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Original

Alteration of bone quality and prevalence of fragility fractures in patients with breast cancer treated with aromatase inhibitors. A case-control study

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Abstract

Purpose: to study the possible association between long-term treatment with aromatase inhibitors and deteriorated bone quantity and quality in postmenopausal women with breast cancer, leading to a higher prevalence of osteoporosis and fragility fractures.

Methods: case and control study. One hundred and four women with breast cancer who had been taking AIs for a median of 3 years were the cases and 104 women of similar age, height and weight made up the control group. We measured biochemical parameters of bone remodeling, vitamin D (25HCC) and PTH. Bone mineral density was determined by bone densitometry in the lumbar spine and in the proximal femur, and TBS in the lumbar spine. Finally, QUS parameters of the dominant foot were estimated.

Results: 46.3 % of patients had osteoporosis compared to 16.1 % of controls 38.4 % of these women had suffered at least one fragility fracture, compared to 20.1 % of controls. Women with AI had lower values of bone mass as well as QUS and TBS. Only 9.6 % of women receiving AI had optimal 25HCC levels (greater than 30 ng/mL) compared to 20.2 % of controls. In the logistic regression analysis, the variables associated with the presence of fragility fractures were the time taking AI, vitamin D levels, TBS and beta-crosslaps (CTX). TBS correlated with QUI ($r = 0.754$. $p < 0.01$).

Conclusions: AIs cause a decrease of bone mass and an alteration in bone quality which increase the risk of fractures. After having had AI for at least 3 years, 46.3 % had densitometric osteoporosis and 38.4 % had suffered at least one fragility fracture. Less than half of the patients had prescribed calcium and vitamin D and less than 20 % some drug for osteoporosis.

Keywords:
Breast cancer. Osteoporosis. Aromatase inhibitors. Fragility fractures. Bone quality. Quantitative ultrasound. Trabecular bone score.

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INTRODUCTION

Breast cancer is the most common tumor in women in the world today, regardless of their age, with its peak incidence occurring between 50 and 69 years of age (1). Worldwide cancer incidence and mortality rates for 2020 were an estimated 19.3 million new cases of cancer and almost 10.0 million deaths. The most commonly diagnosed cancers were female breast cancer with 2.26 million cases (2). Moreover, its high incidence and prevalence of long-term survivors has highlighted the need to study the long-term effect that some treatments may have on the quality of life of these patients (3).

Osteoporosis is also a very prevalent disease, estimated to affect more than 200 million patients worldwide. About one in 3 women after menopause will suffer a fragility or osteoporotic fracture. The wrist, vertebra and hip are the most common fractures (4).

About 70-80 % of early breast cancer patients receive adjuvant endocrine therapy (ET) for at least 5 years and either at the beginning or at another time of treatment these treatments include including gonadotropin-releasing hormone (GnRH) agonists. chemotherapy-induced ovarian failure (CIOF) and aromatase inhibitors (AIs). All these drugs can cause bone loss and increase fracture risk (5).

Most of the published articles on women treated with aromatase inhibitors report loss of bone mass and increased risk of fragility fracture, but few have studied the alteration that these drugs can produce in bone quality. This fact led us to carry out this work.

METHODS

In this case-control study, patients with breast cancer who have received at least 3 years of treatment with aromatase inhibitors are considered cases. The control patients are women of a similar age who did not have breast cancer. We administered a questionnaire to all patients to collect clinical data designed for the purpose.

SAMPLE COLLECTION AND LABORATORY TECHNIQUES

Blood and urine samples were collected in the morning between 8:00 and 9:00 am after an overnight fast. The blood was collected in the appropriate specific tubes for each determination with as little venous compression as possible and was centrifuged at 1,500 g for 10 minutes. Serum was separated into aliquots and stored within one hour of extraction at -20 °C until biochemical analyzes were performed. Glucose, urea, creatinine, calcium, inorganic phosphorus and total proteins were measured using standardized and automated colorimetric techniques in an autoanalyzer (Kodak Ektachem Clinical Chemistry Slides). Most measurements were carried out the same day of the extraction. Serum calcium was corrected according to total protein using the following formula: Corrected calcium = previous calcium (mg/dl)/[0.55 + total protein (g/l)/16]. Tartrate-resistant acid phosphatase (TRAP) was determined by spectrophotometry. Glomerular filtration rate (GFR) was calculated using the MDRD formula (Modification of Diet in Renal Disease) (6). Renal failure was considered with GFR values below 60 ml/m/m^2 (7). Serum levels of 25(OH) vitamin D (25HCC) were measured by immunochemiluminescence. according to the Nichols method (Nichols Institute Diagnostics. San Clemente, California, USA). This method has an intra-assay coefficient of variation of 3.0-4.5 % and inter-assay of 7.1-10.0 %. The values given by the laboratory as normal range between 10 and 68 ng/ml. Serum parathormone (PTH) concentrations for the intact molecule were determined by immunochemiluminescence, according to the Nichols Advantage assay. The normal range in adults is between 6 and 40 pg/ml. with an inter-assay coefficient of variation of 7.0-9.2 %. Type I collagen amino-terminal propeptides (P1NP) and beta-crosslaps in blood were measured by previously described techniques (8,9). The remaining biochemical parameters were determined by colorimetric techniques.

CALCANEUS ULTRASOUND DETERMINATION (QUS)

Ultrasonographic parameters were estimated in the calcaneus of the dominant foot using a Sahara Hologic® ultrasonography (Bedford, Massachusetts, USA). This device measures both Broadband Ultrasound Attenuation (BUA) and Speed of Sound (SOS) in the targeted calcaneal region. The BUA and SOS values are combined into a single parameter called the Quantitative Ultrasound Index (QUI), also known as stiffness, which is obtained by means of the formula: QUI = 0.41(SOS) + 0.41 (BUA) – 571. The T-score values were calculated from the values published as normal for the Spanish population (10).

BONE MINERAL DENSITY (BMD)

This was measured by dual X-ray absorptiometry (DXA). both in the lumbar spine (L2-L4) and in the proximal end of the femur with a Hologic Discovery® densitometer (Hologic Inc. Waltham, Massachusetts, USA). Its accuracy is 0.75-0.16 %. Measurements were

made by the same operator. Therefore, there was no inter-observer variation. The T-score values were calculated from the values published as normal for the Canary Island population (11).

TRABECULAR BONE SCORE (TBS)

All TBS measurements were performed using the TBS iNsight Software. version 2.0.0.1 (Med-Imaps, Pessac, France). The computer program uses the image previously obtained by DXA in the same region of interest of the L2-L4 lumbar spine. The T-score values were calculated from the reference values obtained for the Spanish population (12).

ETHICS

The study was conducted following the standards of the Declaration of Helsinki (13) and was approved by the Ethics Committee of the Hospital Insular de Gran Canaria (Spain). All patients were informed of the objectives of the study and their informed consent was requested.

STATISTICAL ANALYSIS

The categorical variables were summarized using percentages and the numerical variables using means and standard deviations. To study the possible associations between categorical variables, the chi-square test of independence was used and as a measure of association, the odds ratio (OR) with a 95 % confidence interval (95 % CI). In those cases in which there were cells with less than 5 cases, Fischer's exact test was used. To evaluate the association between a quantitative variable and a categorical variable. Student's t-test or ANOVA (if there were more than 2 categories) was used for normally distributed variables or the non-parametric Mann-Whitney U test for non-normal. The normal distribution of values was verified with the Kolmogorov-Smirnov test. Student's t test for paired and unpaired observations or Wilcoxon test and Mann-Whitney test were used as appropriate. The degree of association between two variables was verified by Spearman's coefficient. Logistic regression analysis using a retrospective method based on the Akaike's information criterion was performed to study the association between fractures and the study variables. The resulting model was summarized in *p*-values and adjusted odd ratios which were estimated by 95 % CIs. Statistics were performed with SPSS program (Statistic Package for the Social Sciences, v.25.0) and statistical significance was set at $p < 0.05$.

RESULTS

This is a case-control study where women who had suffered breast cancer and who had received at least 3 years of AI treatment were considered cases, and controls were women with the same age and similar height and weight without breast cancer. Table I shows the baseline characteristics of both groups. Current calcium intake and prevalence of rheumatoid arthritis were similar in both groups with no statistically significant differences. Conversely, the prevalence of fragility fractures was significantly higher in women with breast cancer and treated with AIs. both in total fractures (38.4 % vs 20.1 %) and in vertebral fractures (26.9 % vs 14.4 %) and non-vertebral fractures (15.3 vs 7.6 %). Some patients had both vertebral and non-vertebral fractures so the total sum exceeds that of fractures.

Table II shows the results obtained when analyzing BMD. Patients with breast cancer, treated with AI, were found to have less BMD in each and every one of the anatomical locations where DXA was carried out, the differences being statistically significant in all cases. We consider the existence of densitometric osteoporosis when the T-score < -2.5 in any of the 3 locations: lumbar spine, femoral neck or total hip. 46.3 % of patients with breast cancer and treated with AI had osteoporosis compared to 16.1 % of the control group ($p = 0.01$).

The quality of the vertebral trabecular connections was also estimated by calculating the TBS, which showed lower values in patients with breast cancer and treated with AI (1.313 g/cm^2 ± 0.112 vs 1.452 g/cm^2 ± 0.109. $p = 0.01$). The prevalence of patients with normal TBS, considering this as a value greater than 1,313 g/cm^2, was only 25.1 % compared to 65.4 % of the women in the control group ($p = 0.01$), predominating in patients with breast cancer and treated with AI a partially degraded TBS, between 1,200 -1,350 g/cm^2, in 44.2 % of the cases compared to 25.7 % in the women of the control group, $p = 0.01$.

QUS showed lower values in women treated with AI compared to controls (QUI: 71.3 ± 12.6 vs 77.2 ± 15.4, $p = 0.03$, BUA 53.9 ± 10.6 db/mgHz vs 57.8 ± 11.2 and SOS 1,501 ± 0.6 m/s vs 1,521 ± 24) $p = 0.04$. We obtained a statistically significant correlation between TBS values in the lumbar spine and QUI in the calcaneus ($r = 0.754$, $p < 0.001$) (Fig. 1).

Table III shows the biochemical values related to bone mineral metabolism. Renal function was similar in both groups, as well as calcium, phosphorus, and total serum protein, with no statistically significant differences between the two groups. Women receiving AI showed higher serum levels of some biochemical markers of remodeling, especially indicators of osteoclastic activity, such as CTX and TRAP with statistically significant differences, as well as osteocalcin ($p < 0.05$ in all cases).

Table I. Baseline characteristics of the study population

	Patients	Controls	*p* value
Number	104	104	
Age (years)	62.2 ± 9.3	62.1 ± 9.2	0.800
BMI (kg/m^2)	27.6 ± 5.2	28.7 ± 4.3	0.583
Current calcium intake (mg/day)	651.7 ± 295	569 ± 272	0.406
Rheumatoid arthritis *n* (%)	2 (3.8)	5 (4.8)	0.542
Fragility fractures *n* (%)*	40 (38.4%)	21 (20.1 %)	0.001
Vertebral fractures *n* (%)*	28 (26.9)	15 (14.4)	0.001
Non-vertebral fractures *n* (%)*	16 (15.3)	8 (7.6)	0.004
Years receiving AIs (median. IQ95)	3 (2-5)		
Indicated osteoporosis treatment (%)**	18 (17.3)	24 (23)	0.04
Indicated calcium and vitamin D (%)	45 (43.2)	57 (54.8)	0.03

**The sum does not match because some patients had vertebral and non-vertebral fractures. ** Any treatment: bisphosphonates, SERMs, denosumab...*

Table II. Densitometric parameters. Quantitative and qualitative ultrasounds

	Patients	Controls	*p* value
DXA			
L2-L4 g/cm^2	0.792 ± 0.128	0.864 ± 0.252	0.01
Tscore	-2.4 ± 1.2	-1.7 ± 1.5	0.01
Femoral neck g/cm^2	0.674 ± 0.131	0.712 ± 0.125	0.03
Tscore	-1.5 + 1.2	-1.1	0.03
Total hip g/cm^2	0.897 ± 0.201	1.000 ± 0.147	< 0.05
Tscore	-2.1 ± 1.3	0.5 ± 1.1	< 0.05
Trabecular bone score (TBS)	1.289 ± 0.114	1.359 ± 0.109	0.001
Tscore	-2.3 ± 1.2	-1.2 ± 0.8	0.01
TBS > 1.313 g/cm^2 *n* (%)	26 (25.1)	68 (65.4)	
TBS between 1.350-1.200 g/cm^2 *n* (%)	42 (44.2)	27 (25.7)	0.01
TBS < 1.200 g/cm^2 *n* (%)	32 (30.7)	9 (8.9)	
Osteoporosis* *n* (%)	46.3%	16.1%	0.01
QUS			
QUI	71.3 ± 12.6	77.2 ± 15.4	0.03
Tscore	-1.7 ± 0.8	-1.4 ± 0.9	0.03
BUA (db/mgHz)	53.9 ± 10.6	57.8 ± 11.2	0.04
Tscore	-1.5 ± 0.6	-1.2 ± 0.7	0.04
SOS (m/s)	1,501 ± 18	1,521 ± 24	0.04
Tscore	-1.6 ± 0.7	-1.3 ± 0.8	0.04

**The existence of osteoporosis was considered when the Tscore value was less than -2.5 in any of the 3 anatomical locations (lumbar spine L2L4, femoral neck or total hip).*

We did not obtain statistically significant differences in serum P1NP values, a parameter that indicates osteoblastic activity, nor in serum PTH levels. Vitamin D was determined by its metabolite 25HCC. Women with breast cancer receiving AI had lower vitamin D levels than controls (21.6 ± 9.7 ng/mL vs 25.6 ± 12.5 ng/mL, $p < 0.001$). Only 9.6 % of women receiving AI had optimal 25HCC levels (above 30 ng/mL) while almost half were below 20 ng/mL, the limit that indicates deficiency, compared to 20.2 % of the controls who had 25HCC values above 30 ng/mL.

When carrying out a multidimensional logistic regression study, we found the variables that were statistically significantly associated with the presence of fragility fractures in women receiving AI were, firstly, the time they had been receiving this drug, followed by the serum levels of beta-crosslaps while serum levels of vitamin D, measured as 25HCC, and TBS were negatively associated (lower levels of these variables increased the risk of fracture and vice versa, $p < 0.05$ in all cases).

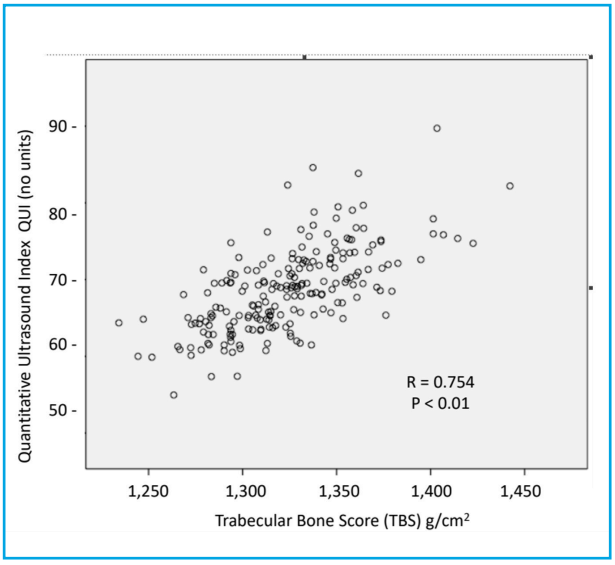

Figure 1. Correlation between QUI and TBS.

Table III. Biochemical and bone mineral metabolism parameters

	Patients	Controls	*p* value
Creatinin (mg/dL)	0.7 ± 0.4	0.9 ± 1.2	0.564
GFR (ml/m/m²)	81.5 ± 12.3	83.6 ± 11.5	0.441
Calcium (mg/dL)	9.4 ± 0.6	9.5 ± 0.7	0.871
Phosphorus (mg/dL)	4.2 ± 0.8	4.3 ± 0.7	0.856
Corrected calcium (mg/dL)	9.4 ± 0.6	9.4 ± 0.7	0.267
Total proteins (g/L)	7.2 ± 0.9	7.3 ± 0.7	0.824
Osteocalcin (ng/mL)	38.9 ± 10.5	17.2 ± 16.8	0.015
P1NP (mg/dL)	32.1 ± 12.7	26.4 ± 18.6	0.07
Beta-crosslaps (CTX) (ng/mL)	0.62 ± 0.34	0.21 ± 0.23	0.001
TRAP (IU/L)	3.7 ± 2.4	1.8 ± 2.1	0.021
PTH (pg/mL)	62.5 ± 12.6	55.1 +14.6	0.276
25HCC (ng/mL)	21.6 ± 9.7	25.6 ± 12.5	0.001
Normal > 30 ng/mL	10 (9.6 %)	21 (20.2 %)	0.001
Insuficiency 20-30 ng/mL	46 (44.3 %)	44 (42.3 %)	
Deficiency < 20 ng/mL	48 (46.1 %)	39 (37.5 %)	

P1NP: procollagen type I aminoterminal; TRAP: tartrate-resistant acid phosphatase; PTH: parathyroid hormone; 25HCC: 25-hidroxicholecalciferol.

DISCUSSION

Aromatase inhibitors are a group of drugs used in the first line of treatment for breast cancer, especially those with positive hormone receptors (14,15). Their use has made it possible to significantly increase the survival of these patients, but they also have notable secondary effects. These include loss of bone mass (16) and increased risk of fragility fractures (14,15,17-21). Thus, the literature shows that in postmenopausal women AIs increase bone turnover and induce bone loss at sites rich in trabecular bone at an average rate of 1-3 % per year which is at least 2-fold higher than bone loss seen in healthy, age-matched postmenopausal women (14,15,22). All of which results in a significantly higher fracture incidence regardless of the AI administered.

The time that the women have been taking AIs seems to be decisive both in the appearance of loss of bone mass and in the risk of suffering a fragility fracture (5,14,18,22,23). Our patients had been receiving an AIs

for a minimum of 3 years, as a criterion for inclusion in the study, and more than 25 % had been receiving the drug for 5 years. Almost 40 % of the patients in our study had suffered at least one fragility fracture at the time of evaluation and 46.3 % had osteoporosis densitometrically, with or without fragility fractures. Even so, less than half (43.2 %) had indicated a calcium and vitamin D supplement and less than 20 % of these same patients had prescribed a drug for the treatment of osteoporosis (17.3 %). We must highlight that of the 43.2 % who had indicated the calcium and vitamin D supplement, 30 % took it irregularly or did not take it at all. These data are unacceptable and force us to try to establish a work protocol in our environment so that all patients with breast cancer who receive treatment with AI are protocolized and undergo at least one bone densitometry at the start of treatment as has been reported (24,25) and indicating at least a calcium and vitamin D supplement. Moreover, the need to be monitored for bone mineral metabolism and receive follow-up as is done with other diseases, such as anticoagulation with dicoumarinics.

Bone densitometry is the current standard-of-care screening tool for fracture risk is bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA) and the most widely used technique (26,27). A decreased bone mineral density (BMD) is a strong risk factor for fractures, and measuring BMD by dual-energy X-ray absorptiometry (DXA) is the gold standard tool for diagnosing osteoporosis. In patients receiving AI, the risk of suffering a fragility fracture has been associated with the loss of bone mineral density produced by this group of drugs (15,17).

Various studies have shown the loss of BMD associated with the use of AIs. In this sense, our patients have shown lower values of bone mineral density in all anatomical locations in which we have performed the determination of bone mass: lumbar spine, L2L4, femoral neck and total hip, compared to women in the control group.

Several studies using quantitative ultrasound (QUS) have generally found good correlation with DXA, prevalent vertebral fractures and risk of future fractures (28-31). QUS is able to predict incident fractures, independently from DXA, possibly by indicating more and different information on the physical properties of bone tissue (eg, structure and elasticity affect ultrasound transmission) that contribute to bone strength and are not recognized by DXA (29,32-35). We have found only two publications from the group of Catalano et al (36,37) relating the QUS to bone quality in patients receiving AI, measuring the QUS in the phalanges of the fingers and none in which the QUS in the calcaneus. Our results show that patients who have received AIs for a minimum of 3 years have an alteration in bone quality, determined by QUS in the calcaneus. The values of all the ultrasonographic parameters, SOS, BUA and QUI, are lower in the women of the group treated with AIs compared to those of the control group, $p < 0.05$ in all cases. To complete the assessment of bone quality, we have done TBS measurements on our patients in the lumbar spine. TBS is a novel gray-level texture measurement based on standard DXA images which correlates with three-dimensional parameters of bone texture and that provides further information on bone strength additional to the standard BMD (38,39). Differently from BMD it may be less affected by spinal degenerative changes (40) and has been shown to be an independent indicator of increased fracture risk and its application improves the 10-year fracture risk prediction attained by FRAX® when considering that patients receiving AIs have a secondary cause of osteoporosis, the risk of fracture increases markedly, which possibly constitutes a better approximation to reality (18,41). In a study similar to ours carried out by Catalano et al. (36,37), they obtained a prevalence of patients who had a TBS with grade 2, between 1,350 and 1,200 greater than 60 % and grade 3, with a TBS < 1,200 of 10 %, similar to our results.

On the other hand, we have obtained a statistically significant correlation between QUI and TBS ($r = 0.754$, $p < 0.01$) as shown in figure 1. Both parameters have been shown to be good indicators of bone quality.

AIs have a marked antiestrogenic action and this produces, at the level of bone metabolism, an increase in bone remodeling at the expense, above all, of an increase in the activity of osteoclasts (15,17,20). This has been shown in our patients, since the group that received AIs for at least 3 years presented an increase in biochemical markers of bone remodeling, CTX and TRAP, as well as osteocalcin. In all cases, these are statistically significant differences. This would indicate a greater bone resorption that would lead to loss of quantity and deterioration of bone quality, which was confirmed by DXA as well as by TBS and QUS.

We determined vitamin D levels by measuring its metabolite 25-hydroxycholecalciferol (25HCC) and found that women affected by breast cancer who received AI had lower 25HCC levels than controls (21.6 ± 9.7 vs 25.6 12.5 ng/mL, $p < 0.01$). Interestingly, less than 10 % of AI-treated women presented 25HCC levels considered optimal (> 30 ng/mL) (42), but this same fact was observed in 20.2 % of the women in the control group. This confirms that most of the women who were part of the study present vitamin D insufficiency as described in other patient groups or even in populations of healthy women (43,44). On the contrary, we did not obtain statistically significant differences in PTH values between both groups. Finally, we observe in table IV that when analyzing a multidimensional logistic regression model, the variables that had a statistically significant association with the presence of fragility fractures were the time they received AIs (each year of treatment doubled the risk of having a fracture) and in-

Table IV. Multidimensional logistic regression model of variables with independent association with the presence of fractures in women with breast cancer

Variable	*p* value	OR (95 % CI)
Time on treatment with AIs (per year)	0.001	2.021 (1.478; 2.794)
Beta-crosslaps (per ng/mL)	0.001	1.921 (1.470; 2.471)
25 (OHD) (per ng/mL)	0.01	0.347 (0.238; 0.507)
TBS (per g/cm^2)	0.04	0.619 (0.406; 0.941)

creased beta-crosslaps or CTX, a marker of bone destruction (8). A decrease in 25HCC levels and TBS values were also associated with the presence of fragility fractures. Our study has several limitations. First, its sample size is relatively small, with just over 100 cases in each group. This was due to the rigor with which we included the patients in each group: they had to have received AIs for at least 3 years without interruption, with the absence of other diseases that could affect the bone. Also, the control group had to be made up of women of similar age, height and weight without breast cancer, which limited the inclusion of controls. Another limitation is that we have collected all the aromatase inhibitors in a single group when differences in their effect on bone mineral metabolism have been described among them. Thus, Exemestane, having a certain androgenic effect, seems to induce a lower loss of bone mineral density (15). We have not been able to carry out an analysis of the different groups of drugs, because the number of patients included in each one would be very small, but it is a continuing line of research.

In conclusion, 38.4 % of women affected by breast cancer who received prolonged treatment with AIs had at least one fragility fracture, and 36.3 % had densitometric osteoporosis. Even so, less than half were prescribed calcium and vitamin D and less than 20 % received any medication for osteoporosis. In these patients, it is advisable to include in their study protocol the performance of a bone densitometry and indicate treatment from the moment they have had a fragility fracture or without them, when this risk is high.

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