patients were selected with a diagnosis of POF.

Inclusion criteria

Forty women with BMD in regions, lumbar spine column and femoral neck, with spontaneous POF.

For POF diagnosis the following criteria was used: >3 months amenorrhoea and the presence of two FSH serum values >40 mUI/ml, obtained with a difference of 1 month, in women under 40 years old.

Women with iatrogenic cause of POF or with chromosomal abnormalities were excluded from the trial.

Forty-two age-matched healthy women were included as controls.

BMD of the femoral neck and spine were measured with dual energy X-ray absorptiometry (DEXA), which was carried out with the same LUNAR brand equipment.

FSH concentrations were measured with quimioluminiscence. Oestradiol concentrations were obtained with radioimmunoassay. All blood samples were obtained in the morning between 08.00 h and 09.00 h after an overnight fasting during the early follicular phase (2nd to 4th day) of progesterone-induced menstrual cycle.

POF group

Twelve women had received some type of hormonal treatment with an average usage time of 4.75 years (1–14 years).

Forty patients had records of BMD of the lumbar spine column; 26 patients had records of BMD of the femoral neck records.

Variables analysed

Patients' age, presence of previous hormonal treatment, FSH values, oestradiol values, BMD values at lumbar spine column, BMD value at femoral neck and relation between these variables.

Data management and analysis of same were carried out through the SPSS Program (Statistical Program for Social Sciences). *t*-student test was applied for media distribution; regression analysis applying (r^2) regression coefficient and β error for relation between the variables. $p < 0.05$ was considered significant.

Results

POF group

Patient's average age was 33.5 years (23–39 years). The age in the beginning of the symptoms was of 28.8 years (age's range between 11 and 37 years old). The average time of evolution of the symptoms was of 4.7 years old.

The period of secondary amenorrhoea until the accomplishment of the BMD was of 2 years. Two months passed between the POF diagnosis (clinic and laboratory) and the accomplishment of this study.

Of the 40 patients, 60% had as initial menstrual cycle the oligomenorrhoea, whereas 40% had secondary amenorrhoea. According to the age of the patients at the beginning of the alterations of the cycle, 6 patients were less than 20 years old, 17 patients were between 20 and 30 years old and the remaining 17 patients were more than 30 years old.

The average treatment time with TH was 1.2 years. The time of treatment with oral contraceptives was 3.8 years. The average age of the patients with treatment was 28.7 years, whereas those who did not receive previous treatment were 35.5 years.

According to the age of beginning of the symptoms, the values of BMD found at the spine level and in femoral neck were worse if the affectation was to precocious ages, agreeing with not reaching the pick of bone mass. The values found concerning spine went inferiors to the found ones in femoral neck.

The average value found for FSH was 80.11 mUI/ml (POF group) vs. 10.5 mUI/ml (control group), $p < 0.0001$.

The average value of oestradiol was 37.2 pg/ml (POF group) versus 45.6 pg/ml (control group), $p = 0.32$.

The average value of BMD at lumbar spine column (L2-L4) was -1.11 SD (POF group) versus 2.4 SD (control group), $p < 0.0001$.

The average value of BMD at femoral neck level was -1.14 SD carried out on 26 patients of POF versus 2.6 SD (control group), $p < 0.0001$.

POF group

57.5% of the patients at lumbar spine column level and 42.3% of the patients at femoral neck level were within osteopenia range.

Taking into account that 12 patients had received previous hormonal treatment; the same determinations were carried out but excluding those 12 patients.

The average FSH value found was 94.7 mUI/ml (IC 95%: 40.6–200 mUI/ml), carried out on 28 of the trial patients.

The average oestradiol value was 40.5 pg/ml (IC 95%: 9–127 pg/ml), carried out on 28 of the trial patients.

For BMD values, at L2-L4 level (28 patients) an average of -1.24 SD (IC 95%: -3.5 to 1.93 SD) was found; and at the femoral neck level (17 patients) an average of -1.34 SD (IC 95%: -2.4 to -0.1 SD) was found (Table I).

The behaviour that the symptoms had at beginning and their effect on the values of BMD in both skeletal regions was analysed. It was taken into account the time of the oligomenorrhoea (with only 3 months of secondary amenorrhoea), and, in a different group, patients who only had as initial symptom the amenorrhoea.

Table I. Hormonal and BMD values in patients with and without Tt.

Determinations	Total average values	Average values in patients without Tt.
FSH (mUI/ml)	80.11*	94.7*
Oestradiol (pg/ml)	37.2	40.5
BMD L2-L4 (SD)	-1.11*	-1.24*
BMD femoral neck (SD)	-1.14*	-1.34*

*p-value < 0.01.

Secondary amenorrhoea

The greater the time of evolution of the symptoms the worse the values found ($R^2 = 0.72$ at L2-L4 level vs. $R^2 = 0.52$ at femoral neck level).

Oligomenorrhoea

The greater the time of evolution of the symptoms the worse the values found, but in a less significant way that the effect of the secondary amenorrhoea on both regions ($R^2 = 0.14$ at femoral neck level vs. $R^2 = 0.12$ at L2-L4 level).

Considering the time of evolution of the symptoms and the values of FSH found, we realised that the passed time of secondary amenorrhoea is not related to the values of FSH, that is to say, always are high FSH values. The average value of FSH found in this group was 97.4 mUI/ml. The same relationship exists between the time of oligomenorrhoea and the values of FSH, being its average value 73.2 mUI/ml.

Relation between the hormonal concentrations found and BMD values:

FSH-BMD lumbar spine column

A correlation exists between the FSH levels and the BMD values at the lumbar spine column, for all the patients: ($r^2 = 0.226$; $\beta = -0.475$; $p < 0.002$). The same relation is observed in patients who have not received previous hormonal treatment ($r^2 = 0.278$; $\beta = -0.552$; $p < 0.002$) (Figure 1).

Oestradiol-BMD lumbar spine column

There is not correlation between the oestradiol levels and the BMD values at L2-L4 level, for all the patients ($r^2 = 0.17$; $\beta = 0.131$; $p = 0.420$). The same relation is observed in patients who did not receive previous hormonal treatment ($r^2 = 0.047$; $\beta = 0.217$; $p = 0.258$; Figure 2).

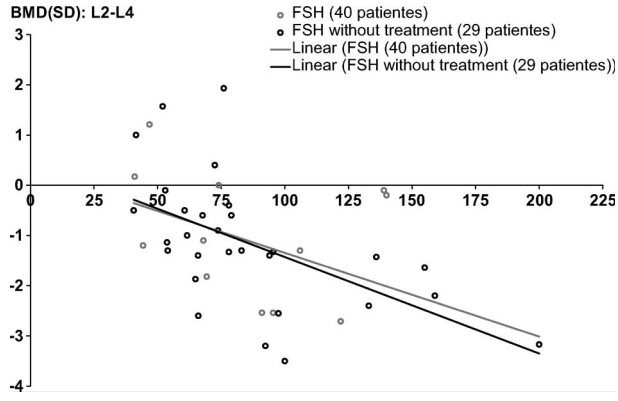

Figure 1. Relation between FSH and BMD lumbar spine.

FSH-BMD femoral neck

A correlation is observed between the FSH values and the BMD value found at this level for all of the patients: ($r^2 = 0.333$; $\beta = -0.577$; $p < 0.002$).

Within the group of patients who did not receive treatment this relation increases with the increment in the FSH figures ($r^2 = 0.673$; $\beta = -0.820$; $p < 0.0001$; Figure 3).

Oestradiol-BMD femoral neck

There is no relation between the oestradiol values and those for BMD at this level, for all the patients ($r^2 = 0.001$; $\beta = 0.034$; $p = 0.868$). The same happens for the patients who did not receive previous hormonal treatment ($r^2 = 0.018$; $\beta = 0.133$; $p = 0.599$; Figure 4).

Discussion

In this work, the patients showed an average time of evolution of the symptoms of 5.2 years. If we take into account only the period between the clinic of secondary amenorrhoea and the moment the patients had the BMD done, the time was 2 years, whereas the time between the diagnosis of POF (clinical + laboratory) and the accomplishment of this study was 2 months. So, a substantial loss of bony mass occurs quickly in these women. Possibly, the explanation can be explained by the effect that has the ovarian declination before the development of the POF. FSH values was higher in women with POF compared with controls, it was statistically significant.

During this work/trial it was found that 42.3% of the women with spontaneous POF had a BMD lower than 1.00 SD at femoral neck level, while at spinal column level the percentage was 57.5%; therefore, these patients have an increased risk to develop a fracture.

The BMD average for L2-L4 was −1.11 SD, while it was −1.14 SD for the femur, statistically different compared with controls. That is to say that both sites are equally affected. It must be borne in mind that these patients have years of oligomenorrhoea and those alterations in laboratory values commence at this period. Either the patients who had as beginning symptom the oligomenorrhoea or secondary amenorrhoea had high values of FSH (>70 UI/ml).

We found high FSH values with normal oestradiol levels in our patient population and if we bear in mind that, during the transition stage to this pathology, the same hormonal environment is observed, we can state that these patients have been exposed to high FSH values for years, a situation that would cause bone loss and which is reflected in the BMD values found.

If we take the values of those patients who did not receive any type of previous hormonal treatment, the values for L2-L4 are −1.24 SD and for the femoral neck is −1.34 SD. That is to say that the presence of the treatment improves the values in both skeletal regions, the treatment average being 4.75 years.

In the present trial, we find that the FSH values correlate with BMD both at L2-L4 and at femoral level thus, at increasing FSH values, lower BMD values are found. This applies to both groups of

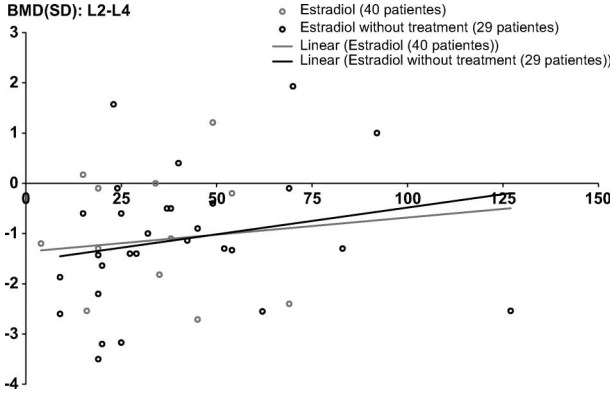

Figure 2. Relation between oestradiol and BMD lumbar spine.

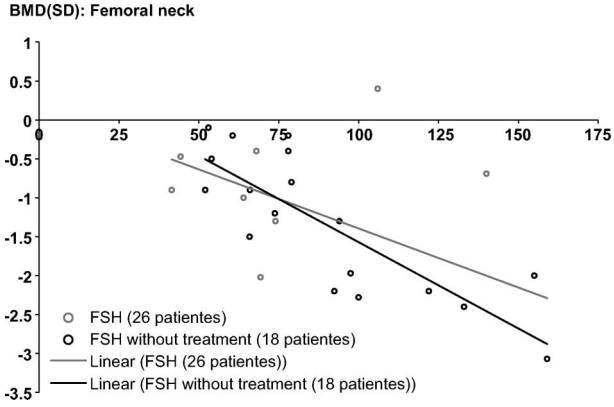

Figure 3. Relation between FSH and BMD femoral neck.

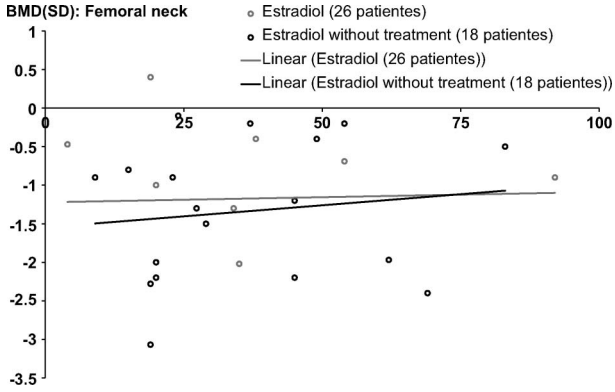

Figure 4. Relation between oestradiol and BMD femoral neck.

patients, total and without previous treatment. No correlation was found between oestradiol levels and BMD values of both skeletal regions, nor was there any variation because of the absence of treatment.

If FSH does, in fact, exert an independent-oestrogen action upon osteoclasts to promote bone resorption in human beings [14], this would lead to a new extension of the hypothalamus-hypofisiary-gonadal axis to include the skeleton.

These results should stimulate additional research of the multiple levels of skeletal regulation by the pituitary and gonad glands that simply change the focus from the oestrogen deficiency as a cause of bone loss [15].

Conclusions

In patients with spontaneous POF, there are average BMD values ranking from osteopenia at the time of the diagnosis, both at lumbar spine column as well as at the femoral neck.

High FSH concentrations, but not oestradiol concentrations, are positively associated with bone mass loss both at lumbar spine column and femoral neck level.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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