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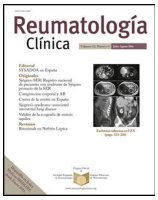

Original Article

Impact of an osteoporosis specialized unit on bone health in breast cancer survivals treated with aromatase inhibitors

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ABSTRACT

Objective: Considering the increased fracture risk in early breast cancer patients treated with aromatase inhibitors (AI), we assessed the impact of a preventive intervention conducted by a specialized osteoporosis unit on bone health at AI treatment start.
Material and methods: Retrospective cohort of postmenopausal women who started treatment with AI after breast cancer surgical/chemotherapy treatment and were referred to the osteoporosis unit for a comprehensive assessment of bone health. Bone densitometry and fracture screening by plain X-ray were performed at the baseline visit and once a year for 5 years.
Results: The final record included 130 patients. At AI treatment start, 49% had at least one high-risk factor for fractures, 55% had osteopenia, and 39% osteoporosis. Based on the baseline assessment, 79% of patients initiated treatment with bisphosphonates, 88% with calcium, and 79% with vitamin D. After a median of 65 (50–77) months, 4% developed osteopenia or osteoporosis, and 14% improved their densitometric diagnosis. Fifteen fractures were recorded in 11 (8.5%) patients, all of them receiving preventive treatment (10 with bisphosphonates). During the follow-up period, patients with one or more high-risk factors for fracture showed a greater frequency of fractures (15% vs. 3%) and experienced the first fracture earlier than those without high-risk factors (mean of 99 and 102 months, respectively; $P = 0.023$).
Conclusions: The preventive intervention of a specialized unit at the start of AI treatment in breast cancer survivors allows the identification of patients with high fracture risk and may contribute to preventing bone events in these patients.

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Impacto de una unidad de osteoporosis en la salud ósea de pacientes con cáncer de mama en tratamiento con inhibidores de la aromatasa

Palabras clave:
Osteoporosis
Fracturas óseas
Medicina preventiva
Inhibidores de la aromatasa
Cáncer de mama

RESUMEN

Objetivo: Evaluar el impacto de la intervención preventiva de una unidad de osteoporosis en supervivientes de cáncer de mama que inician un tratamiento con inhibidores de la aromatasa (IA).
Material y métodos: Estudio retrospectivo en mujeres posmenopáusicas con cáncer de mama precoz que iniciaron un tratamiento con IA tras la cirugía y/o quimioterapia, derivadas a la unidad de osteoporosis para una evaluación de la salud ósea, incluyendo densitometrías óseas y búsqueda sistemática de fracturas mediante Rx al inicio del tratamiento y anualmente durante 5 años.
Resultados: Se incluyeron 130 pacientes. Al inicio del tratamiento con IA el 49% tenía al menos un factor de riesgo alto para fracturas, el 55% osteopenia y el 39% osteoporosis. Tras la evaluación inicial, el 79% de las pacientes inició un tratamiento con bifosfonatos, el 88% con calcio y el 79% con vitamina D. Tras una mediana de 65 (50-77) meses, el 4% desarrolló osteopenia u osteoporosis y el 14% mejoró el diagnóstico densitométrico. Se registraron 15 fracturas en 11 (8,5%) pacientes, todas ellas en tratamiento preventivo.

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Durante el seguimiento, las pacientes con ≥1 factores de riesgo altos registraron una mayor frecuencia de fracturas (15 vs. 3%) y un menor tiempo hasta la primera fractura (media de 99 vs. 102 meses; p = 0,023). *Conclusiones:* La intervención preventiva de una unidad de osteoporosis al inicio del tratamiento con IA en supervivientes de cáncer de mama permite identificar pacientes con un elevado riesgo de fracturas y puede contribuir a la prevención de eventos óseos en estas pacientes.

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Introduction

Breast cancer is the malignancy with the greatest incidence worldwide and contributes remarkably to cancer-associated mortality in women; in Spain, 27,747 new cases were diagnosed in 2015.[1] However, breast cancer has higher survival rate than other types of cancer, regardless of the patient's age at diagnosis.[2] Hormone therapy, used after surgical removal of early-stage hormone receptor-positive tumors, has shown to significantly reduce the relapse rate.[3,4] In the last decade, treatment with aromatase inhibitors (AI) in postmenopausal women has emerged as an alternative to the traditional hormone therapy based solely on tamoxifen. AI can be introduced in three treatment regimens, with no proven advantage of one strategy over the others[5,6]: (a) as monotherapy (5-year treatment with AI only), (b) as sequenced therapy (2 years of tamoxifen treatment followed by 3 years of AI treatment, or vice versa), and (c) as extended therapy (5 years of tamoxifen treatment followed by 5 years of AI treatment).

One of the major drawbacks of AI treatment is the increased rate of bone loss, which has been estimated to be 1–2% yearly in the healthy population and may reach up to 5% during treatment with anastrozole.[7,8] The AI-associated bone loss leads to an increased fracture risk: while postmenopausal breast cancer survivors have a 15% greater risk compared with healthy population, women treated with AI have 30% greater risk of fracture than the age-adjusted healthy population.[9–11] The fracture incidence varies depending on the AI used: a 5.8% incidence has been reported with letrozole treatment,[12] a 6.8% incidence with exemestane treatment,[13] and a 11% incidence with anastrozole.[14] Furthermore, the treatment approach regimen also seems to influence the fracture risk, which is significantly greater in sequential therapy although no differences between monotherapy and extended therapy have been found.[15]

In addition to AI treatment, breast cancer survivors are exposed to other factors associated with fracture risk such as demographical and clinical characteristics (aging, low weight, and previous fractures), and cancer treatment (use of corticosteroids and, to a lesser extent, chemotherapy and radiotherapy).[16–18] Based on bone mineral density (BMD) measures and the presence of risk factors, various criteria have been proposed to assess the fracture risk in breast cancer survivors and to guide a preventive intervention during AI treatment.[18–21] However, data regarding the efficacy of this intervention in real-life practice are limited, and the assessment of bone health in patients elected for AI treatment is uncommon in routine clinical practice.

In this study, we investigate the impact of a monographic bone health assessment on fracture risk in a retrospective cohort of breast cancer survivors treated with AI. In our center, patients were assessed in an osteoporosis-specialized unit, using the densitometric cutoffs proposed by the National Osteoporosis Foundation (NOF) and considering the optimized risk factor list available at the time for risk assessment and decision-making on preventive treatment prescription.

Methods

Study design and population

This study is based on a retrospective record of postmenopausal women, survivors to a non-metastatic breast cancer, who initiated adjuvant treatment with AI and were referred to the Osteoporosis Unit of the Basurto University Hospital (Spain) between January 2006 and December 2010 for bone health assessment. Only patients with surgically removed hormone receptor-positive cancers treated with AI for at least 3 years were considered for the study. Patients diagnosed with osteomalacia or imperfect osteogenesis were excluded from the record. Patients signed an informed consent before their clinical data were transferred, and the study protocol was approved by the independent ethics committee of our center. At the first assessment visit (baseline), scheduled at the beginning of AI treatment, all patients were provided with written recommendations on dietary and lifestyle habits for fracture prevention (adapted from Ruiz et al., 2004, see Supplementary Material).[22] At baseline, a preventive treatment was established following the T-score cutoffs recommended by the NOF in 2003[19,20]: *T*-scores <−1.5 and <−2.0 for patients with and without other risk factors, respectively. The risk factors considered in the assessment included two different sources: when available, the algorithm proposed by Hadji et al.[18] was used whereas, before its publication, the risk factor list proposed by the Spanish Society of Rheumatology[21] was considered (Fig. 1). After the baseline assessment, patients were followed-up every 6 months for 5 years. Densitometric controls were performed every 2 years.

Baseline variables and measurements

Data collected at baseline included demographic characteristics (i.e. age, weight, and height), lifestyle habits potentially associated with bone loss (i.e. smoking history and alcohol consumption), risk factors for fractures, and the presence of comorbidities. Tumor characterization included the date of diagnosis, the stage, the presence of hormone and Her-2 receptors, and adjuvant treatment with chemotherapy and/or radiotherapy. The presence of osteopenia/osteoporosis was determined by a central bone densitometry (*dual energy X-Ray* absorptiometry [Electric Lunar DPX-NT, General Electric Healthcare, United Kingdom]) of the hip, femur, and column (from L1 to L4), performed after starting treatment with AI and every 2 years during the follow-up. The lowest *T*-score in any of the assessed areas was compared with the mean *T*-score of overall women aged between 20 and 40 years. Normality was considered when the patient's *T*-score was ≥−1 standard deviations (SDs) with respect the reference population mean. Accordingly, osteopenia was considered when the *T*-score decreased from −1.1 to −2.4 SDs, and osteoporosis when the *T*-score decreased −2.5 or more SDs with respect the reference population mean. The presence of an osteoporotic fracture on X-ray films was also considered for osteoporosis diagnosis. The screening of low-energy fractures

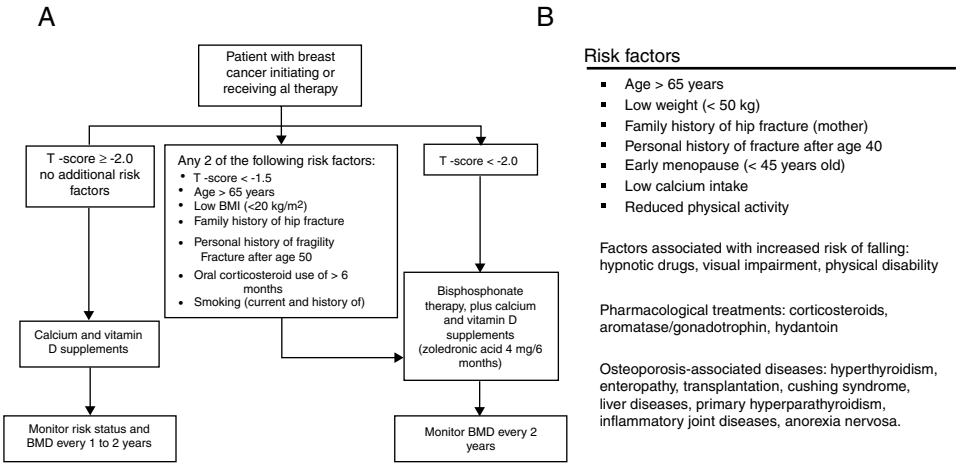

Fig. 1. Criteria used for establishing preventive treatment at the baseline visit. (A) Algorithm proposed by Hadji et al.[18] (B): risk factor list proposed by the Spanish Society of Rheumatology.[21]

was performed by dorsal and lumbar plain X-ray when a new risk factor for osteoporotic fractures was identified in a follow-up visit. Vertebral fractures were considered when the X-ray revealed a ≥20% deformity, according to the classification of Genant et al.[23]

Endpoints

The study endpoints included the presence of a fracture not present at the beginning of AI treatment, and a new diagnosis of osteopenia or osteoporosis during the follow-up. Only image-confirmed fractures (i.e. X-ray, computerized axial tomography, or magnetic resonance image) due to bone fragility were considered. Accident- or sport-related fractures were excluded from the analysis. In addition to the diagnosed fractures, we used column X-ray (thoracolumbar spine, lateral view) to investigate the presence of fractures in all patients with risk factors, and those who referred back pain and had not been previously explored by X-ray. Osteopenia or osteoporosis diagnosis was established by bone densitometry as described for the baseline visit.

Statistical analysis

Normally-distributed quantitative variables were described as the mean and SD, whereas variables showing a skewed distribution were described as the median and the interquartile range (IR), defined by 25 and 75 percentiles. Qualitative variables were described as frequency and percentage. The prevalence of high-risk and moderate-risk factors for fracture was calculated according to the consensus statement of the Spanish Society of Rheumatology.[16] The incidence of fractures was described as cumulative survival (using the Kaplan–Meier estimate), and cumulative frequency and percentage for the overall population and for patients with moderate- or high-risk factors, according to the updated consensus of the Spanish Society of Rheumatology.[16] The proportion of patients with fractures or newly diagnosed osteoporosis/osteopenia in each group was compared using the chi-square test with a significance α-level of 0.05. All analyses were performed using the IPSS statistical package (IBM SPSS Statistics for Windows, Version 20. Armonk, NY).

Results

Patient characteristics

Between January 2006 and December 2010, 209 breast cancer survivors were referred to the osteoporosis unit for bone health assessment upon beginning AI treatment. Of them, 166 met all inclusion criteria and none of the exclusion criteria but 36 rejected entering the study, leading to a final sample of 130 women with a mean (SD) age of 62.3 (8.5) years. The tumor was at stage T1 in 72 (56%) patients, and 76 (60%) patients were node-negative. All tumors were hormone receptor positive (94% had estrogen receptors and 89% progesterone receptors), and 12 (9%) were Her-2 positive. Eighty-three (64%) patients received adjuvant treatment with chemotherapy after surgical excision of the tumor.

Table 1 summarizes the risk factors found in the baseline visit. Forty-nine percent of patients had one or more high-risk factors, and 47% had one or more moderate-risk factors. None of the patients had been treated with corticosteroids in the 12 months prior to starting treatment with IA. Of all fractures recorded before the beginning of AI treatment, 11 were low-energy fractures: 6 vertebral fractures, 5 wrist fractures (one patient experienced 2 wrist fractures) and 1 foot fracture.

The baseline examination of BMD was performed in a median (IR) of 3 (1–8) months after starting treatment with AI. Mean values of BMD at baseline for the overall study sample in the assessed regions were the following: 0.940 in the column (*T*-score −2.02), 0.875 in the hip (*T*-score −1.05), and 0.829 in the femoral neck (*T*-score −1.26). The exam revealed the presence of osteoporosis in 50 patients (39%) (the mean BMD was 0.820 in the column [*T*-score −3.01], 0.811 in the hip [*T*-score −1.59], and 0.776 in the

Table 1
Risk factors in study sample.[a]

	Frequency (%) (*N* = 130)
High risk	
Age ≥ 65 years	45 (35%)
Low BMI (<20 kg/m^2)[b]	1 (0.9%)
Previous fracture[b]	30 (23%)
Family history of hip fracture[b]	1 (0.8%)
Moderate risk	
Alcohol consumption (>80 g/day)	2 (1.6%)
Currently smoking or smoking history[b]	33 (25%)
Chronic kidney disease	1 (0.8%)
Liver failure	1 (0.8%)
Hyperparathyroidism	1 (0.8%)
Malabsorption	2 (1.5%)
Early menopause (≤45 years old)	32 (25%)

[a] According to the consensus statement (2011 update) of the Spanish Society of Rheumatology.[16]
[b] Considered risk factors by Hadji et al.[18]

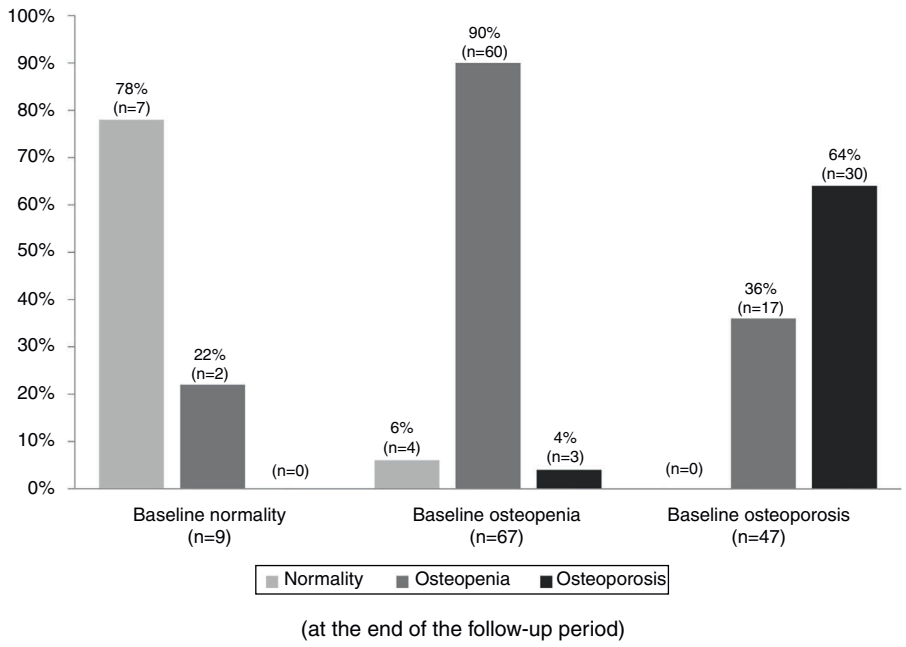

Fig. 2. Changes in the bone mineral density diagnosis during 5 years of treatment with aromatase inhibitors in patients with BMD assessment at the end of the follow-up ($n = 123$). Patients were classified into three groups according to the baseline BMD assessment: normality, osteopenia, and osteoporosis. The percentages displayed in the bar diagram correspond to patients with normality, osteopenia, and osteoporosis at the end of the follow-up period.

Table 2
Aromatase inhibitors treatment.

	Frequency (%) ($N = 130$)
Type of AI	
Anastrozole	70 (54%)
Letrozole	37 (28%)
Exemestane	23 (18%)
Treatment regimen	
Monotherapy	90 (69%)
Sequenced therapy	30 (23%)
Extended therapy	10 (8%)

AI: aromatase inhibitor.

femoral neck [*T*-score −1.72]). Osteopenia was identified in 71 patients (55%) (the mean BMD was 0.984 in the column [*T*-score −1.65], 0.894 in the hip [*T*-score −0.89], and 0.847 in the femoral neck [*T*-score −1.1]). Only 1 (1%) patient received treatment with bisphosphonates in the 12 months preceding the baseline visit.

Aromatase inhibitors treatment and cancer progression

Patients were treated with AI for a median (IR) of 60 (36–60) months. Table 2 summarizes the main characteristics of AI treatment, including the treatment regimen administered. Seven (5%) patients received hormonal treatment in the 12 months preceding the baseline visit.

At the time of starting the analysis, 15 (11%) patients had cancer relapse (local in 2 cases, and metastatic in 13 cases), and 13 (10%) had died, 9 of them because of cancer.

Fracture incidence and risk factors

The proportion of patients experiencing fractures was greater among those with at least one high-risk factor than those without high-risk factors (15% vs. 3%). Furthermore, the time to first fracture was significantly shorter in patients with at least one high-risk factor: mean of 99 months (95% CI 88–111) vs. 102 months (95% CI 98–105) ($P = 0.023$). On the other hand, the proportion of fractures among patients with moderate-risk factors was similar to that of patients without moderate-risk fractures (9.8% vs. 7.6%), and no significant differences were observed in the time to first fracture: mean of 106 months (95% CI 99–114) and 96 months (95% CI 90–101) for patients with and without moderate-risk factors, respectively ($P = 0.290$). The baseline risk factors identified in patients experiencing a fracture were age over 65 years (8 patients), previous fracture (3 patients), early menopause (i.e. before 45 years of age) (3 patients), smoking history or currently smoking (2 patients), liver failure (1 patient), and hyperparathyroidism (1 patient). The comparative analysis of each risk factor did not reveal significant differences regarding fracture incidence.

Preventive intervention and bone events

The comprehensive assessment of bone health was performed in a median (IR) of 3 (1–8) months after initiating AI treatment. The baseline assessment was performed considering the risk factors proposed by the Spanish Society of Rheumatology in 101 patients (77.7%) and the risk factors proposed by Hadji et al. in 29 patients (22.3%). As a result of the assessment, 102 (79%) patients started treatment with bisphosphonates, administered orally in 94 (72%) patients (alendronate, risedronate or ibandronate) and intravenously in 8 (6%) patients (zoledronate). Reasons for using the intravenous route were low tolerability to an oral bisphosphonate (5 cases), osteoporosis with multiple fractures (1 case), and worsening in the BMD score during treatment with oral bisphosphonates (2 cases). Overall, 114 (88%) patients received calcium supplement and 102 (79%) vitamin D supplement.

Table 3 summarizes the mean BMD values and *T*-scores of patients with and without bisphosphonate treatment at baseline and at the end of the follow-up period (median follow-up of 65 months; IR 50–77). Overall, 97 patients (79%) maintained their baseline BMD diagnosis (i.e. normality, osteopenia or osteoporosis), 5 (4.1%) experienced a worsening of their BMD diagnosis, and 17 (14%) an improvement. Fig. 2 summarizes the BMD diagnosis at the end of the follow-up period, grouped according to the baseline BMD diagnosis.

Table 3
Bone mineral density (BMD) measurements at baseline and at the end of the follow-up period. Results are presented as mean g/cm^2 (*T*-score).

	Osteoporosis at baseline		Osteopenia at baseline		Normality at baseline	
	Baseline BMD	Final BMD	Baseline BMD	Final BMD	Baseline BMD	Final BMD
Patients treated with bisphosphonates						
Column	0.820 (−3.01)	0.885 (−2.47)***	0.959 (−1.84)	1.006 (−1.44)**	1.252 (0.60)	1.304 (1.00)
Total hip	0.811 (−1.59)	0.822 (−1.49)*	0.892 (−0.90)	0.887 (−0.93)	1.083 (0.65)	1.070 (0.55)
Femoral neck	0.776 (−1.72)	0.792 (−1.56)	0.849 (−1.10)	0.852 (−1.07)	0.993 (0.10)	0.990 (0.05)
Patients not treated with bisphosphonates						
Column	–	–	1.053 (−1.13)	1.051 (−1.09)**	1.216 (0.31)	1.110 (−0.49)
Total hip	–	–	0.899 (−0.86)	0.893 (−0.89)	1.050 (0.41)	1.006 (0.29)
Femoral neck	–	–	0.842 (−1.10)	0.838 (−1.19)*	0.965 (−0.13)	0.921 (−0.47)

* $P<0.05$.
** $P<0.01$.
*** $P<0.001$.
(*T*-test for paired differences between final and baseline *T*-score).

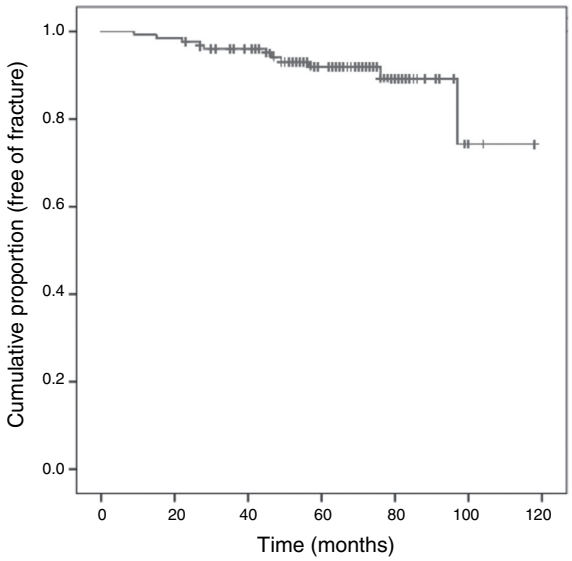

Fig. 3. Survival curve for fractures (Kaplan–Meier estimate).

Following the screening criteria for low-energy fractures detailed in the methods section, 77 patients (59.7%) underwent plain X-ray at baseline visit, and 117 (90.0%) during the follow-up period. During that time, 11 patients (8.5%) experienced a total of 15 fractures; Fig. 3 shows the survival curve of recorded fractures. In 5 patients (45%), the fracture occurred during the first 3 years of AI treatment. In most cases, patients experienced only one fracture, with the exception of two patients who experienced 2 and 4 fractures, respectively during the follow-up. Regarding the fracture location, 9 (60%) affected the vertebrae, 4 (26%) the limbs, 1 (7%) the pelvis-sacrum, and 1 (7%) the rib. No hip fractures were recorded. Eighty percent of vertebral fractures were asymptomatic and were therefore identified by X-ray in a follow-up visit. All patients who experienced a fracture were receiving preventive treatment for bone loss: 9 were being treated with calcium, vitamin D, and bisphosphonates (administered orally and intravenously in 7 and 2 patients, respectively), one was being treated with a bisphosphonate and vitamin D, and one was being treated with calcium and vitamin D.

Regarding the fractures in patients treated with the various AIs, of 71 patients receiving anastrozole, 6 (8%) experienced a fracture; all of them had a history of previous fracture (5 vertebral, 1 in the wrist, and 1 in the sacrum), 5 had osteoporosis at baseline and 1 osteopenia. Of 36 patients treated with letrozole, 1 (3%) experienced a fracture; the patient had previous vertebral fracture and osteoporosis at baseline. Finally, of 23 patients treated with exemestane, 4 (18%) experienced a fracture; all of them had a history of previous fracture (2 vertebral, one in the wrist, and one patient had fractures in the rib, wrist, and vertebrae), 3 had osteoporosis at baseline and 1 osteopenia.

Discussion

Despite the risk of bone loss associated with AI treatment, bone health assessment in patients starting hormone treatment after breast cancer surgery is unusual in real-life practice. Our results show that breast cancer survivors who initiate treatment with AI have a high prevalence of fracture risk factors and may benefit from a specialized assessment in an osteoporosis unit at the beginning of AI treatment.

In our cohort, which included women with a mean age (62 years) similar to that found in large trials assessing the efficacy and safety of AI,[8,24,25] nearly half of the patients had one or more high-risk factors for fracture, indicating that patients starting treatment with AI in real-life practice have a risk profile for bone events. In addition to age, a history of previous fracture is one of the most relevant risk factors.[18,26] In the overall population, women with a previous fracture have 86% more risk of experiencing a new fracture, and some authors have suggested that the risk associated with this event could be independent of the patient's BMD.[26,27] However, information about previous fracture in patients initiating treatment with AI is limited and large trials assessing the efficacy of AI treatment do not explore the presence of bone injuries actively. As a result, low-energy fractures (mostly asymptomatic, as commonly occurs in vertebral fractures) may be unnoticed, leading to an underestimation of the prevalence of previous fractures. In our retrospective cohort, 23% of patients had a history of previous fracture, mostly vertebral (4.6%) or wrist (3.0%) fractures. The prevalence of previous fracture reported in other observational studies assessing bone health in patients receiving hormone treatment is disparate. In line with our results, Servitja et al. reported a prevalence of 4.1% and 3.2% for vertebral and wrist fractures, respectively,[28] while the corresponding percentages in the cohort of Bouvard et al. were 20.0% and 8.0% – even after excluding patients diagnosed with osteoporosis at the beginning of AI treatment.[29] Despite these differences, the greater prevalence of vertebral and wrist fractures compared with other locations is common in all studies, and it is consistent with the epidemiology of low-energy fractures in Spain.[30]

The baseline assessment of the BMD revealed a remarkable number of patients (93%) with T-scores in the range of osteoporosis/osteopenia. During the 5 years of follow-up, only 2.4% of patients developed osteoporosis, a proportion remarkably lower than that reported in randomized clinical trials assessing the efficacy of AI

(nearly 5%).[8,13] Moreover, 14% of patients improved the BMD diagnosis, despite AI treatment.

During the follow-up, 8.5% of patients experienced at least one fracture, nearly half of them during the first three years. Interestingly, no hip fractures were reported; this finding is clinically significant, as it is among the fractures with greater morbidity and mortality risk.[31–33] With the exception of Jackesz et al., who reported a particularly low fracture incidence during AI treatment (2% in 28 months of follow-up),[34] most of the large randomized controlled trials reported greater incidence rates than that observed in our cohort: 7% in 58 months of follow-up (2–3 years with AI),[25] 9% in 60 months of follow-up,[35] and 11% in 68 months of follow-up.[36] It is worth mentioning that due to the lack of fracture screening in patients initiating AI treatment – both in the real clinical setting and in large clinical trials – the real fracture incidence might be even greater than reported.

In the general population, treatment recommendations for the prevention of bone events are based mainly on BMD and/or the presence of osteoporotic fractures.[16] However, due to the increased risk of bone loss associated with AI treatment, various authors have stressed the need for extending the circumstances for initiating preventive treatment by also considering the baseline risk factors for fractures.[10,18,19] In fact, our study patients with high-risk factors for fractures (according to the updated consensus of the Spanish Society of Rheumatology)[16] experienced the first fracture significantly earlier than those without high-risk factors. As a retrospective study based on real-life practice, our intervention evolved throughout the study period by adopting the various risk factors lists proposed for making decisions on preventive treatment. At the time of study start, our baseline assessment was performed based on the *T*-score cutoffs proposed by the NOF[19] and the risk factors described by the Spanish Society of Rheumatology.[21] Later on, we used the comprehensive algorithm proposed by Hadji et al.[18], which maintained the same *T*-score thresholds and simplified the risk factor list – albeit preserving key risk factors such as age, weight/BMI, health behavior, personal/family history, and corticosteroid use. Irrespective of the risk factors considered, 79% of patients in our cohort received preventive treatment for bone events. The analysis of fractured patients revealed that all of them had been identified as risk profiles for fracture in the baseline visit and hence experienced the fracture despite treatment with bisphosphonates, calcium and/or vitamin D. In a previous observational study describing the results of a preventive action based solely on the assessment of the BMD, 15 of 27 patients experiencing a fracture had not been identified as having a risk profile and therefore had not been treated.[37]

In addition to the moderate size of our cohort, the scope of our results must be appraised considering two important characteristics of the study design, both associated with the intrinsic limitations of studies based on real-life practice. First, no control group was included (i.e. patients without bone health assessment at the beginning of AI treatment). The recent approval of AI treatment at the time of study start precluded the use of a historical reference in our center. Likewise, we could not use large clinical trials as a reference for fracture incidence because the lack of screening for low-energy fractures hampered any comparison between our results and those reported in these trials. Second, the traditional lack of consensus regarding the risk factors to be included in a treatment-decision algorithm precluded a consistent assessment throughout the study period. In our osteoporosis unit, the algorithm proposed by Hadji et al. was adopted rapidly as we found it the most easy-to-apply and convenient option for establishing a preventive treatment. However, the baseline assessment of many patients was performed before the publication of the algorithm. It is noteworthy that most risk factors were consistent in both lists, including the above-mentioned key risk factors. Irrespective of the risk factors considered for the assessment, the DMO cutoffs for establishing preventive treatment where consistent throughout the time period.

Our specific assessment of bone health in patients beginning AI treatment, which included the screening for asymptomatic fractures, revealed a high prevalence of fracture risk factors, even greater than that observed in randomized trials assessing the efficacy and safety of AI. This finding supports the implementation of a systematic evaluation of bone health in patients who start treatment with AI. Furthermore, the low incidence of bone events reported during the 5 years of follow-up suggests that the assessment and treatment algorithm used may contribute to the prevention of bone events in these patients, and stresses the need for randomized controlled trials to confirm the efficacy of this intervention.

Ethical responsibilities

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflicts of interest

P. Martínez, E. Galve, V. Arrazubi, M.A. Sala, S. Fernández, C.E. Pérez, J.F. Arango, and I. Torre declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.reuma.2017.08.005.

References

1. SEOM. Las cifras del cáncer en España [Internet]; 2017. Available from: http://www.seom.org/seomcms/images/stories/recursos/Las_cifras_del_cancer_en_Esp_2017.pdf [accessed 17.07.17].
2. Chirlaque MD, Salmerón D, Ardanaz E, Galceran J, Martínez R, Marcos-Gragera R, et al. Cancer survival in Spain: estimate for nine major cancers. Ann Oncol. 2010;21 Suppl 3:iii21–9.
3. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365:1687–717.
4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet. 1998;351:1451–67.
5. Dowsett M, Cuzick J, Ingle J, Coates A, Forbes J, Bliss J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. J Clin Oncol. 2010;28:509–18.
6. Josefsson ML, Leinster SJ. Aromatase inhibitors versus tamoxifen as adjuvant hormonal therapy for oestrogen sensitive early breast cancer in

post-menopausal women: meta-analyses of monotherapy, sequenced therapy and extended therapy. Breast. 2010;19:76–83.
7. Rizzoli R, Body JJ, DeCensi A, De Censi A, Reginster JY, Piscitelli P, et al. Guidance for the prevention of bone loss and fractures in postmenopausal women treated with aromatase inhibitors for breast cancer: an ESCEO position paper. Osteoporos Int. 2012;23:2567–76.
8. Eastell R, Adams JE, Coleman RE, Howell A, Hannon RA, Cuzick J, et al. Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. J Clin Oncol. 2008;26:1051–8.
9. Chen Z, Maricic M, Pettinger M, Ritenbaugh C, Lopez AM, Barad DH, et al. Osteoporosis and rate of bone loss among postmenopausal survivors of breast cancer. Cancer. 2005;104:1520–30.
10. Servitja S, Martos T, Rodriguez Sanz M, Garcia-Giralt N, Prieto-Alhambra D, Garrigos L, et al. Skeletal adverse effects with aromatase inhibitors in early breast cancer: evidence to date and clinical guidance. Ther Adv Med Oncol. 2015;7:291–6.
11. Chen Z, Maricic M, Bassford TL, Pettinger M, Ritenbaugh C, Lopez AM, et al. Fracture risk among breast cancer survivors: results from the Women's Health Initiative Observational Study. Arch Intern Med. 2005;165:552–8.
12. Coates AS, Keshaviah A, Thurlimann B, Mouridsen H, Mauriac L, Forbes JF, et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. J Clin Oncol. 2007;25:486–92.
13. Bliss JM, Kilburn LS, Coleman RE, Forbes JF, Coates AS, Jones SE, et al. Disease-related outcomes with long-term follow-up: an updated analysis of the intergroup exemestane study. J Clin Oncol. 2012;30:709–17.
14. Cuzick J, Sestak I, Baum M, Buzdar A, Howell A, Dowsett M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. Lancet Oncol. 2010;11:1135–41.
15. Aydiner A. Meta-analysis of breast cancer outcome and toxicity in adjuvant trials of aromatase inhibitors in postmenopausal women. Breast. 2013;22:121–9.
16. Pérez Edo L, Alonso Ruiz A, Roig Vilaseca D, García Vadillo A, Guañabens Gay N, Peris P, et al. Actualización 2011 del consenso Sociedad Española de Reumatología de osteoporosis. Reumatol Clin. 2011;7:357–79.
17. Maxwell C, Viale PH. Cancer treatment-induced bone loss in patients with breast or prostate cancer. Oncol Nurs Forum. 2005;32:589–603.
18. Hadji P, Body J-J, Aapro MS, Brufsky a, Coleman RE, Guise T, et al. Practical guidance for the management of aromatase inhibitor-associated bone loss. Ann Oncol. 2008;19:1407–16.
19. Perez EA, Weilbeacher K. Aromatase inhibitors and bone loss. Oncology. 2006;20:1029–48.
20. Dawson-Hughes B. Physician's guide to prevention and treatment of osteoporosis [Internet]. National Osteoporosis Foundation; 2003. Available from: https://www.ars.usda.gov/research/publications/publication/?seqNo115=150021 [accessed 02.01.15].
21. Panel de expertos del Documento de Consenso 2006 de la SER sobre la osteoporosis posmenopáusica. Documento de consenso 2006 de la Sociedad Española de Reumatología sobre la osteoporosis posmenopáusica. Reum Clin. 2007;3 Suppl 1:26–32.
22. Ruiz VG, Genovés JS, Borrás JJG, Catalá JC. Osteoporosis. Guía práctica de actuación en Atención Primaria [Internet]. Versión actualizada; 2004. Available from: http://publicaciones.san.gva.es/comun/pdf/osteoporosis.pdf [accessed 17.07.17].
23. Genant H, Wu C, van Juijk C, Nevitt M. Vertebral fracture assessment using a semi quantitative technique. J Bone Miner Res. 1993;8:1137–48.
24. Crivellari D, Sun Z, Coates AS, Price KN, Thürlimann B, Mouridsen H, et al. Letrozole compared with tamoxifen for elderly patients with endocrine-responsive early breast cancer: the BIG 1-98 trial. J Clin Oncol. 2008;26:1972–9.
25. Coleman RE, Banks LM, Girgis SI, Kilburn LS, Vrdoljak E, Fox J, et al. Skeletal effects of exemestane on bone-mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES): a randomised controlled study. Lancet Oncol. 2007;8:119–27.
26. Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas P, et al. A meta-analysis of previous fracture and subsequent fracture risk. Bone. 2004;35:375–82.
27. Taylor BC, Schreiner PJ, Stone KL, Fink HA, Cummings SR, Nevitt MC, et al. Long-term prediction of incident hip fracture risk in elderly white women: study of osteoporotic fractures. J Am Geriatr Soc. 2004 Sep;52:1479–86.
28. Servitja S, Nogués X, Prieto-Alhambra D, Martínez-García M, Garrigós L, Peña MJ, et al. Bone health in a prospective cohort of postmenopausal women receiving aromatase inhibitors for early breast cancer. Breast. 2012;21:95–101.
29. Bouvard B, Hoppé E, Soulié P, Georgin-Mege M, Jadaud E, Abadie-Lacourtoisie S, et al. High prevalence of vertebral fractures in women with breast cancer starting aromatase inhibitor therapy. Ann Oncol. 2012;23:1151–6.
30. Gimeno J. Epidemiología de las fracturas osteoporóticas. Mortalidad y morbilidad. Rev Osteoporos Metab Miner. 2010;2:55–9.
31. Azagra R, López-Expósito F, Martin-Sánchez JC, Aguyé A, Moreno N, Cooper C, et al. Changing trends in the epidemiology of hip fracture in Spain. Osteoporos Int. 2014;25:1267–74.
32. Kanis JA, Odén A, McCloskey EV, Johansson H, Wahl DA, Cooper C. A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int. 2012;23:2239–56.
33. Youm T, Koval KJ, Zuckerman JD. The economic impact of geriatric hip fractures. Am J Orthop (Belle Mead NJ). 1999;28:423–8.
34. Jakesz R, Jonat W, Gnant M, Mittlboeck M, Greil R, Tausch C, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: Combined results of ABCSG trial 8 and ARNO 95 trial. Lancet. 2005;366:455–62.
35. Rabaglio M, Sun Z, Price KN, Castiglione-Gertsch M, Hawle H, Thürlimann B, et al. Bone fractures among postmenopausal patients with endocrine-responsive early breast cancer treated with 5 years of letrozole or tamoxifen in the BIG 1-98 trial. Ann Oncol. 2009;20:1489–98.
36. Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF, et al. Results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet. 2005;365:60–2.
37. Bouvard B, Soulié P, Hoppé E, Georgin-Mege M, Royer M, Mesgouez-Nebout N, et al. Fracture incidence after 3 years of aromatase inhibitor therapy. Ann Oncol. 2014;25:843–7.