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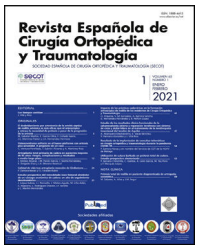

ORIGINAL PAPER

[Translated article] Evaluation of factors related to the occurrence of new fragility fractures: A case–control study

Á. Oteo-Álvaro[a,*], M.T. Marín Becerra[b], T. Fernández-Fernández[c], G. Arrieta-Bartolomé[c]

[a] *Hospital Universitario HM Madrid, HM Hospitales, Madrid, Spain*
[b] *C.S. General Ricardos, Madrid, Spain*
[c] *Hospital General Universitario Gregorio Marañón, Madrid, Spain*

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KEYWORDS
Fragility fractures;
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Bone mineral density

Abstract
Introduction: Fragility fractures (FF) are frequent in osteoporotic patients. There are a series of risk factors and clinical variables that could predict their appearance.
Material and method: A retrospective observational study of cases and controls was carried out. Cases were defined by the presence of FF (326 participants) and controls by patients with similar characteristics without FF (629 participants).
Results: Certain factors increase the risk of FF, such as a previous diagnosis of type 2 DM (OR: 2.001), 1 ng/mL elevations of CTX (OR: 1.88), having a parental history of hip fracture (OR: 1.667), 5-year increase in age (OR: 1.39), and 1 kg/m^2 increases in BMI (OR: 1.041). In contrast, other factors evaluated decreased this risk, such as maintaining 25(OH)D levels $\geq$ 30 ng/mL (OR: 0.686) and a *T*-score ≥ -2.5 (OR: 0.642).
Conclusions: Levels of 25(OH)D $\geq$ 30 ng/mL and a *T*-score at the femoral neck ≥ -2.5 are protective factors for FF, while a previous diagnosis of type 2 DM, an elevated CTX, a parental history of hip fracture, an increase of 1 kg/m^2 in BMI and an increase in age by 5 years would be predisposing to FF.

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* Corresponding author.
E-mail address: angel_oteo@telefonica.net (Á. Oteo-Álvaro).

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PALABRAS CLAVE
Fracturas por fragilidad;
Osteoporosis;
Factores de riesgo;
Vitamina D;
Densidad mineral ósea

Evaluación de los factores relacionados con la aparición de nuevas fracturas por fragilidad: un estudio de casos y controles

Resumen
Introducción: Las fracturas por fragilidad (FF) son frecuentes en pacientes osteoporóticos. Existen una serie de factores de riesgo y variables clínicas, que podrían predecir su aparición.
Material y método: Se realizó un estudio observacional retrospectivo de casos y controles. Los casos estuvieron definidos por la presencia de una FF (326 participantes) y los controles por pacientes de similares características sin FF (629 participantes).
Resultados: Ciertos factores aumentan el riesgo de FF, como un diagnóstico previo de DM tipo 2 (OR: 2,001), las elevaciones de 1 ng/mL del CTX (OR: 1,88), tener antecedentes parentales de fractura de cadera (OR: 1,667), el aumento en 5 años en la edad (OR: 1,39) y los incrementos de 1 kg/m^2 del IMC (OR: 1,041). Por el contrario, otros factores evaluados disminuyen ese riesgo, como mantener unos niveles de 25(OH)D $\geq$ 30 ng/mL (OR: 0,686) y un T-score $\geq -2,5$ (OR: 0,642).
Conclusiones: Niveles de 25(OH)D $\geq$ 30 ng/mL y un T-score en el cuello femoral $\geq -2,5$ son factores protectores de las FF, mientras que el diagnóstico previo de DM tipo 2, un CTX elevado, el antecedente parental de fractura de cadera, un incremento de 1 kg/m^2 del IMC y el aumento de la edad en 5 años serían predisponentes a padecer FF.

Introduction

Osteoporosis (OP) is a disease characterised by gradual and painless loss of bone, increasing the risk of fragility fractures (FF) in the event of low-energy trauma.[1] It is diagnosed primarily by measurement of bone mineral density (BMD) by bone density scan (BDS). The BDS T-score is considered the gold standard for distinguishing between normal values (−1 and above), osteopenia (between −1 and −2.5), osteoporosis (−2.5 or less), and severe osteoporosis (−2.5 associated with FF).[2] The presence of some FF can establish a diagnosis of OP, as is the case with vertebral and hip fracture.[3]

We know that one in 3 women and one in 5 men over 50 years of age will suffer an FF in their lifetime.[4] The most characteristic FF are those located in the hip, vertebral bodies, humerus, wrist, ribs, tibia (excluding the ankle), pelvis, and other femoral fractures.[3,5,6] It should be noted that those who suffer a first FF have in turn an increased risk of further FF, which rises exponentially with age.[4,7,8] Despite the significant impact of FF on health and quality of life,[8] their consequences and treatment are underestimated.

We know there are a series of risk factors (RF) and clinical, analytical, and densitometric situations that influence an individual's predisposition to develop the disease and its FF. The RF are divided into two groups: non-modifiable, such as age and sex, and modifiable related to lifestyle, such as smoking or alcohol consumption, among others. Most RF act by causing a decrease in BMD and only a few are identified as independent RF (BMD, RA, CG treatment, parental history of hip fracture, and probably diabetes mellitus [DM]).[1,9,10]

Vitamin D aids intestinal absorption of calcium from food, has a regulatory effect by decreasing the level of parathyroid hormone (PTH), ensuring adequate bone turnover and mineralisation, increasing BMD.[1] There is general consensus that older people have lower than normal serum vitamin D levels. Restoring these levels is important for calcium and bone homeostasis and therefore for overall health[11] and is necessary to optimise an adequate response to antiresorptive therapies.[12] 25(OH)D is considered a marker of body vitamin D status[11]; and it is recommended that serum levels should be maintained above 30 ng/mL (75 nmol/L).[12]

According to several studies, there appears to be an inverse relationship between serum 25(OH)D levels and iPTH.[13,14] Increased serum PTH levels stimulate bone turnover, leading to predominantly cortical bone loss, increasing the risk of fracture.[15]

Study hypothesis. Our study hypothesis indicated that there are clinical, analytical, and densitometric variables related to the onset of FF. This retrospective, observational study was conducted to determine their effect, its aims are:

- Primary aim. To evaluate RF and certain clinical, analytical, and densitometric variables.
- Secondary aim. To evaluate the therapeutic groups with which participants were being treated (Fig. 1).

Material and method

Study design

A retrospective case–control study was conducted using data collected at the first visit from the medical records of patients seen in a hospital bone metabolism unit from January 2019 to December 2020. All patients had been previously evaluated by physicians from different specialties and referred to this unit as candidates for evaluation to rule out metabolic bone diseases.

All subjects seen during this period of time were included, and a total of 955 patients were recruited. Two groups were established, defined by the presence or absence of an FF (case and control groups, respectively).

The variables collected were as follows:

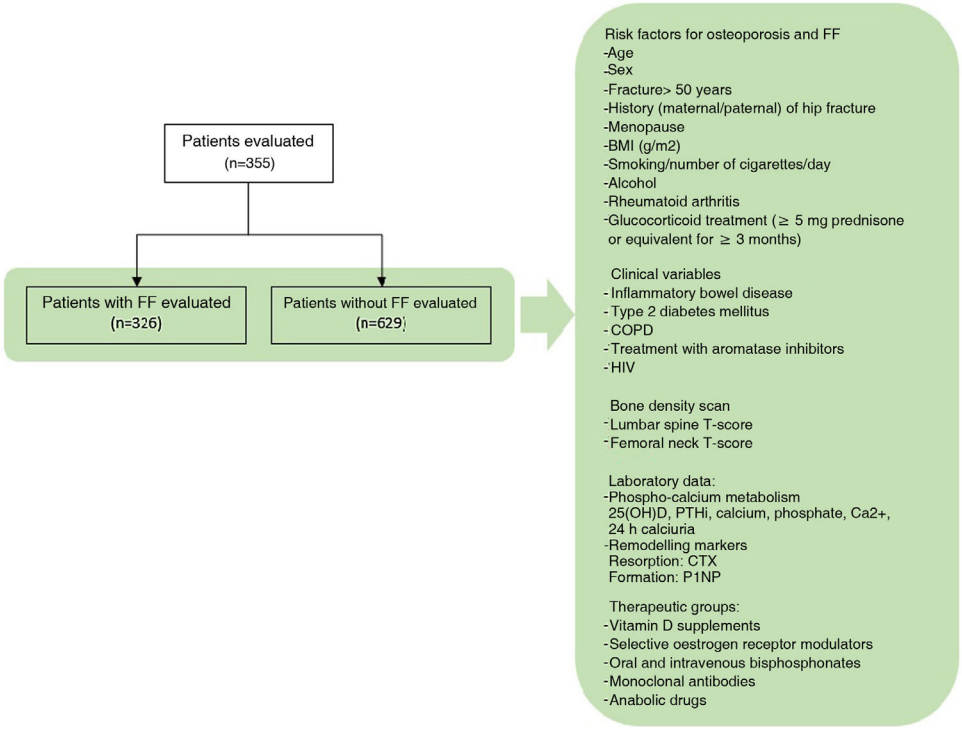

Figure 1 Patient flow. Variables evaluated.

- RF for OP. Age, sex, history of fracture at age over 50 years, parental history (maternal or paternal) of hip fracture, menopause, BMI (kg/m^2), smoking and number of cigarettes per day, alcohol consumption, diagnosis of RA, glucocorticoid treatment (>5 mg prednisone or equivalent for >3 months).
- Clinical variables. Previous diagnosis of inflammatory bowel disease, type 2 diabetes mellitus, COPD, treatment with aromatase inhibitors, and presence of HIV.
- Laboratory data related to phospho-calcium metabolism: 25(OH)D, PTHi, calcium, phosphate, Ca2+, 24 h calciuria, and the remodelling markers, C-terminal cross-linking telopeptide of type 1 collagen (CTX) and procollagen type 1 N-telopeptide (P1NP). The recommendations of the National Bone Health Alliance[16] were followed to collect the remodelling markers, and bloods were taken after an overnight fast and in the early hours of the morning. Electroluminescence testing was used (Cobas®8000: modules e602 and e801, Roche Diagnostics).
- BMD results (lumbar spine and femoral neck T-score). The recommendations of the International Society for Clinical Densitometry Position Development Conference were followed, whereby vertebrae with a density greater than 1SD with respect to adjacent vertebrae are excluded from analysis, accepting in this case the value obtained from 2 contiguous vertebrae.[17]

The following therapeutic groups with which the participants were being treated were identified: vitamin D supplementation, selective oestrogen receptor modulators, oral and intravenous bisphosphonates, monoclonal antibodies, and anabolic drugs.

Statistical analysis

All the results of the analysis variables were obtained for the overall evaluable sample and according to the presence of fracture. For all analysis variables, descriptive results were presented, including measures of central tendency and dispersion for quantitative variables, and absolute and relative frequencies for qualitative variables, with 95% confidence intervals in both cases. In no case were missing data or missing values imputed from available data. Statistical significance of the comparison between the 2 groups (with fracture versus without fracture) was determined using the Mann–Whitney U-test for independent samples for quantitative variables, since normality could not be confirmed for most variables using the Shapiro–Wilk test, Fisher's exact test for binary variables, or Mantel–Haenszel exact test for ordinal variables. Statistical tests were performed at the 5% significance level and bilateral in all cases. No adjustments were made to control for type I error despite multiplicity.

A stepwise selection for explanatory variables was applied to analyse the possible prognostic factors for the presence of fracture (yes/no). Variables with statistical significance in the univariate analysis and variables indicated as prognostic factors in other previously published studies were included.

Having obtained the final model, the variables which in the regression model presented statistical significance ($p < .05$) were considered prognostic factors. The statistical significance of the interaction between the factors detected and the multicollinearity of the explanatory variables found were also assessed using the VIF (variance inflation factor) statistic.

Table 1 Site of FF. One patient may have more than one fracture.

	n	%
Clinical vertebral fractures	216	66.26
Single	172	79.63
Multiple	44	20.37
Non-vertebral fractures	147	45.09
Distal radius fracture	59	18.09
Proximal humerus fracture	32	9.81
Hip fracture	25	7.67
Pelvis fracture	11	3.37
Sacral fracture	6	1.84
Rib fracture	4	1.23
Other fractures	10	3.07
Multiple fractures	69	21.16

Multiple fractures include vertebral and non-vertebral fractures.

The statistical programme SAS version 9.4 (TS1M5) was used to perform the statistical analyses.

Ethical aspects

The investigators respected the fundamental principles of the Declaration of Helsinki and the Council of Europe Convention on Human Rights and Biomedicine, as well as all current legislation related to the study. The study was approved by HM Hospitales Clinical Research Committee with registration number 20.01.1519-GHM.

Results

A total of 955 individuals were evaluated. The proportion of women evaluated was significantly higher than that of men. Two groups were made. The case group comprised 321 individuals (33.6%) compared to 634 (66.4%) in the control group.

Fragility fractures

A history of FF after the age of 50 years was collected. The most frequently recorded FF were clinical vertebral fractures, followed by distal radius, proximal humerus, and hip fractures (Table 1).

Risk factors and clinical variables

The patients with FF were significantly older, had a higher frequency of parental history of hip fracture, and higher BMI. Postmenopausal women were more frequent in this group and time since menopause was longer. Also significant in the FF group was a previous diagnosis of type 2 DM and COPD. The presence of smoking was similar in both groups, although the mean number of cigarettes per day was higher in the FF group.

Table 2 describes the RF and clinical variables of the participants.

Laboratory data

A significant proportion of patients had mean 25(OH)D levels below 30 ng/mL. Participants in the FF group had significantly lower values than the non-FF group. Of the bone remodelling markers, the resorption marker CTX had a higher mean value in the FF patients (Table 3).

Bone density scan values

The mean lumbar spine T-score in the FF group was similar to that of the non-FF group; however, the mean femoral neck T-score of the FF group was significantly lower than that of the group without FF (Table 4).

Therapeutic groups collected in the study

Of the total sample, the following therapeutic groups were determined from the participants: vitamin D supplementation (47.5%), oestrogen receptor modulators (2.1%), oral bisphosphonates (10.5%), intravenous bisphosphonates (0.9%), monoclonal antibodies (8.4%), and anabolic drugs (2.7%). Of the total number of patients evaluated, 652 subjects (68.2%) were receiving some treatment for OP. Of these, 232 belonged to the group with fracture (35.58%) and 420 to the group without fracture (64.4%). Although 47.5% were on vitamin D supplementation, the 25(OH)D values remained below 30 ng/mL in 35.2%.

Predictors of the presence of fragility fractures

A total of 952 participants out of the total were analysed due to lack of necessary data in 3 participants. Prior diagnosis of type 2 DM, CTX elevations of 1 ng/mL, a parental history of hip fracture, 5-year increments in age, and a 1 kg/m^2 increase in BMI all implied an increased risk of FF, while maintaining values of 25(OH)D $\geq$ 30 ng/mL and a femoral neck T-score ≥ -2.5 reduce the risk of FF (Table 5). Fig. 2 shows the odds ratios (OR) of prevalences obtained from

Table 2 Patient characteristics.

Risk factors	Total ($n = 955$)	With fracture ($n = 326$)	Without fracture ($n = 629$)	p
Age				<.0001*
Mean (SD), 95% CI	64.7 (10.8), 64.0–65.4	69.8 (10.5), 68.6–70.9	62.1 (9.9), 61.3–62.9	
Median (min./max.)	64.0 (20.0/98.0)	70.0 (37.0/98.0)	61.0 (20.0/89.0)	
P25; P75	57.0; 72.0	62.0; 78.0	55.0;69.0	
Parental history of hip fracture				.0015[a]
No	767 (80.3%)	243 (74.5%)	524 (83.3%)	
Yes	188 (19.7%)	83 (25.5%)	105 (16.7%)	
BMI (kg/m^2)				.0012*
Mean (SD), 95% CI	24.6 (4.1), 24.4–24.9	25.2 (4.4), 24.7–25.7	24.3 (3.9), 24.0–24.6	
Median (min./max)	24.3 (14.7/40.8)	24.9 (15.1/40.8)	23.9 (14.7/39.8)	
P25; P75	21.6; 27.1	22.0; 27.9	21.5; 26.7	
Sex, n (%)				.0002[a]
Male	73 (7.6%)	40 (12.3%)	33 (5.2%)	
Female	882 (92.4%)	286 (87.7%)	596 (94.8%)	
Menopause ($n = 882$), n (%)	$n = 882$	$n = 286$	$n = 596$	.2069[a]
No	36 (4.1%)	8 (2.8%)	28 (4.7%)	
Yes	846 (95.9%)	278 (97.2%)	568 (95.3%)	
Smoking, n (%)				.6578[a]
No	782 (81.9%)	270 (82.8%)	512 (81.4%)	
Yes	173 (18.1%)	56 (17.2%)	117 (18.6%)	
Number of cigarettes/day				.0904*
Mean (SD), 95% CI	12.2 (8.7), 10.9–13.5	14.2 (10.3), 11.5–17.0	11.2 (7.8), 9.8–12.6	
Median (min./max.)	10.0 (1.0/40.0)	11.0 (1.0/40.0)	10.0 (1.0/40.0)	
P25; P75	6.0; 20.0	6.0; 20.0	5.0; 20.0	
Alcohol consumption, n (%)				.3496[a]
No	804 (84.2%)	280 (85.9%)	524 (83.3%)	
Yes	151 (15.8%)	46 (14.1%)	105 (16.7%)	
Rheumatoid arthritis, n (%)				.3226[a]
No	945 (99.0%)	321 (98.5%)	624 (99.2%)	
Yes	10 (1.0%)	5 (1.5%)	5 (.8%)	
Treatment with glucocorticoids, n (%)				.3194[a]
No	927 (97.1%)	314 (96.3%)	613 (97.5%)	
Yes	28 (2.9%)	12 (1.5%)	16 (2.5%)	
Inflammatory bowel disease, n (%)				1.0000[a]
No	940 (98.4%)	321 (98.5%)	619 (98.4%)	
Yes	15 (1.6%)	5 (1.5%)	10 (1.6%)	
Type 2 diabetes mellitus, n (%)				<.0001[a]
No	901 (94.3%)	292 (89.6%)	609 (96.8%)	
Yes	54 (5.7%)	34 (10.4%)	20 (3.2%)	
COPD, n (%)				.0219[a]
No	937 (98.1%)	315 (96.6%)	622 (98.9%)	
Yes	18 (1.9%)	11 (3.4%)	7 (1.1%)	
Treatment with aromatase inhibitors, n (%)				.0952[a]
No	913 (95.6%)	317 (97.2%)	596 (94.8%)	
Yes	42 (4.4%)	9 (2.8%)	33 (5.2%)	
HIV, n (%)				.3414[a]
No	955 (99.9%)	325 (99.7%)	629 (100.0%)	
Yes	1 (.1%)	1 (.3%)	0 (0%)	

RF and clinical variables of all patients, group with FF and group without FF.
SD: standard deviation; CI: confidence interval.
[a] Fisher's exact test.
* Independent Student's *t*-test.

Table 3 Laboratory data related to phospho-calcium metabolism.

	Total	With fracture	Without fracture	*p*
25(OH)D (ng/mL), mean (SD), 95% CI	28.9 (14.3), 28.0–29.8	26.3 (15.1), 24.3–28.3	30.3 (13.1), 29.0–31.5	<.0001*
Median (min./max.)	27.3 (3.4/94.5)	24.5 (4.4/91.0)	28.2 (6.5/94.5)	
P25; P75	19.2; 36.4	15.2; 32.4	21.2; 37.7	
25(OH)D < 30 ng/mL, n (%)	560 (58.6%)	162 (70.1%)	232 (55.8%)	.0004[a]
25(OH)D > 30 ng/mL, n (%)	395 (41.4%)	69 (29.9%)	184 (44.2%)	
PTHi (pg/mL), mean (SD), 95% CI	58.2 (26.1), 56.5–59.8	61.1 (29.9), 57.2–65.0	57.5 (24.2), 55.2–59.8	.3865*
Median (min./max.)	53.0 (12.0/283.0)	53.1 (17.8/191.0)	52.0 (15.4/137.7)	
P25; P75	40.4; 68.8	40.5; 75.5	40.8; 70.0	
PTHi (pg/mL) ≤ 65, n (%)	669 (70.1%)	156 (67.8%)	219 (70.3%)	.5329[a]
PTHi (pg/mL) > 65, n (%)	286 (29.9%)	74 (32.2%)	123 (29.7%)	
Calcium (mg/dL), mean (SD), 95% CI	9.4 (0.9), 9.5–9.5	9.5 (0.6), 9.4–9.6	9.5 (0.6), 9.5–9.6	.8179*
Median (min./max.)	9.5 (3.1/11.5)	9.5 (4.0/11.1)	9.5 (3.1/11.3)	
P25; P75	9.2; 9.8	9.3; 9.8	9.3; 9.8	
Phosphate (mg/dL), mean (SD), 95% CI	3.6 (.5), 3.6–3.7	3.6 (.5), 3.6–3.7	3.6 (.5), 3.6–3.7	.7140*
Median (min./max.)	3.6 (2.1/5.7)	3.6 (2.2/5.2)	3.6 (2.2/5.2)	
P25; P75	3.3; 3.9	3.3; 3.9	3.3; 4.0	
Calcium 2+ (mg/dL), mean (SD), 95% CI	4.8 (.4), 4.8–4.8	4.7 (.4), 4.7–4.8	4.8 (.4), 4.8–4.8	.0630*
Median (min./max.)	4.9 (2.6/6.0)	4.8 (3.0/6.0)	4.9 (2.7/5.9)	
P25; P75	4.6; 5.0	4.5; 5.0	4.6; 5.1	
24 h calciuria (mg/24 h), mean, 95% CI	171.0 (91.0), 163.3–178.6	209.4 (100.3), 165.0–253.9	249.0 (123.4), 213.9–284.0	.1847*
Median (min./max.)	161.0 (.0/578.5)	216.0 (2.0/473.0)	264.3 (45.0/578.5)	
P25; P75	106.0; 230.0	148.5; 266.0	146.0; 314.0	
Remodelling markers	.5 (1.6), .4–.6	.7 (3.4), .2–1.1	.4 (.2), .4–.4	.8767*
CTX (ng/mL), mean (SD), 95% CI				
Median (min/max)	.4 (.0/49.9)	.4 (.0/49.9)	.4 (.0/1.6)	
P25; P75	.3; .6	.2; .6	.3; .5	
P1NP (ng/mL), mean (SD), 95% CI	51.3 (32.7), 49.2–53.4	55.8 (33.3), 51.3–60.2	50.7 (26.7), 48.0–53.5	.3279*
Median (min/max)	48.8 (.0/492.4)	50.8 (.0/244.6)	50.4 (.0/129.0)	
P25; P75	32.1; 66.6	33.6; 71.5	32.6; 65.5	

Laboratory data for total participants, group without FF and group with FF.
SD, standard deviation. CI, confidence interval.
[a] Fisher's exact test.
* Independent student's *t*-test.

Table 4 Bone density scan values.

	Total	With fracture	Without fracture	*p*
Lumbar spine T-score, mean (SD), 95% CI	−2.3 (1.3), −2.4/−2.2	−2.3 (1.3), −2.6/−2.1	−2.4 (1.1), −2.5/−2.2	.8832*
Median (min./max.)	−2.6 (−5.3/5.7)	−2.6 (−5.3/2.2)	−2.6 (−4.4/4.5)	
P25; P75	−3.1; −1.7	−3.2; −1.7	−3.1; −1.8	
Femoral neck T-score, mean (SD), 95% CI	−1.9 (1.0), −2.0/−1.9	−2.2 (.8), −2.4/−2.1	−1.9 (.9), −2.0/−1.8	.0019*
Median (min./max.)	−2.0 (−4.8/2.8)	−2.2 (−4.8/−.2)	−2.0 (−4.2/2.5)	
P25; P75	−2.6; −1.4	−2.9; −1.7	−2.5; −1.4	

Bone density scan results for total participants, group without FF and group with FF.
SD: standard deviation; CI: confidence interval.
* Independent student's *t*-test.

Table 5 Association of risk factors, laboratory data, bone density scan results, and FF. Crude prevalence odds ratios estimated by logistic regression analysis.

	Odds ratio	95% CI	Regression coefficient	*p*	VIF
Type 2 diabetes mellitus	2.001	1.098–3.681	.67	.031	1.028
CTX (ng/mL)	1.88	1.102–3.208	.554	.044	1.036
Maternal/paternal history of hip fracture	1.667	1.169–2.378	.497	.006	1.008
Age (years) [unit = 5]	1.39	1.289–1.500	.306	<.001	1.067
BMI (kg/m^2)	1.041	1.003–1.079	.054	.005	1.122
25(OH)D $\geq$ 30 ng/mL	.686	.507–.929	−.395	.011	1.02
Femoral neck *T*-score ≥ -2.5	.642	.458–.900	−.395	.011	1.133

CI: confidence interval; VIF: variation inflation factor.

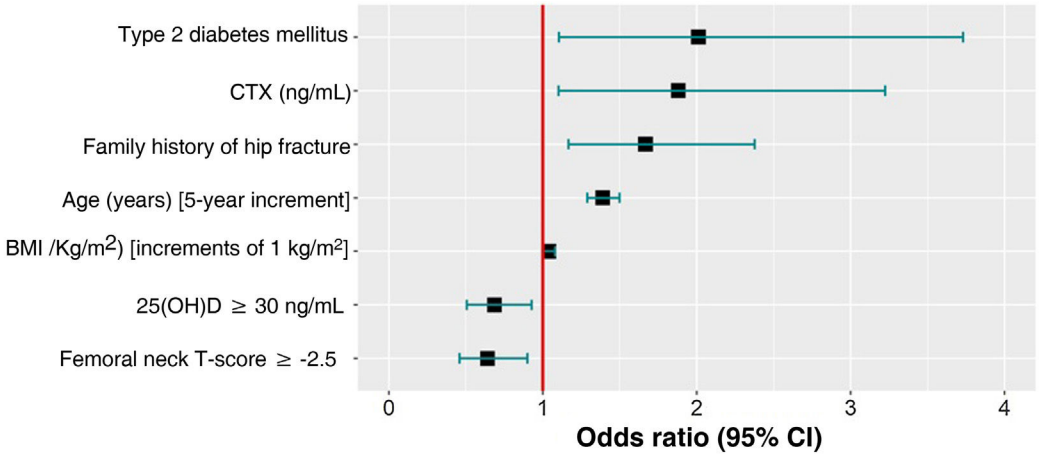

Figure 2 Odds ratio (OR) obtained from the logistic regression model.

the backward logistic regression model, for the independent variables.

Discussion

A significant relationship was found between previous diagnosis of type 2 DM, increased CTX, parental history of hip fracture, increased age, and BMI with the presence of FF. Conversely, a protective effect against FF was observed if 25(OH)D $\geq$ 30 ng/mL levels and a femoral neck T-score ≥ -2.5 were maintained.

The ratio of women to men (92.4% and 7.6%, respectively) in this study is common in bone metabolism units where OP is one of the main reasons for consultation.

In our series, 33.6% of the participants had a history of FF after the age of 50 years, higher than in other studies[1,8,18,19] probably due to their population characteristics.

There is controversy about the role of type 2 DM on bone health. For some authors, a previous diagnosis of type 2 DM is considered a BMD-independent RF for the onset of all types of FF.[9,10,20–22] We found a significantly higher proportion of participants with a previous diagnosis of type 2 DM in the patients in the FF group compared to the non-FF group (10.4% vs. 3.2% respectively), responsible for an increased risk for FF. As this is an RF, we do not know other clinical data of the disease that could influence its effect, and therefore these results are of limited value.

Elevated CTX levels, considering its wide variability, are associated with an increased risk of fracture in older women.[3,23,24] In our study, higher CTX values were observed in the FF group, and were significant in the multivariate model. The presence of acute fracture causes a transitory elevation of the bone modelling markers,[25] although because in our study we collected a history of fracture after the age of 50 years and not acute fracture, we consider that if there is acute fracture, its influence would be minimal.

Some studies highlight the relationship which exists between parental history of hip fracture[26–28] and age[5] as a BMD-independent RF which favours the onset of new FF. Our data are consistent in finding a significant association between parental history of hip fracture (25.5% compared to 16.7%) and greater age (70 years compared to 62 years) in the group with FF.

Although the relationship between OP and a low BMI[29] is well known, we found a significant relationship between an increase in BMI and FF. Other recent studies also point in this direction,[30,31] although it could be influenced by the association between obesity, physical exercise, and DM,[31] and specific studies are needed in this population subgroup.

Values of 25(OH)D above 30 ng/mL are significantly associated with a reduced risk of FF.[32,33] We found mean 25(OH)D levels of 26.3 ng/mL in patients with FF. Interestingly, 47.5% were receiving vitamin D supplementation, and nevertheless 35.2% had vitamin D levels <30 ng/mL. These data indicate the need to periodically assess 25(OH)D levels to keep them

within the current recommendations of international clinical guidelines.[34]

For each SD that reduces BMD in relation to the mean reference value, the relative risk of a fracture doubles compared to an individual with normal BMD,[35] although we must bear in mind that the results of the lumbar spine T-score may not be representative of the patient's real BMD status in certain situations, such as axis abnormalities (scoliosis), degenerative processes (osteoarthritis), surgical elements (osteosynthesis), among others.[17] In our series, only femoral neck T-score ≥ -2.5 was associated with a reduction in the risk of fracture.

The main limitation of our study related to its design as a retrospective observational case–control study. This makes it less internally valid than a traditional clinical trial, while a potential recruitment bias could not be avoided, due to the number of participants and the inclusion of each and every one of the patients attended during the established period of time, we consider that this potential bias is minimised. In addition, the data from our study in real clinical practice will be useful for decision making and to support the data obtained in traditional clinical trials.

Conclusions

In patients with FF, determining RF and certain clinical, analytical, and densitometric variables is a necessity to prevent further fracture. Maintaining a level of 25(OH)D $\geq$ 30 ng/mL and a femoral neck T-score ≥ -2.5 would act as protective factors, while a previous diagnosis of type 2 DM, elevated CTX, parental history of hip fracture, a 1 kg/m^2 increase in BMI, and 5-year age increment would predispose to FF.

Level of evidence

Level of evidence II.

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Authorship

AOA participated in the conception and design of the study, data collection and interpretation, and drafting the manuscript. MTMB, TFF, and GAB participated in the collection and interpretation of data and critical review of the intellectual content.

Conflict of interests

AOA, MTMB, TFF, and GAB have no conflict of interest to declare with respect to this manuscript. AOA has received speaker's honoraria for Theramex, Grunenthal Pharma, and Pfizer. MTMB has received speaker's honoraria from Lilly, GSK, Boehringer Ingelheim, Sanofi, and AstraZeneca. TFF and GAB have no conflict of interests to declare.

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