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Evaluation of the absolute risk of fracture by means of tool FRAX® in a Spanish cohort

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Date of receipt: 13/10/2010
Date of acceptance: 14/11/2010

SEIOMM work scholarship to attend the 31th Congress ASBMR (Denver, 2009)

Summary

The FRAX® tool has been developed as an aid to predict the 10-year probability of hip and major osteoporotic fracture using country-specific data. This algorithm combines clinical risk factors with or without the bone mineral density (BMD) measurement to identify subjects in high risk of fragility fracture. The aim of this study was to challenge the Spanish version of the WHO fracture risk assessment tool FRAX® on a cohort of women with BMD measurement indication.

*Methods:*Clinical and BMD data from a large population cohort taken from metropolitan area of Barcelona were used for this study. Inclusion criteria were: age range 40-90 yrs, clinical risk factors, femoral neck BMD T-score available and follow-up longer than 7 years. Main outcome was: major osteoporotic fracture at least 7 years after the first BMD measurement. The total number of predicted fractures by the FRAX algorithm was compared with the total number of new registered fractures during the follow-up time in the study population and expressed as observed - expected fracture (O/E) ratio. Results were stratified by age; BMD results and number of clinical risk factors were included in the FRAX algorithm.

Results: 8450 women were included, 69% were under 60 years and 14% presented a previous fracture. After follow-up, 10% had a major osteoporotic fracture. Wrist was the most incident fracture site and hip accounted only for 0.9% of the total. The 52% of the main fractures happened in women with none or only one risk factor. The fracture ratio (O/E) was 0.8 [CI 95%: 0.7 ; 1.1] for hip fractures and 3.1 [CI 95%: 2.8 ; 3.5] for the main osteoporotic fractures. The O/E ratio was lower as higher was the age of women (for those older than 70 O/E=1.9 [CI 95%: 1.6 ; 4.3]), longer the follow-up time (for those with more than 10 years O/E=2.7 [CI 95%: 2.2 ; 3.4]) or fewer number of risk factors (O/E=3.2 [CI 95%: 2.7 ; 3.9]).

Conclusions: The Spanish version of the FRAX® algorithm for this population is reasonably well adjusted to predict hip fractures but underestimates the observed main osteoporotic fracture incidence, independently of the T-score, and number of risk factors.

Key words: o*steoporosis, fractures, absolute risk, FRAX, double energy X-ray absorptiometry, DXA, Spanish population.*

Introduction

The preoccupation in the clinical management of osteoporosis with criteria for cost-effectiveness has shown up the necessity to improve the identification of the people who will benefit from specific treatment. This concern has stimulated the development of procedures for evaluating the risk of fracture using the principal risk factors.

The estimation of the risk of fracture is the most rational approach for taking therapeutic decisions regarding a patient with suspected bone fragility.

The group of experts in bone metabolism diseases who collaborate with the World Health Organisation (WHO) have developed an instrument for identifying those persons at highest risk of fracture in the period of 10 years subsequent to the evaluation. The new instrument, called FRAX®, combines the principal factors for risk of fracture with the alternative of incorporating measurement of bone mineral density (BMD) when this is available[1].

The FRAX® tool has been developed by a group of researchers led by Prof. John Kanis, with the support of many experts and scientific organisations. To facilitate its application the authors have carefully selected those risk factors which should be included, limiting them to those which have the greatest ability to predict fractures. The tool is accessible through an internet portal: (http://www.shef.ac.uk/FRAX).

Among those factors related to fractures, reduced BMD has been identified as one of the main ones due to its close relationship with bone resistance. Other factors have been identified which also contribute significantly to the risk of fracture. Notable amongst those are: family antecedence of fragility fractures, personal history of fragility fractures, low body weight, the habit of smoking and age. This last factor reinforces the negative effect of reduced BMD, or of other factors, it being one of the most significant predictors of fracture independent of BMD.

The degrees of risk which FRAX® uses for the prediction of osteoporotic fractures have been derived from the combination of multiple studies of the incidence of fractures in different cohorts. The studies of the incidence of femoral fractures are the most frequent, due to the fact that, in the majority of cases, these events require hospitalisation or surgical intervention, elements which are easily traceable in health records. With the object of compensating for the lower level of availability of data on other fractures, the FRAX® model assumes that the *ratio* between femoral fractures and other osteoporotic fractures is similar in different populations, accepting this *ratio* as a constant. This constant was obtained from studies carried out in the population of Mälmo (Sweden)[2,3].

This element which currently characterises FRAX® is presumed to allow the application of the model to different countries in which different incidences of hip fracture are recognised[4]. At present, version (3.1) of FRAX® allows the calculation of the absolute risk of fracture for the populations of 26 countries in 5 continents.

FRAX® estimates the risk of fracture for one of the four principal osteoporotic fractures, which are fracture of the proximal femur, of the wrist, of the proximal third of the humerus and vertebral fractures. The region of the femur receives special attention, with individualised evaluation, due to its clinical importance, and because of the greater quality of the epidemiological data.

With the aim of adapting the FRAX® model to the Spanish population, the authors have used information published on the incidence of proximal femoral fractures recorded in Barcelona (1984), the Canaries (1990), Zamora (1991), in prospective studies in Seville and Madrid (1989), and on the incidence in Cantabria with follow up over a long period of time[4]. A representation of a number of studies on the incidence of hip fractures in various regions of Spain is shown in figure 1, indicating those which were used in the development of FRAX®.

The importance of the application of the version of FRAX® for Spain in our community requires the validation of the tool.

The aim of this study is the assessment of the version of the FRAX® tool developed for Spain for the calculation of the individual's absolute risk of fracture over a period of 10 years in a cohort of the female population with indications for the carrying out of a bone densitometry (BD).

Material and method

The ability of the FRAX® tool designed for Spain to predict fractures was evaluated in a cohort of the female population followed in successive visits over a period of time longer than 7 years. The design corresponds to a retrospective longitudinal study. The cohort was made up of women older than 40 years of age with indications for bone densitometry and from whom had been gathered, during their follow up visits, information on the incidence of bone fractures.

During their first visit a BD of the hip and spine was carried out following a specific protocol, as well as a structured interview and a validated survey of calcium consumption. The results of the femoral bone measurements from the first visit and the clinical risk factors (CRF) considered by FRAX® were estimated.

Measurement of bone mineral density

The acquisition method was adjusted to the measurement protocol recommended by the makers of the measurement equipment, using the measurement of the region of interest in absolute values (g/cm^2) and as a T-score (comparison of the result of the measurement with respect to reference values obtained from the healthy Spanish population between 20 and 40 years of age). During the period of time covered by this study different measurement equipment was used from the same manufacturer Lunar Corp. - GE Healthcare Madison WI, US (models: DPX, DPX-L and Prodigy).

Population of the study

For the selection of the participants in the cohort the CETIR (Centre for Technical Studies with Radioactive Isotopes) database was used. This is a medical centre in the city of Barcelona dedicated to diagnostic imaging and in which bone densitometries using the technique of dual energy X-ray absorptiometry (DXA) have been carried out since 1989. The database systematically brings together the principal clinical risk factors and the BMD in the femoral neck since 1992.

At each visit questions from an epidemiological questionnaire were asked, taking anthropometric measurements. The questionnaire gathered data about family and personal history of osteoporosis, co-morbidity, treatments, period of application, bone fractures, smoking habits, consumption of alcohol and of calcium, calculating this last element using a questionnaire about eating habits. The indication for the measurement of BMD was made in accordance with the presence of CRFs, following the strategic lines of selective screening proposed by the clinical guides published in Spain and reports of the Catalan Agency for the Evaluation of Technology and Medical Research[5-7].

The inclusion criteria were: 1) female sex, 2) a measurement of bone mineral density having been taken in the proximal third of the femur, 3) availability of valid data from an epidemiological survey from the first visit, and 4) availability of follow up with more than one visit after the first baseline study, during a period of time which coincides with the period of up to 10 years foreseen by the FRAX® tool, after the first visit.

Table 1. Clinical risk factors. Percentages of the total cohort analysed

Clinical risk factors		n	%
Age (years)	< 60	5,831	69.0
	60-69	2,267	26.8
	≥ 70	352	4.2
Body mass index (kg/m^2)	< 25	3,317	39.3
	25-30	3,741	44.3
	> 30	1,392	16.5
Family antecedents of fractures		2,101	24.9
Personal antecedents of osteoporotic fractures		1,146	13.6
Corticoids		254	3.0
Rheumatoid arthritis		74	0.9
Current smoking habit		596	7.1
Alcohol consumption		3	--
T-score in femoral neck	>-1	2,745	32.5
	-2.5 a -1	4,490	53.1
	<-2.5	1,215	14.4
Number of risk factors:	0	124	1.5
	1	4,733	56.0
	2	2,901	34.3
	3	583	6.9
	≥ 4	109	1.4

Using these criteria a cohort of women was selected in whom had been carried out measurements of BMD in the upper third of the femur between January 1992 and February 2009, using the aforementioned DXA (dual energy X-ray absorptiometry) densitometers.

All the BD examinations were carried out within a set protocol in which were recorded the biographical data of the patient, information about the method used in the DXA measurement, indication of the test, medical report, questionnaire on the presence of principal clinical risk factors, toxic habits, lifestyle, gynaecological history, treatments and intake of calcium calculated by means of a questionnaire about the dietary use of the main foods which contain calcium, and its frequency. The main variable of the study was the presence of fragility fractures observed during the follow up. At each visit the patient was asked about the number and location of fractures which had occurred since the last visit. The osteoporotic fractures which FRAX® assesses are found in the upper third of the femur, in the vertebrae, in the wrist and in the humerus. Other fractures attributed to bone fragility, such as those of the pelvis, ribs, fingers, etc., were not considered in this study[3]. The vertebral fractures recorded were always those which

Table 2. Estimation of the hazard *ratios* of total fracture of the principal risk factors

Variable	HR	CI 95%
Age (≥ 60, < 70 years)	2.0	1.7 ; 2.3
Age (≥ 70 years)	2.5	1.9 , 3.3
Family antecedence of osteoporosis or fracture	1.1	1.0 ; 1.3
Secondary osteoporosis	2.3	1.7 ; 3.1
Rheumatoid arthritis	2.7	1.7 ; 4.3
Antecedents of osteoporotic fractures[1]	1.5	1.2 ; 1.9
Corticoids	2.0	1.5 ; 2.7
Nuliparity (no gestation of more than 6 months)	0.94	0.8 ; 1.2
No maternal lactation	1.1	0.9 ; 1.2
BMI: overweight or sedentary obesity (≥ 25 kg/m^2)	1.2	1.1 ; 1.4
Sedentariness	1.2	1.0 ; 1.4
Tobacco consumption: active smoker	0.8	0.6 ; 1.1
Low daily intake of calcium (<500 mg/day)	0.8	0.6 ; 1.0

1: personal antecedence of fracture of the humerus, forearm, vertebra and/or hip.
HR: hazard *ratio*; IC 95%: confidence interval of 95%

could be confirmed by radiography or by analysis of vertebral fracture using DXA. The diagnosis of vertebral deformity fractures was carried out using Genant's semi-quantitative method, which is used to diagnose vertebral deformity when there is a loss of one of the three vertebral heights of the vertebral body (using the lateral projection) of at least 20%. The method classifies the fractures according to type of deformity and their severity (a reduction of 20-25% in anterior, medial or posterior height, Grade I or light; loss of 25-40%, Grade II or moderate; and if the loss is higher than 40%, Grade III or severe)[8].

Fractures associated with moderate or severe trauma were excluded. The result of the BMD was recorded as a T-score and stratified in three categories: normal BMD (T-score >-1); low bone mass (T-score between -1 and -2.5); and osteoporosis (T-score <-2.5).

The personal history recorded any pathologies which the patient had suffered and the drugs they were consuming or had consumed, as well as the personal and family history of osteoporotic fractures and of osteoporosis. With the aim of adapting to the FRAX® model, those pathological antecedents which contribute secondarily to the reduction of bone mass (hyperparathyroidism, diabetes *mellitus*, anorexia nervosa, anaemia, hyperthyroidism, gastrectomy, etc.) were selected. Antecedence of rheumatoid arthritis, or the intake of glucorticoids were recorded in a differentiated way. Data on gynaecologicial history were registered, such as age of menarche and age of menopause, number of gestations (of over 6 months), maternal lactation and antecedence of hysterectomy continued to be recorded. Finally, the following variables were taken into account: level of physical activity (sedentariness, yes/no). Consumption of tobacco (active smoker, ex-smoker or non-smoker) and daily intake of calcium (expressed in mg/day).

The probability of proximal femoral fracture and of the main regions of the skeleton were calculated for each woman using the FRAX® tool in its version for Spain.

Statistical analysis

An initial descriptive analysis was carried out, calculating the frequencies and percentages for each of the categorical variables. For the quantitative variables the average and standard deviation (SD) was calculated. To determine the association between the different risk factors and the study's main variable (osteoporotic fracture), the relative risk (RR) was calculated with the confidence interval (CI) corresponding to 95%, using the Cox model. To evaluate the predictive capacity of the FRAX® model the *ratio* of the fractures expected from the model, as a result of the sum of the probabilities of fracture for each patient, to the number of fractures observed in the follow up period was calculated. Similarly, the ROC (Receiver Operating Characteristics) curves were estimated to evaluate the capacity to predict fractures using solely the CRFs or the measurement of BMD, and the FRAX® tool which combines the CRFs and the measurement of the BMD in the femoral neck.

The results are considered to be statistically significant with p value of $p<0.05$. The statistical software package Stat 11.0 for Windows was used for the management of the data and in the statistical analysis.

Results

The CETIR database includes 190,939 records of first BD carried out in different women from January 1992 to February 2008. Applying inclusion and exclusion criteria, a sample was obtained of 171,408 (90%) women, of whom 50,106 (29%) had at least one follow BD.

A follow up of 5-6 years was reached in 14.9% of cases, of 7-8 years in 9.3%, 9-10 years in 4.8% and over 10 years follow up in 2.8% of cases. With the aim of having a sufficient number of cases the decision was taken to position the minimum threshold for follow up at 7 years after the first visit, with 17% (8,450 women) complying with this requirement. The average period of follow up in the cohort selected was 9.2 years (7-14.5 years).

The average age was 55.9 years (±7.4 SD). 69.1% of the cohort were younger than 60 years of age and only 4.2% were more than 70 years of age. The average age of onset of menarche was 13 years (±1.6 SD) and the average age at which menopause had started was 46.4 years (±5.9 SD).

A description of the principal risk factors for osteoporosis are shown in table 1. It is notable that 24.9% had family antecedence of osteoporosis or of osteoporotic fracture, and 3% had taken corticoids. 13.6% of the women included in the study were found to have had at least one antecedent osteoporotic fracture. The most frequent fractures prevalent were those of the forearm (627 fractures), the antecedent which, out of the whole sample, is present in 7.4% of the cases. In relation to obstetric history, 12.9% had had no gestation of over 6 months and 40.2% had not had maternal lactation on any occasion.

The description of the modifiable risk factors shows that 39.2% of the women studied had a BMI lower than 25 kg/m^2, and 70.6% had a level of physical activity which was sedentary, or of low intensity. 7.1% declared themselves to be active smokers, and 7.7 said they had a daily intake of calcium lower than 500 mg/day.

With respect to the measurement of BMD in the femoral neck, 14.4% of the cohort was classified

Table 3. *Ratio* of total observes fractures to those predicted with the FRAX® model

Total	OBS	PRE	O/P	CI 95%
	842	353	2.4	2.1 ; 2.7
BMD				
Normal	184	57	3.2	2.4 ; 4.4
Osteopenia	449	178	2.5	2.1 ; 3
Osteoporosis	209	117	1.8	1.4 ; 2.2
Age				
< 55	275	101	2.7	2.2 ; 3.5
55-65	354	143	2.5	2 ; 3
65-75	201	100	2.0	1.6 ; 2.6
≥ 75	12	8	1.4	0.5 ; 4.3
Risk factors				
< 2	443	138	3.2	2.7 ; 3.9
2-3	373	203	1.8	1.6 ; 2.2
≥ 4	25	12	2.0	1.1 ; 4.9

OBS: observed. PRE: predicted. O/P: observed/predicted *ratio*. CI 95%: confidence interval of 95%. Risk factors: BMI<20, personal antecedence of fracture, family antecedence of fracture, smoker, rheumatoid arthritis, corticoids, secondary osteoporosis and alcohol

Table 4. *Ratio* of hip fractures observed to those expected with the FRAX® model

Hip	OBS	PRE	O/P	CI 95%
	72	88	0.8	0.6 ; 1.1
BMD				
Normal	7	2	2.7	0.6 ; 12.1
Osteopenia	34	34	1.0	0.6 ; 1.6
Osteoporosis	31	51	0.6	0.4 ; 0.9
Age				
< 55	8	14	0.6	0.2 ; 1.4
55-65	31	31	1.0	0.6 ; 1.6
65-75	31	37	0.8	0.5 ; 1.3
≥ 75	2	5	0.4	-0.2 ; 3.2
Risk factors				
< 2	38	32	1.2	0.7 ; 1.9
2-3	29	51	0.6	0.3 ; 0.9
≥ 4	5	4	1.2	0.1 ; 25.6

OBS: observed. PRE: predicted. O/P: observed/predicted *ratio*. CI 95%: confidence interval of 95%. Risk factors: BMI<20, personal antecedence of fracture, family antecedence of fracture, smoker, rheumatoid arthritis, corticoids, secondary osteoporosis and alcohol

as osteoporotic, and 53.1% showed reduced bone mineral density (T-score between -1 and -2.5).

In the information collected during the follow up regarding specific antifractural treatments (with calcitonin, hormone replacement therapy, oestrogen receptor modulators, tibolone, etidronate, alendronate, risedronate and strontium), distinct from calcium and vitamin D, can be seen in 13.0% of women aged less than 55 years received one of the therapies indicated; in the group between 55 and 65 years of age 18.5% received some type of treatment; those between 65 and 75 years of age, 19.6%; and in women over 75 years of age 35.7% were treated. Overall, 16.2% of the cohort received antifractural treatment with at least one of these therapeutic agents during the follow up period. In terms of calcium and vitamin D supplements, what is notable is the progressive increase in the number of patients treated according to age. Among women aged below 55 years 12.9% received supplements; of those between 55 and 65 years, 24.1%; of those between 65 and 75 years, 35.8% and in women older than 75 years, 50.0%.

Figure 2 shows the results of the BMD, stratifying the cohort by baseline age of the patients. The BMD (and the T-score) diminished inversely with an increase in the age of the population. At the start of the decade of the 50s, 5.4% of the cohort was classified as osteoporotic (T-score equal to or lower than -2.5), reaching 46.0% in those women over 70 years of age.

In the follow up, 10.0% of the patients suffered an osteoporotic fracture in one of the principal regions of the skeleton (proximal femur, vertebrae, humerus, forearm). The forearm was the region which suffered a high incidence of fractures (4.5%), while the upper third of the femur only represented only 0.9% of the total. 9.1% of the women who did not have less than two risk factors suffered an osteoporotic fracture. On the other hand, 22.9% of the women who had four or more risk factors evaluated with FRAX® suffered from one of the principal osteoporotic fractures. The rate of incidence of fractures in the cohort of the Spanish population is 11 fractures/1,000 patients/years.

Table 2 presents the relative risk for the different factors studied in relation to the risk of fragility fracture. An age of over 70 years is the factor which has a hazard *ratio* (HR) of greatest magnitude (2.5 [CI 95%: 1.9 ; 3.3]), followed by antecedence of rheumatoid arthritis, secondary osteoporosis, consumption of corticoids and personal history of osteoporotic fracture.

Tables 3 and 4 show the principal fractures, and those of the hip, observed during the follow up and those expected according to the FRAX® model. The *ratio* of the hip fractures observed to those predicted by FRAX® is similar (O/E = 0.8 [CI 95%: 0.6;1.1]). For the main osteoporotic fractures, the number of fractures observed is a little more than double that foreseen by the FRAX® model (O/E = 2.4 [CI 95%: 2.1; 2.7]). This underestimation is reduced among women of greater age or with a greater risk of fracture.

Figures 3 and 4 show the ROC curves and the area under the curve when the predictive capacity of the FRAX® models and of the BD is estimated. In this cohort the two measurements have an area under the ROC curve similar to that for the hip fracture, 0.77 and 0.74 respectively. Whereas, for the total fractures the result is slightly lower (FRAX® model = 0.62 and BD = 0.61).

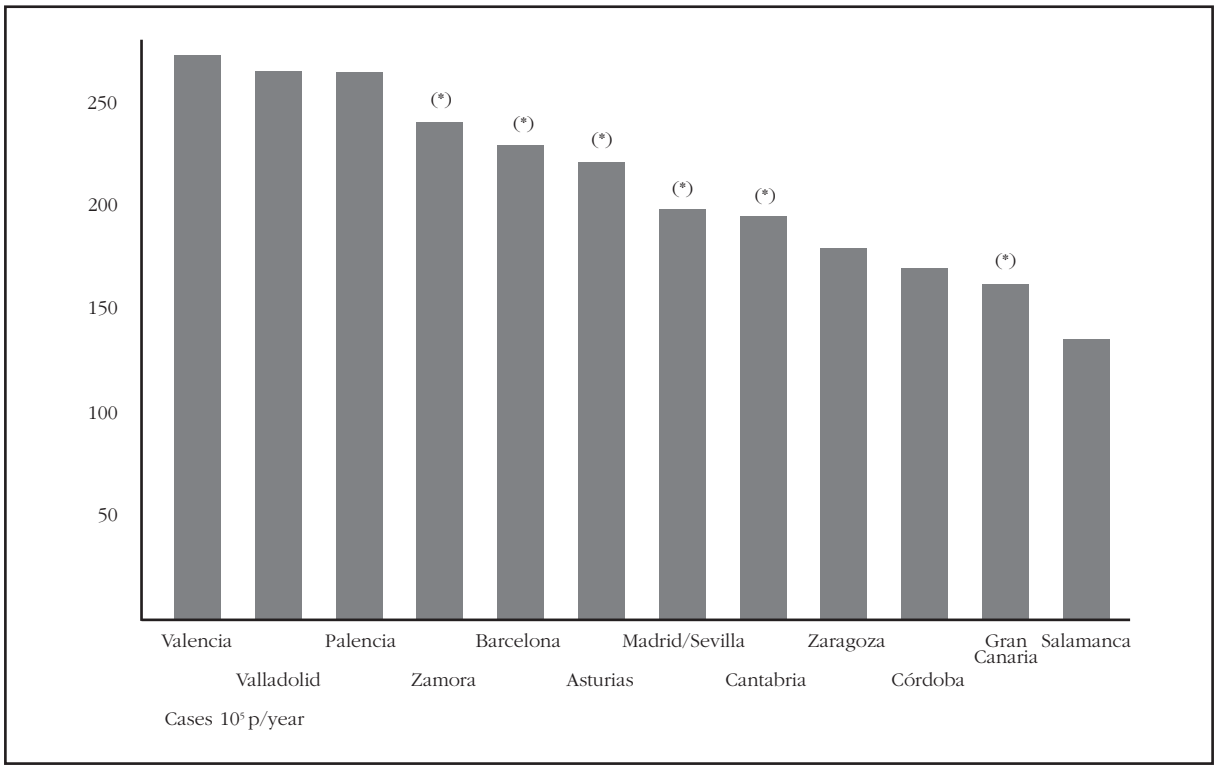
Discussion

The development of the FRAX® tool is, without a doubt, a significant advance in the clinical management of osteoporosis. From a practical point of view it is certainly an achievement to be able to estimate the risk independently of the measurement of bone density, but a calculation would be better. In the current version, the bone measurement is limited to a single region of interest, the femoral neck. This element may, potentially, limit the capacity of the tool to identify subjects with high risk. Another controversial characteristic is the assessment of the CRFs; some of these are assessed globally, such as history of previous fractures (no matter if they be single or multiple) or the accumulated dose of corticoids. Its application remains limited to women who have not received earlier treatment. Despite these limitations, it represents an instrument designed to help the taking of therapeutic decisions which has enormous potential in the approach to osteoporosis in Spain[9]. As with any new method or instrument, its application in our community needs to pass through a process of validation and adjustment.

The validation of the FRAX® model means checking that the number of fractures predicted coincides with the number of fractures actually occurring over the period of 10 years. In addition, the process of evaluation of the fractures which occur requires prolonged and complex follow up with large sample sizes. Since its recent promulgation there have been studies in other countries aimed at the validation of FRAX®. On this basis an appropriate way of using the FRAX® tool in the Canadian population has been proven. In turn, in a group of the French population, the female cohort of the OFELY study, it can be seen that the incidental fractures observed over a period of 10 years showed a relationship with the age of the patients, and with low BMD similar to that foreseen by the FRAX® tool. However, in women aged over 64 years with low bone density (T-score <-1), FRAX® undervalued the number of fractures predicted by 48% in relation to those observed in this cohort, which requires a revision of the algorithm to adjust it to the French population[10-12].

In this retrospective follow up study in a broad group of the Spanish population the *ratio* of the rate of fractures observed to those predicted by the FRAX® tool (O/E) for the region of the femur is 0.8% [CI 95%: 0.6; 1.1], a value close to the "ideal" scenario in which the number of fractures predicted by the FRAX® toll is similar to the number of fractures observed in the Spanish population. Various plausible explanations may be offered

Figure 1. Studies of incidence of femoral fracture in different regions of Spain



which would justify this performance in hip fractures, such as maybe the significantly higher average age of the femoral fractures, the limiting of mobility after this type of fracture, as well as the known fact of the increase in mortality, which together would impede the prolonged follow up of these patients. However, the small proportion of cases of fractures of the femur in the cohort studied necessitates caution with the projection of the result.

Advanced age and reduced BMD (lower T-score) are factors associated with a higher rate of osteoporotic fractures, including those of the femur. BMD stands out as one of the principal risk factors, with a greater predictive capacity of new fractures than the other CRFs, although with FRAX® it is seen as an optional factor, since there is still limited access to bone densitometry for wide sections of the population.

In the evaluation of its diagnostic performance by estimating the sensitivity and specificity (ROC curves) of the FRAX® model in which are combined the CRFs and BMD, a slightly better performance can be seen when CRFs and BMD are combined, compared with the use of BMD alone, although the difference is small (area below the curve of 0.77 vs 0.74 for hip fractures, and 0.62 vs 0.61 in the principal osteoporotic fractures) in relation to that originally developed based on a Swedish population[2].

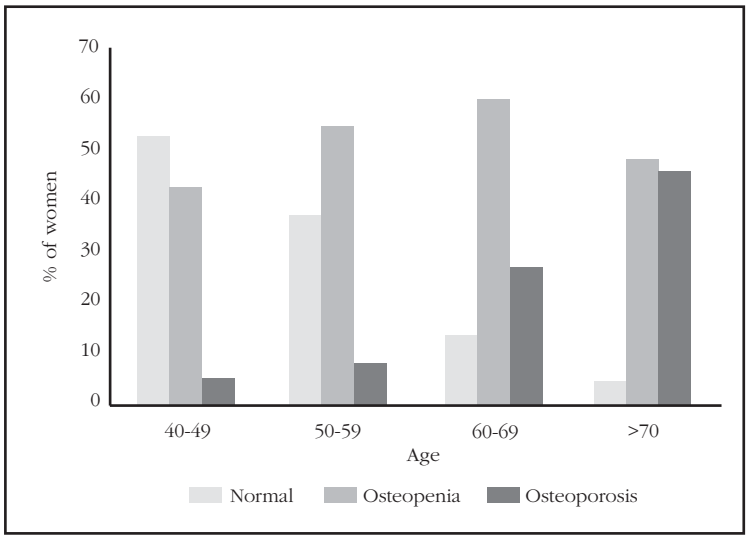
In vertebral fractures, those cases which have been confirmed by radiography have been used. From 1998, the response protocol in medical centres considered the carrying out of an analysis of vertebral fractures by means of a DXA study (thoracic and lumbar spine lateral projection) in those cases where there was a reduction in height of greater than 2 cm compared to an earlier visit, of 4 cm compared to historic height remembered by the patient, or suspicious evidence in the PA projection of the lumbar spine. All in all, it is assumed that a proportion of vertebral fractures are not recorded in the follow up period.

The number of fractures recorded in the follow up period probably could have been higher if the patients had not received treatment, or if all the vertebral fractures had been recorded. In spite of the fact that the cohort was selected on the basis of indications for bone densitometry, the number of patients who received some kind of antifractural therapeutic agent was relatively modest (20.7%), and similar to the percentage of patients in which this was accompanied by calcium of vitamin D supplements (23.2%).

The rate of principal osteoporotic fractures observed was higher than the level of fractures predicted by FRAX® (observed, 842 vs predicted, 353), O/P *ratio* = 2.4 [CI 95%: 2.1 : 2.7]. The undervaluation of fracture in the main regions of the skeleton was independent of the T-score reached, or of the number of CRF's present.

The O/P fracture *ratio* maintained an inversely proportional relationship to the age of the women, such that at greater ages the difference between observed and predicted fractures tends to dimi-

Figure 2. Percentages of women with osteoporosis as a function of their age



nish. It is also observed that there is a slight reduction in the difference when the follow up period is longer (in the follow up periods longer than 10 years the O/P = 2.7 [CI 95%: 2.2 ; 3.4]) or when a high number of risk factors coincide (for those cases without any risk factors O/P = 4.2 [CI 95%: 3.5 ; 5.3]).

The FRAX® model evaluated predicts the principal fragility fractures in only a third of patients evaluated. There are, at the moment, no other studies which evaluate the performance of FRAX® in our population applying a similar method. Despite this, it is interesting to highlight the fact that this tendency has also been observed in the ECOSAP study[13,14]. In this study a follow up was made over 3 years of a cohort composed of 5,201 women. The application of FRAX® showed some similar results, despite the fact that the methodology used was different. The quantitative ultrasound method was used for the bone measurements and the follow up period was less. The authors confirmed a good performance for FRAX® for femoral fractures with a O/P fracture *ratio* ≈ 1, but maintaining an underestimation of risk of principal osteoporotic fractures with a O/P *ratio* ≈ 2.

The fact that there is a coincidence in the incidence of femoral fractures, and a high coincidence with the average rate of hip fractures which come from the epidemiological studies selected for FRA® in Spain can be deduced from The performance of FRAX® in the two cohorts of Spanish women. Similarly, both studies indicate that the FRAX® tool does not properly estimate the global risk of fracture (principal osteoporotic fractures).

In the absence of consistent epidemiological studies on the incidence of other fragility fractures, both studies suggest that the relationship between femoral fractures and the principal osteoporotic fractures in our population is different to that applied by the FRAX® model originating in Sweden[2,3].

The number of women who have been subject to such a prolonged follow up only consist of 17% of those women in whom a first BD was carried out. This small share of patients is due in great measure to the selection of the patients. Those women who display the most risk factors or who have a more precarious state of health receive greater medical attention, and therefore a closer follow up.

On the other hand, the suspicion that not all fractures occurring in the cohort were recorded (especially vertebral fractures) and the potential protective capacity of the specific treatments which were followed for some time of the follow up period by 19.5% of the cohort, gives support to the idea that the O/P fracture *ratio* could be even more unbalanced.

One aspect not considered in the results of this study is the performance of FRAX® in the Spanish male population. The validation of the FRAX® model in the female population, which deals with CRF and BDM measurements, means that the prediction of fractures in a prolonged period of time coincides reasonably well with the rate of fractures observed. At present, the model developed for Spain has performed as an imperfect tool which needs to be adapted for its application in our population.

Conclusion

The WHO's method for arriving at the rate of osteoporotic fractures in Spain is, in general, consistent with the observational clinical data for femoral fractures. However, the current version of the FRAX® tool underestimates the incidence of the other osteoporotic fractures, independently of the T-score, the number of risk factors and the follow up time. What is required, therefore, is a greater number of epidemiological studies of the incidence of the principal osteoporotic fractures to explain these differences.

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Figure 3. Area under the ROC curve from the FRAX® model (curve configured by means of points joined by lines) and the result of the BD (bone density, in the point curve graph) for hip fracture

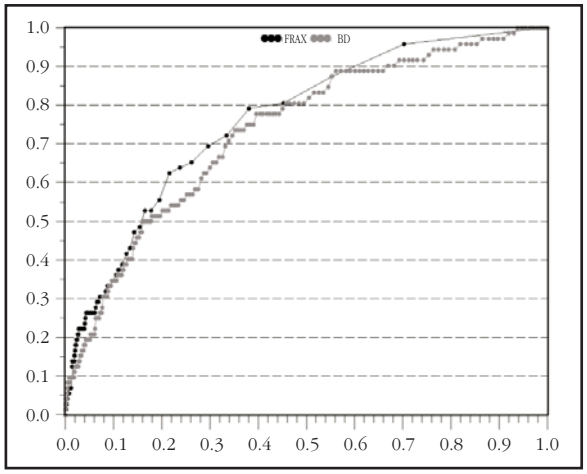
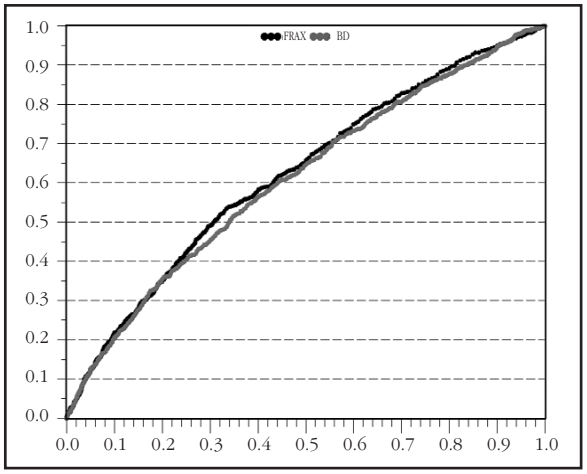


Figure 4. Area under the ROC curve from the FRAX® model (coloured black) and the result of the BD (bone density, coloured grey) for the total of fractures



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