Identification of patient with high risk of fracture

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At a time when we have advanced enormously in the knowledge of the natural history of osteoporosis and of the drugs which we use in its treatment, it is necessary to identify those patients at greatest risk in order to focus on them diagnostic therapeutic resources before the final complication, the fracture, appears. This is especially important in the context of finite resources which should be located in the population which would most benefit from them. It is the case, also, that we now know more about the potential risks and limitations of some treatments – for example, the powerful anti-catabolics about which we lack data on their safety beyond 10 years of treatment, or the anabolics, which are considered to be indicated for a maximum of two years – for which reason we need to know at what moment in the natural history of the disease the global risk to the patient is sufficiently important to initiate appropriate treatment.

In addition, in recent years we have progressed much in the understanding of the role of low bone mineral density (BMD) in the genesis of osteoporotic fractures. We know that these fractures can appear in subjects without densitometric criteria for osteoporosis, and inversely, many patients with densitometric criteria for osteoporosis do not suffer fractures. This has allowed the development of models which integrate the information provided by different independent risk factors for the development of osteoporotic fractures, from which is calculated the absolute risk of fracture in the following years. This information regarding the absolute risk of fracture in the following 5 to 10 years has received significant criticism due to its imprecision in some populations, but it is clearly a step forward to give an absolute value which is much more informative for those patients and for doctors not expert in osteoporosis, with its concepts such as T-score, risk gradient, or relative risk. These formulae also allow the calculation of the thresholds for certain diagnostic interventions – for example, to request a densitometry – or therapies – to start a certain treatment – cost effectively.

It means also, that universal screening for osteoporosis by means of densitometry is not feasible due to an unfavourable cost-benefit relationship due to its lack of sensitivity (see more later). In addition, as has been mentioned, the diagnosis and treatment of osteoporosis should be established from an integrated assessment of risk of fractures and not solely by means of BMD.

Some of the main determinants of risk of fracture are:
- Normalised T-score value (T-score): for each standard deviation (SD) of relative risk of fracture it increases approximately in the range 1.5 to 2.0 times (2.6 for measurements in the hip).
- Markers for remodelled bone, where they are found, whose elevation is a risk factor for osteoporotic fracture independent of BMD (relative risk 2), although this has not been confirmed in all studies.
- Osteoporotic risk factors independent of BMD (Tables 1 to 3), whose combined predictive value is higher than that of the measurement of BMD (particularly in the prediction of hip fractures); in the case of non-vertebral fractures especially important also are the risk of fall, and the type of fall, as well as the risk factors for falls (Table 4).
Lastly, it should not be forgotten that the individual risk of fracture is basically dependent on age and life experience (Table 2).

Main risk factors for osteoporosis

The most predictive factor for the development of fractures is determining the BMD, however, other risk factors such as age, previous personal or family history of fractures (Table 3), can be more significant than the measurement of bone mass itself for the prediction of risk of fracture (Figure 1).

While being similar to those of osteoporotic fracture, the risk factors of low BMD or of accelerated loss of BMD are of very limited value in the estimation of the actual risk in a subject (the combination of risk factors only explains 20-40% of the variation in bone mass), however, the risk factors for fracture can, in fact, be useful for the identification of those subjects at highest risk.

The National Osteoporosis Foundation selected, already in 1998, five risk factors for hip fractures in Caucasian postmenopausal women especially useful in clinics – for having prognostic capability and for being accessible and common in the population: the presence of low BMD; personal history of fracture after 40 years of age; history of hip, vertebral and forearm fracture in close family, thinness (lower quartile in weight), and smoking.

As has already been suggested, the University of Sheffield, with the support of the WHO, have recently released a scale of risk for the calculation of the absolute risk of osteoporotic fracture in the following 10 years (FRAX™), based on predictive risk factors and adjusted for the different rates of osteoporotic fractures in different countries, among them, ours. In addition, these calculations can be made without knowing the BMD value and with a simple series of clinical data (Table 5, Figure 2).

Even more recently, professors of statistics at the University of Nottingham have published another model for calculating the absolute risk of fracture at 5 and 10 years (QFracture™) developed and tested in the primary healthcare system of England and Wales. It includes a higher number of medical antecedents, and does not use BMD (Table 6, Figure 2).

Scales of risk of low bone mass

Many tools have been developed to assess the risk of osteopenia or osteoporosis with high-to medium sensitivity but with low specificity. For the prediction of low bone mass (Table 7), the better validated questionnaires include the ORAI test with 3 items, and the SCORE test, with 6 items. The NOF also recommends assessing those patients with one of the main risk factors: age ≥ 65, BMI < 22 kg/m², personal or family history of osteoporotic fracture or smoking. In their last update, they also inclined towards the use of the FRAX™ tool for the assessment of absolute risk of fracture, especially in people without densitometric criteria for osteoporosis.
Recently, in our country, the performance of four scales for the selection of patients with low bone mass (ORAI, OST, OSIRIS and Body Weight Criterion BWC) in a series of 655 postmenopausal women with an average age of 54.2 ± 5.4 years, have been reviewed. According to the scales, densitometry was indicated in 45% (ORAI), 46% (OST), 37% (OSIRIS) and 70% (BWC) of patients. The sensitivity of the scales increased with age and was maximum for BWC (> 83%) and minimum for OSIRIS (only 58%), with the OST (69.2%) and ORAI (69.2%) scales being of intermediate sensitivity.

However, the application of these rules for clinical decision-making for the selection of patients chosen for evaluation of bone mass has shown, in general, a lack of predictive capacity and the necessity to validate locally all of these scales. In addition, the correlation between these scales and the presence of osteoporotic fractures was evaluated, which, although higher for ORAI and ABONE, was, in all cases, low.

Nowadays, with the availability of calculation of absolute risk of fracture with the FRAX™ or QFRACTURE™ tools (see below), it would seem more advisable to request densitometry in those subjects who present a significant risk of fracture at 10 years, although not sufficiently high to justify immediate treatment. Therefore, from the point of view of the diagnosis of osteoporosis, densitometry should be requested when the resulting information is key to indicating or selecting the most appropriate treatment.

**Scales for the risk of osteoporotic fracture**

There are different scales for the prediction of the presence of non-diagnosed vertebral fractures, as well as for the calculation of the future risk of fracture. The majority of these have been developed using data from big clinical trials or from classic cohorts. This shows the necessity of their being validated in local populations before their generalised application.

For example, we have the scales derived from the FIT (Fracture Intervention Trial) study of the prediction of non-diagnosed vertebral fractures (history of vertebral fracture (+6 points), of non-vertebral fracture (+1 point), age (+1 for 60-69; +2 for 70-79; +3 for > 80 years of age), loss of height (+1 for 2-4 and +2 for > 4 cm) and having been diagnosed with OP (+1 point), with a cut-off point of 4 points to identify 60-65% of women with vertebral fracture (sensitivity) with a specificity of...
Table 5. Variables included in the FRAX™ scale for the calculation of absolute risk of osteoporotic fracture in the following 10 years (adapted from reference 9) (Available at http://www.shef.ac.uk/FRAX/tool_SP.jsp?locationValue=4)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>The model allows ages between 40 y 90 years. If lower or higher ages are entered the programme will calculate the probabilities at 40 and 90 years, respectively</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Man or woman. Enter that which corresponds</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>Should be entered in kg</td>
</tr>
<tr>
<td><strong>Height</strong></td>
<td>Should be entered in cm</td>
</tr>
<tr>
<td><strong>Previous fracture</strong></td>
<td>A previous fracture makes reference to a fracture occurring spontaneously in adult life or a fracture caused by a trauma which, in a healthy individual would not have occurred. Both clinical and morphometric. Enter yes or no</td>
</tr>
<tr>
<td><strong>Parents with hip fracture</strong></td>
<td>Questions about the history of hip fracture in mother or father of the patient. Enter yes or no</td>
</tr>
<tr>
<td><strong>Active Smoker</strong></td>
<td>Enter yes or no, depending on whether the patient currently smokes tobacco</td>
</tr>
<tr>
<td><strong>Glucocorticoids</strong></td>
<td>Enter yes if the patient is currently exposed to oral glucocorticoids or has been exposed to oral glucocorticoids in the past 3 months, with a daily dose of 5 mg or more of prednisolon (or an equivalent dose of another glucocorticoid) (see also the notes on risk factors)</td>
</tr>
<tr>
<td><strong>Rheumatoid arthritis</strong></td>
<td>Enter yes in cases in which the patient has a confirmed diagnosis of rheumatoid arthritis. If not, enter no</td>
</tr>
<tr>
<td><strong>Secondary osteoporosis</strong></td>
<td>Enter yes in cases in which the patient has a disorder closely associated with osteoporosis. This includes diabetes type 1 (insulin dependent), osteogenesis imperfecta in adults, untreated chronic hyperthyroidism, hypogonadism or premature menopause (&lt;45 years), chronic malnutrition or malabsorption and chronic liver disease</td>
</tr>
<tr>
<td><strong>Alcohol, 3 or more doses a day</strong></td>
<td>Enter yes, in cases where the patient drinks 3 or more doses of alcohol a day A dose of alcohol varies slightly between countries from 8 to 10 mg of alcohol. This equates to a glass of beer (285 ml), glass of spirits (30 ml), a medium-sized glass of wine (120 ml) or a glass of aperitive (60 ml)</td>
</tr>
<tr>
<td><strong>Bone Mineral Density (BMD)</strong></td>
<td>The BMD in the Femoral neck is entered as a T-score or Z-score. The field should be left blank for patients for whom the BMD has not been determined. (The technique and place of examination refers to dual energy X-ray absorptiometry in the femoral neck. The T-score scales are based on reference values established by the National Health and Nutrition Examination Survey (NHANES) for women between 20 and 29 years of age. The same absolute values are also used for men. In spite of the fact that the model is based on the BMD in the femoral neck, it is considered that in women the total hip also predicts in a similar way, the risk of fracture)</td>
</tr>
</tbody>
</table>
Table 6. Variables included in the QFRACtURE™ scale for the calculation of absolute risk of osteoporotic fracture in the following 10 years (adapted from reference 10) (Available at http://www.clinrisk.co.uk/qfracture/)

<table>
<thead>
<tr>
<th>Variable</th>
<th>For both sexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>The model accepts ages between 35 and 85 years. If lower or higher ages are entered the programme will calculate probabilities at 35 and 85 years, respectively</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>Expressed as kg/m²</td>
</tr>
<tr>
<td>Smoking</td>
<td>Non-smoker, ex-smoker, light, moderate or heavy smoker</td>
</tr>
<tr>
<td>Consumption of alcohol</td>
<td>Trivial (&lt;1 measure a day), low (2-3 measures a day), moderate (4-6 measures a day), significant (7-9 measures a day), very significant (&gt;9 measures a day)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Diabetes type 2</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Asthma</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Use of tricyclic anti-depressants</td>
<td>Positive if more than 2 prescriptions in last 2 months</td>
</tr>
<tr>
<td>Use of corticosteroids</td>
<td>Positive if more than 2 prescriptions in last 2 months</td>
</tr>
<tr>
<td>History of falls</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Chronic hepatopathy</td>
<td>Yes/no</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Only in women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of hormone replacement therapy</td>
<td>Equine or not, balanced with progestagens or not, continuous or intermittent, high or low doses, tibolone</td>
</tr>
<tr>
<td>Parental history of hip fracture</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Clinical climacteric symptoms (vaginal dryness, sofocos – flushing, discharge)</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Intestinal malabsorption (including Crohn Disease, ulcerous colitis, celiac disease, steatorrhea, blind loop syndrome)</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Other endocrinopathies (thyrotoxicosis, hyperparathyroidism, Cushing syndrome)</td>
<td>Yes/no</td>
</tr>
</tbody>
</table>

68-70%); also, from the cohort of the study of osteoporotic fractures (SOF), the FRACTURE™ index which has been validated in Europe, calculates the risk of vertebral, **hip and non-vertebral fractures** (BMD expressed as a T-score if it is known (+1 point for values between -1 and -2; +2 points between -2 and -2.5; +3 points if < -2.5), existence of fractures from 50 years of age (+1 point), weight less than or equal to 57 kg (+1 point), smoking (+1 point), necessity of using arms to get up out of a chair (+ 2 points), age (+ 1 point for 65-69, +2 for 70-74, +3 for 75-79, +4 for 80-84, +5 for ≥ 85 years), the cut-off point is ≥ 6 points or 4 points if BMD is not known), vertebral and non-vertebral.

The OFLEY Study⁹ identified independent predictors of **osteoporotic fractures** in (672) healthy postmenopausal women (age ≥ 65 years, previous falls, BMD of total hip ≤ 0.736 g/cm², force of the left hand ≤ 0.6 bar, maternal history of fracture, low levels of physical activity and history of fragility fracture).

A model for prediction of osteoporotic fracture (**hip, wrist or forearm, rib and vertebra**) in women with densitometric osteopenia (T-score in peripheral bone ≤ -1.8, poor perception of state of health and low mobility) has also been developed which identifies a subgroup of the population which has almost double the risk of fracture (4.1% vs 2.25%)⁹.

To calculate the risk of **non-vertebral fracture** (hip, leg, pelvis, humerus, clavicle), in 2,546 postmenopausal women with osteoporosis and...
high risk included in the placebo groups of the pivotal clinical trials of risedronate over 3 years, were found six factors highly predictive of these types of fractures (the existence of a previous non-vertebral fracture – on entering the study -, number of vertebral fractures present, blood concentration of 25 (OH) vitamin D, age, height and T-score in the femoral neck)\textsuperscript{16}.

The data from the Canadian Multicentre Osteoporosis Study (CaMos) allowed the generation of another model for identifying the risk of vertebral and non-vertebral fractures in 5,143 postmenopausal women\textsuperscript{17}. The risk factors for the main types of non-vertebral fractures (wrist, hip, humerus, pelvis or ribs) in a multivariable model were quality of life, BMD in the femoral neck, previous fracture of the forearm and loss of weight.

There is also available another predictive algorithm for fracture of the hip at 5 years obtained using data from an observational cohort of 93,676 women of the WHI study, validated in 11,798 peri-menopausal women (Kuopio Osteoporosis Risk Factor and Prevention study OSTPRE)\textsuperscript{18}. However, their sensitivity and specificity were low.

From data from the EPIDOS prospective study\textsuperscript{19}, information was obtained on the clinical risk factors for identifying among older women (n= 1,588) with low weight (< 59 kg) and low BMD (T-score between -3.5 and -2.5) those at greater risk of hip fracture (risk twice as high as the average risk for women of a similar age identified by: age, history of falls, capacity to walk in tandem (dynamic equilibrium), the speed of walking, visual acuity, with a sensitivity for fracture of the hip of 37% and a specificity of 85%).

Kanis et al\textsuperscript{4} studied the clinical risk factors for fractures of the hip and other osteoporotic fractures in men and women older than 50 years of age using information from nine large epidemiological studies and validated their results in another eleven studies. The highlights from their results are that the predictive models for fracture of the hip were better than those for other types of osteoporotic fractures, that BMD was the most powerful predictor of hip fractures, that BMD and clinical risk factors predicted hip fractures better in the younger population (50-60 years) than in the older one (80-90), and that in hip fractures, clinical information did not improve the prediction of risk of models based solely on BMD.

In the prediction of distal forearm fractures, the prospective study Kuopio\textsuperscript{18} of 11,798 peri-menopausal women (Kuopio Osteoporosis Risk Factor and Prevention study OSTPRE) found independent predictors during a follow up of five years after an earlier wrist fracture to be postmenopausal status, age and nulliparity. However, their sensitivity and specificity were low.

Also, an attempt has been made to estimate the risk of distal forearm and proximal humeral fracture using data from the Study of Osteoporotic...
Fractures\textsuperscript{21}. Other factors associated with a higher risk of fracture of the forearm independent of DMO were: poor visual acuity, number of falls and frequent walking. Factors independently associated with an increase in the risk of fracture of the proximal humerus were: a recent decline in state of health, diabetes mellitus in treatment with insulin, infrequent walking and indicators for neuromuscular weakness. The data appear, therefore, to support the hypothesis that distal forearm fractures frequently occur after a fall in relatively healthy women with low BMD, who are active and with good neuromuscular function, while proximal fractures of the humerus happen most frequently as a result of a fall in women with low BMD, with a worse state of health, less active than average and with a worse neuromuscular function.

**Calculation of the absolute risk of fracture**

The use of BMD alone informs only part of the risk of fracture, which is clearly multifactorial, as is evident when you consider that the loss of BMD between the ages of 50 and 90 years predicts a relative risk of 4 for a hip fracture, while its actual incidence increases some 30 times in this period. At 50 years of age, up to 5\% of women have osteoporosis but only 20\% of them will actually suffer a fracture in the following 10 years – which signifies poor positive predictive value. In addition, the sensitivity is also low, given that more than 95\% of fragility fractures appear in women without densitometric criteria for osteoporosis\textsuperscript{9,22}. The low sensitivity of densitometry, and its cost, make it its use to screen the recently menopausal population non-viable.

The information derived from those risk factors independent of DMO improve the sensitivity for any value of specificity chosen\textsuperscript{22}. It has been possible to show and validate the fact in other populations that, in the case of the fracture of the hip, the risk gradient associated with the presence of clinical risk factors is similar to that of densitometry as a sole source of information. This implies that the validation of risk can be improved with the integration of clinical risk factors, both if BMD values are available, or if they are not\textsuperscript{9,22}.

In addition, it has already been said that it is necessary to know the absolute risk of fracture of the patient, given that it is more informative regarding the true risk of suffering a fracture in future years, and, in addition, it is an easier and more sensible concept for patients and clinicians than other measures such as T-score, gradients of risk or relative risk\textsuperscript{9}.

**The FRASTM Index**

A team from the University of Sheffield led by Prof. Kanis, and under the auspices of the World Health Organisation, started some years ago to identify the important risk factors from nine prospective population cohorts: the Rotterdam Study, the European Vertebral Osteoporosis Study, later, the European Prospective Osteoporosis Study (EVOS/EPOS), the Canadian Multicentre Osteoporosis Study (CaMos), as well as the studies of Rochester, Sheffield, Dubbo Osteoporosis Epidemiology Study (DOES), a cohort from Hiroshima and two from Gothenburg. From the information obtained a tool for the calculation of absolute risk of osteoporotic fracture in the following 10 years\textsuperscript{9} (FRASTM) has been created based...
on predictive risk factors, and adjusted for rates of osteoporotic fractures in different countries (Figure 2). This calculation can be made without knowing the value of BMD and with a simple series of clinical data (Table 5). The predictive adequacy of these variables for calculating the FRAX index had been identified earlier through meta-analysis. The fractures were identified by self-reporting in 3 cohorts and through medical records in the remaining studies.

Four models for calculating the absolute risk of fracture at 10 years were generated, which did not include non-vertebral fractures: of the hip with or without BMD being known, and other major osteoporotic fractures (clinical vertebral, forearm and proximal humeral) with or without BMD being known, in those in which the fracture and the death of the subject were computed by means of a Poisson regression as a function of continuous risk. The incidence of fractures was adjusted for some counties, among them ours.

The model has unarguable advantages: the availability of both tables to be downloaded from the web, as well as an on-line calculator, which in a few seconds allows the absolute risk to be obtained, the use of the Poisson regression which solves some problems to do with the time frame (10 years), the combined use of different cohorts, the calculation of the moment of appearance of the fracture or of death... The FRAX model considers, also, all the causes of death, as well as the impact of the risk factors for osteoporosis on other causes of death (for example; tobacco and cardiovascular death). However, there are also weaknesses: as in the majority of population studies it can be biased to exclude those subjects who are most infirm and at greater risk of fracture. There are also limitations derived from the cohorts used themselves with regard to the categorisation and recording of fractures or risk factors – such as the use of BMI which can be seen to be affected by a reduction in height which the vertebral fractures cause – instead of weight, in various countries – including in ours – it has been reported that the index has underestimated (by up to 50%) the true rate of fractures, in spite this, the high percentage of subjects for who the model would indicate treatment has been challenged23.

The QFRACTURE™ index
As was mentioned earlier, very recently a new algorithm has been published for the risk of fractures (QFractureScores), for the estimation of the individual risk of hip or osteoporotic fracture at 10 years 10. Using data from 357 primary care clinics in England and Wales a model was generated, and validated in another 178 clinics. The cohort included 1,183,663 women and 1,174,232 men between 35 and 85 years of age. In this cohort a series of variables was identified, mainly highly predictive clinical variables and independently associated with the risk of fracture (Table 6, Figure 2). Some of these variables were only predictive in women, in spite of which, the algorithm for risk of hip frac-
ture performed better in men than in women and explained 63.94% of the variability in women and 63.19% in men. Compared with FRAX™, the contrast statistics were similar to or better with this new algorithm than with FRAX™.

Both this algorithm and the previous one allows the calculation of risk at 10 years in both sexes, although while QFracture is valid for ages between 30 and 85 years, FRAX is for those between 40 and 90 years. FRAX includes in its model fractures of the humerus, along with the hip, vertebral, distal radius fractures which also QFracture includes. QFracture has been developed and validated in a single, representative, very broad population from the primary care environment, whilst FRAX was generated and validated using different cohorts from clinical trials and prospective studies carried out at different times. QFracture, in addition, has a more detailed assessment of tobacco and alcohol consumption, whose effects have been shown to be dose dependent, and includes more clinical risk factors through which it is possible to give a more individualised assessment of risk of fractures. It highlights the recording of falls and the detailed assessment of the type of hormone replacement therapy, along with other details of medical history (cardiovascular disease, type 2 diabetes, hepatopathy...) and concomitant treatments (tricyclic antidepressants). On the other hand, QFracture is still pending validation and calibration for other populations, especially outside the United Kingdom.

Among their advantages are the absence of laboratory data or of measurement of BMD (given that this is not usually recorded in the clinical histories which are the source of the cohort), thus it can be used for self-assessment of risk, as well as for carrying out an opportunistic search for patients at highest risk.

The main criticisms of these models are directed at their use as tools to establish criteria for indication of treatment or of densitometric evaluation. There is therefore a predictable potential impact of these models on payment economic viability of densitometers and treatments. What seems clear up to now is the absence of studies which have shown prospectively the precision of the instrument and, what is more important, the inability to date of demonstrating the efficacy of anti-osteoporotic drugs which we have available in subjects selected solely on the basis of risk factors, or, as well, subjects with osteopenia. In addition, for some, the improvement in the predictive ability of the risk factor models is poor, especially in the case of hip fractures in people over 70 and in non-vertebral fractures.

However, these calculation tools are a clear advance in the recognition of absolute risk as a key factor for guiding doctors and patients in taking decisions such as the necessity for additional complementary tests or the indication of, and necessity for, drug treatments. One of the most controversial points will be setting the thresholds for intervention. With respect to this, some cut-off points have been proposed for absolute risk, of 20% for major osteoporotic fractures and of 3% for hip fractures, although with the use of low cost generic drugs, at least in the United Kingdom, a higher cut-off point of 7% for major fractures could be cost-effective. QFracture offers us instead cut-off points derived from percentile 90 of which is 8.75% in men and 8.75% in women.

In conclusion, as is stated in SEIOMM’s Guide to Clinical Practice1-2 or the European Guide3, the strategy of searching for cases of osteoporosis recommended continues to be an opportunistic search, in that also this can collaborate2-3, although some authors4-20 have carried out a reasonable critique of the models for the prediction of the risk of osteoporotic fractures based on that fact that the statistical association does not presuppose discriminatory capacity, on its poor predictive capacity and in the absence of tests of the efficacy of treatment in subjects selected solely due to risk factors. In any case, those patients with personal or family history of fracture, thin, and older, show an elevated risk of fracture on any of the scales or in any of the models on which we have commented.

Bibliografía


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