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Risk of fracture in the FRODOS cohort. Comparative study of the application of the Spanish, French, British and Swedish FRAX® models

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Summary

Background and objectives: Studies on the validation of FRAX® in Spain show an underestimation of the risk of principal osteoporotic fractures (POFs) and more accurate predictions for femoral fractures (FF). It has been suggested that this algorithm may be improved with more specific data on the epidemiology of these fractures in Spain. The objectives of this work were to describe the baseline risk of fractures according to the Spanish FRAX® model in the participants of the FRODOS cohort, and to compare these data with the application of other European models of FRAX® in the same cohort.
Methods: Observational study in a population cohort of 2,968 postmenopausal women (59-70 years of age). The online desktop version of FRAX® was used for multiple data entries to calculate the risk of POFs and FFs at 10 years using the Spanish, French, British and Swedish models in the same cohort.
Results: The lowest risk corresponded to the Spanish model: FF: 1.22% (36 expected fractures) and POF: 5.28% (n=197), while the highest risk was for the Swedish model: FF: 3.15% and POF 13.51% (n=401). The models for France and the United Kingdom had intermediate values.
Conclusion: In a Spanish cohort of 2,968 postmenopausal women the percentage risk of expected fractures at 10 years increased following a south-north latitude gradient when different European FRAX® models were applied. The results for the incidence of fractures on the FRODOS cohort predicted for the coming years will confirm, or not, the usefulness of this analysis.

Key words: *FRAX, osteoporosis, risk of fracture.*

Introduction

Osteoporotic fractures are one of the principal causes of morbidity in postmenopausal women in the industrialised nations.

If to this morbidity are added the predicted aging of the population and the exponential increase in the direct and indirect costs resulting from the diagnosis and treatment of osteoporosis, according to the assessment provided by models of health economics, it may be confirmed that this disease constitutes a significant public health problem[1].

It is for these reasons that for more than two decades various research groups have created different tools to optimise the diagnosis, calculate the risk of associated and secondary fracture, and improve the prevention and treatment of osteoporosis[2]. One of the most widely-used tools is the FRAX® index[3].

The FRAX® model is a computer algorithm created for the prediction of the absolute risk of osteoporotic fractures at 10 years for men and women between 40 and 90 years of age. It is based on an arithmetic formula (not publicly available) which combines the weightings of different clinical risk factors, to which calculation it is possible to add, or not, values for bone mineral density in the femoral neck. Finally, all this is adjusted automatically to the rates of fracture and expected deaths for each country, according to the results obtained from the original cohorts[3]. The expression of the risk of fracture is grouped into two categories: femoral fracture (FF) and principal osteoporotic fracture (POF), a category which includes femoral fracture, plus clinical vertebral fractures, proximal fractures of the humerus and Colles, or distal forearm fractures.

This model was developed under the auspices of the WHO at the Centre for Bone Metabolic Diseases at the University of Sheffield (UK), and used 9 different population cohorts (US, Asia, Australia and Europe including Spain). To date 58 models have been produced, adjusted for 53 countries, including most of the countries of Europe and North America, but also the other continents[4].

Studies evaluating the FRAX® model in the Spanish population have tended to disagree, since expected fractures appear to be underestimated when compared to those actually observed, especially with the POFs, while the results for the FFs alone are more consistent[5-7]. The hypotheses for explaining this disagreement, as suggested in an editorial specifically on this subject[8], would indicate that its principal cause is that the Spanish version for the calculation of risk at 10 years for POF uses data extrapolated from the original Malmö cohort (Sweden), while for the calculation of risk of FF, its own data was used. Other explanations for these disparities could be the different baseline risk for osteoporosis in each cohort, the loss of cases during follow up, as well as the small total number of fractures observed[5-8].

In spite of these drawbacks, the use of this index has become widespread, and has also generated Spanish studies which describe in an isolated way the prevalence of factors included in FRAX®[9,10], the influence of the index at the point of prescribing drugs[11], or which compare the usefulness of this index with densitometry to calculate risk thresholds for fracture[12-14].

As already mentioned, the published results of research and the opinions of experts suggest that the Spanish version of FRAX® could be improved. On the other hand, the underestimation of fractures observed compared with those expected using the index indicates that the epidemiology of the fractures in Spain would be closer to those of European countries with a higher incidence of fractures. For these reasons, we decided to apply the Spanish FRAX® model to a prospective cohort from our country (FRODOS) and compare their results with those obtained by applying to the same cohort different European FRAX® models such as those of France (as the closest country), of the United Kingdom (having an intermediate rate of fractures) and of Sweden (having the highest rate of fracture in Europe).

Methodology

The FRODOS (FRacturas Osteoporóticas De OSona) cohort, designed for the study of risk factors for fragility fractures, is formed of 2,968 postmenopausal women (aged between 59-70 at the time of recruitment) from the general population of the region of Osona (Barcelona). The FRAX® risk was calculated using the baseline data of this cohort, created between the years of 2006 and 2008. The cohort is populational, the selection of the sample was randomised by municipality of residence and did not exclude participants under active antiosteoporotic treatment, nor those with diseases which could have affected bone metabolism[15-16]. The participation index was 71.1%, with 2,968 subjects out of a total 4,175 having been invited to participate. Information gathered from the women participating in the cohort included: a clinico-epidemiological questionnaire which recorded, among other things, all the FRAX® variables, as well as lumbar and femoral dual X-ray densitometry (DXA), vertebral morphometry (MXA) and determination of the baseline for markers for bone turnover.

To calculate the risks at 10 years of POF and FF in Spain, France, the United Kingdom and Sweden the on-line desktop version of FRAX® for multiple data entry was used, which allowed the entry of the original computerised database, and the performance of the required analysis. For each woman the estimated probability of POF and FF was calculated following the model for each country. The expected fractures were the result of the sum of the probabilities for each patient. The risk factors used to calculate this index were: age, weight, height, previous fractures (including the presence of morphometric vertebral fractures), family history (father or mother) of hip fracture, smoking habit, use of glucocorticoids, diagnosis of rheumatoid arthritis, alcohol consumption, bone mineral density (BMD) – T-score measured in the

femoral neck and secondary osteoporosis, defined as the presence of at least one of the following pathologies: diabetes type 1, hyperthyroidism, premature menopause, malnutrition and chronic hepatopathy.

Statistical Analysis

A descriptive analysis was carried out in the sample, calculating the frequencies and percentages of each of the categorical variables. For the quantitative variables the mean and standard deviation were calculated. The statistical software package IBM SPSS Statistics version 20 was used for the analysis.

Results

Table 1 shows the baseline characteristics of the 2,968 participating women. To this information one needs to add the fact that 19% (n=563) were receiving some kind of antiosteoporotic treatment. The mean age was 65.50±3.57 years, and body mass index 28.28±4.9 kg/m^2. One in five participants had an earlier fracture, and little more than 5% were taking oral glucocorticoids. 3.1% of the women were smokers and 0.5% had rheumatoid arthritis. Finally, 26.7% of the women (n=791) had some process labelled according to the FRAX® criteria as secondary osteoporosis. The mean T-score in the neck was -1.18±0.98, which corresponds with osteopenia according to WHO criteria.

Table 2 shows the probabilities with a confidence interval of 95% of suffering FF and POF at 10 years in the FRODOS cohort using the FRAX® models for Spain, France, the United Kingdom and Sweden. The lowest probability corresponded with the Spanish model, and the highest with the Swedish.

The POF/FF relationship was 4.36 for Spain, France and Sweden, while for the United Kingdom it was 5.98.

Finally, the characteristics of the Spanish cohorts for which the FRAX® index is available are described in Table 3.

Discussion

This study describes in the Spanish cohort of FRODOS (a prospective cohort of 2,968 postmenopausal women) the clinical risk factors which the FRAX® model includes and the derived risk of suffering an osteoporotic fracture in 10 years. The innovative aspect is the comparison with the results of expected fractures not only applying the Spanish model but also the French, British and Swedish model to the same cohort.

For the creation of the FRAX® index, data from different prospective European, Asiatic and North American cohorts were used which included the analysis of events from more than a million people/year. The popularisation of this this index is evident from the fact that its use has generated hundreds of articles, and FRAX® has been included in different guides to clinical practice[17].

However, while recognising the merits of this initiative for its daily clinical application, Siris and Delmas, already in 2008, also subscribed to the view that the importance of FRAX® would lie in formulating new health-economic strategies for the prevention and treatment of the risk of fractures in each country, even though the non-availability of adequate epidemiological data, and the use of derived or indirect data would increase the possibility of its inappropriate use[18].

The Spanish FRAX® model currently in use was created with Spanish mortality data and studies of the incidence of hip fracture carried out in Barcelona, Seville, Madrid, the Canary Islands, Cantabria and Zamora, while the calculation of the POF, with no Spanish data available, used the FF/POF relationship derived from the Malmö studies, which was 0.60 (6.98/11.6)[5].

Without denying the merit of their having been the first works which recorded in an organised way the epidemiology of femoral fractures in our country, the representativeness of the Spanish cohorts included in the original development of FRAX® has been questioned, principally for not using in all cases population-based studies, but also due to the low number of individuals and events included, and the great variability in the incidence of fractures between the different autonomous communities of Spain[8,19].

Ideally, in order for a model for the prediction of clinical risk such as FRAX® to be used with confidence in daily clinical practice it ought to comply with at least two conditions: having demonstrated its validity in other population groups similar to the original ones; and helping to resolve problems for users less experienced in the field of osteoporosis, be they general practitioners or health care planners[20-22]. It is evident that if the first point is not complied with there should not be a move towards the generalisation of its use since we would be doing this on an inappropriate basis[2,8,17,20-22]. The Spanish FRAX® model has been evaluated in three cohort studies[5-7] which clearly differ, but which, in having a sufficient number of participants and events, agree in their conclusions: the Spanish FRAX® model clearly predicts a lower number of POFs than are observed, while the prediction of FFs is somewhat closer to what actually happens; however, the predictive power measured by the area under the curve of the ROC curves is no higher than 70%. Other cohorts such as those from the ESOVAL[10] study and our cohort, FRODOS are in the follow up phase and their results are expected in the next few years.

To obtain the results commented on in this work the software for multiple entries facilitated by the FRAX® licence was used, which avoided predictable errors generated by manual entry. In applying the Spanish FRAX® model to the FRODOS cohort the baseline risks of fracture expected at 10 years were 1.22 and 5.28% for FF and POF respectively. These results are lower than those reported in the ECOSAP study which were 3.67 and 8.78% respectively[5], slightly higher than those of the FRIDEX cohort, 0.95 and 3.8%[7], and similar to those of the Valencia group (1.9 and 5.5%)[10],

while Tebé et al. reported only the risk for POF, which was 4.6%[6]. These disparities and similarities may be explained mainly by the different average ages, which is to say, the higher the age the higher risk, and vice versa, while the cohorts with average ages of around 65 years had intermediate results.

On the other hand, the asymmetric prevalences of the risk factors may also add to the explanation of these differences[8].

In applying the French model of FRAX® to our cohort, chosen for geographic proximity and epidemiological similarity, risks for FF of 1.54% and for POF of 6.64% were found. Although these probabilities are slightly higher than those found with the Spanish model, the results are superimposable at confidence interval of 95%. However, the application of the British model does increase slightly the possibility of FF, duplicates the prediction of POF, while the Swedish model shows nearly a three-fold increase in the prediction of both types of fracture. It is worth remarking that the FF/POF relationship was 0.23 in the Spanish, French and Swedish models, while in the British it was 0.16. This would confirm that the Spanish and French models apply the aforementioned Swedish formula, while the British model would use its own formula.

To try to overcome the absence of FRAX® models, in some areas applications from other countries have been used with their local cohorts. In Poland the British model was used in a study of 500 women to evaluate an overestimation in predictions[23], while a study carried out in Denmark applied the Swedish tool with an excellent correlation between events observed and predicted[24]. On the other hand, a recent update of the Italian FRAX® model revealed notable changes in the risks for FF, and thus, in the FF/POF relationship. In the discussion the authors indicate the importance of having coherent data and models[25]. Among these authors is John Kanis, one of the creators of the FRAX® model and defender of the validity of this system against various criticisms it has received[26].

Thus, in the search for new options to improve the understanding of the epidemiology of osteoporosis in Spain and increase the options for strategic approaches to this pathology, we present the baseline risk of expected fractures in our cohort using the Spanish FRAX® model, along with a comparative exercise by applying the models of other European countries. These results will see their true relevance when compared with the incidence of fractures in the coming years.

Table 1. Baseline characteristics of the women in the cohort FRODOS

Age (years), mean ± SD	65.50±3.6
BMI (kg/m²), mean ± SD	28.68±4.9
Previous fracture, n (%)	646 (21.8%)
Family history of fracture, n (%)	659 (22.2%)
Smokers, n (%)	92 (3.1%)
Consuming alcoholic beverages, n (%)	42 (1.4%)
Treatment with glucocorticoids, n (%)	167 (5.6%)
Rheumatoid arthritis, n (%)	15 (0.5%)
Secondary osteoporosis, n (%)	791 (26.7%)
T-score femoral neck, mean ± SD	-1.18±0.98

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Table 2. Expected fracture at 10 years in the cohort according to different models FRODOS

		Spain		France		United Kingdom		Sweden
	n	% (IC 95%)	n	% (IC 95%)	n	% (IC 95%)	n	% (IC 95%)
MOP*	157	5.28 (4.5-6.1)	197	6.64 (5.7-7.5)	329	11.09 (10.0-12.2)	401	13.51 (12.3-14.7)
FF**	36	1.22 (0.8-1.6)	46	1.54 (1.1-2.0)	55	1.87 (1.4-2.3)	94	3.15 (2.5-3.8)

* Major osteoporotic fractures.
** Femoral fractures.

Table 3. Baseline characteristics of participants in the Spanish cohort and their FRAX® assessment

	FRODOS* n=2,968	ESOSVAL[10] n=5,310	ECOSAP[5] n=5,201	TEBE ET AL.[6] n=1,231	FRIDEX[13] n=770
Age, mean (SD) (Min - Max)	65.5±3.6 (59-70)	64.3±9.3 >50	72.3±5.3 (65-100)	56.1±7.8 (40-90)	56.8±8.0 (40-90)
Risk MOP	5.28%	5.50%	8.78%	4.60%	3.80%
Risk FF	1.22%	1.90%	3.67%	-**	0.95%

* Current results.
** Unpublished data.

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