




Revista de
Osteoporosis y Metabolismo Mineral

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Osteoporosis. Definition. Epidemiology

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Definition

Osteoporosis is a global health problem whose importance is going to increase with the aging of the population. It is defined as a systemic disorder of the skeleton characterised by low bone mass and deterioration of the microarchitecture of the bone tissue, with the consequent increase in bone fragility and the greater susceptibility to fractures¹. Bone resistance reflects essentially the combination of bone density and bone quality. In turn, the concept of bone quality seeks to integrate all those factors apart from bone mass which determine bone fragility, including the microarchitecture, the degree of turnover, the accumulation of lesions or microfractures, or the degree of mineralisation^{1,2}.

It is a process which is preventable and treatable, but which lacks warning signs prior to the appearance of fractures, leading to the fact of few patients being diagnosed at early stages and treated effectively. Therefore, in some studies it has been confirmed that 95% of patients who presented with a fracture did not have an earlier diagnosis of osteoporosis³.

In 1994 the World Health Organisation (WHO) established some definitions based on measurements of bone mass in the lumbar spine, hip or forearm of white postmenopausal women⁴. Thus, normal bone mass is considered to be having a bone mineral density (BMD) value higher than -1 standard deviation (SD) in relation to the average for young adults (T-score >-1); osteopenia, having BMD values between -1 and -2.5 SD (T-score between -1 and -2.5); osteoporosis, having BMD values lower than -2.5 SD (T-score lower than -2.5), and osteoporosis is established when, along with the above conditions, are associated one or

more fragility fractures (Table 1). It is also possible to consider the Z-score in groups of patients such as children and young adults, which expresses the bone mass in comparison with that expected in those of equal age and sex⁵.

Epidemiology

In 1995 Melton et al estimated the prevalence of osteoporosis according to the WHO criteria in white women over 50 years of age, which was 15% when measured in the three usual places (spine, hip or wrist) and 30% when measured in all of them⁶. The prevalence increases with age from 15% for the ages between 50 and 59 years, up to a prevalence greater than 80% for women aged over 80 years of age⁷. According to data from the NHANES III study, in men over 50 years of age, the prevalence of osteoporosis is 8%⁸.

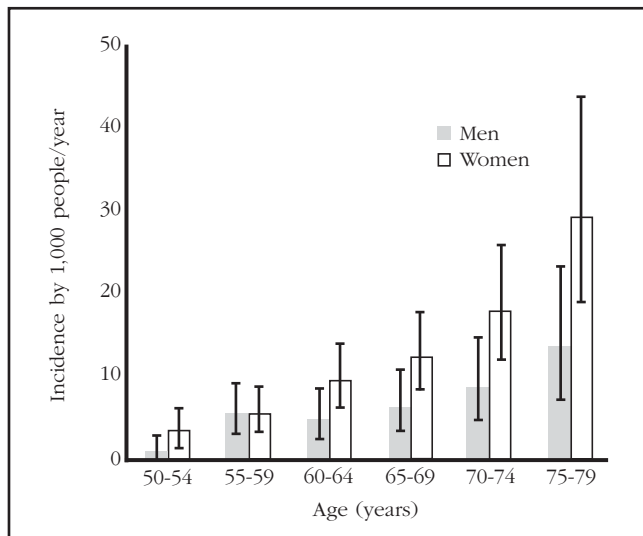
In Spain, it is calculated that 2 million women and 800,000 men have osteoporosis, and a study of Díaz Curial et al., in which DXAs were carried

Table 1. Diagnostic criteria for osteoporosis of the WHO

| Assessment | Value of BMD |
|--------------|--------------------------------|
| Normal | T-score >-1 SD |
| Osteopenia | T-score between -1 and -2.5 SD |
| Osteoporosis | T-score < -2.5 SD |

T-score: value of BMD compared with average value for young adults expressed in terms of standard deviation (SD)

Figure 1. Incidence of vertebral fracture as a function of age: EPOS study (adapted from Roy DK et al., 2003)



out on 1,305 Spanish women between 20 and 80 years of age found a prevalence of osteoporosis in women over 50 years of age of 26.07% (95% CI, 22.57-29.57%)⁹. Studies in men indicate that the prevalence is 8.1% in those older than 50 years of age¹⁰, increasing with age to 11.3% in those over 70 years of age¹¹.

The most direct consequence of osteoporosis is an increase in fragility fractures. Osteoporotic fractures are those located in zones of low BMD, or those which happen after falling over. The presence of fragility fractures is associated with a higher risk of having new osteoporotic fractures, as well as an increase in mortality and a reduction in the quality of life in men and women¹². Osteoporotic fractures can be present in multiple locations, but fractures of the proximal extremity of the femur, distal radius and vertebrae are considered to be typically osteoporotic – the last being the most frequent.

In general, osteoporosis has been evaluated by measuring the BMD, which has a direct correlation with bone resistance, and which constitutes a good parameter for the prediction of risk of fracture. However, BMD is not the only parameter which predicts the risk of fracture, since there are also other significant factors such as age (it increases with age), sex (higher in women), race (higher in northern European countries) and concomitant diseases. Nowadays, to decide when to initiate treatment for osteoporosis not only is BMD evaluated, but also the individualised absolute risk of fracture at 5-10 years, incorporating risk factors independent of BMD such as age, sex, weight, previous fractures, family antecedence of fractures, smoking, consumption of glucocorticoids, intake of alcohol, and others¹⁵.

Osteoporosis in men represents a significant and growing health problem which is underdiagnosed in the general population. It is characterised

as having a higher morbimortality than in women and a higher prevalence of secondary osteoporosis. Thus, in men younger than 70 years of age with osteoporosis, between 40 and 60% have secondary osteoporosis. The most significant causes, quantitatively, are those associated with excess alcohol, that induced by glucocorticoids and primary or secondary hypogonadism.

For little known reasons, hospital mortality due to fracture of the hip and vertebrae in men is double that in women (10% as opposed to 4.7%) and mortality in the year of fracture is also higher in men compared to women (35-37% compared to 28%). In addition, after a low trauma fracture the relative risk of another fracture is also higher in men (RR: 3.4; CI 95%: 2.68-4.48) in comparison with women (RR: 1.95; CI 95%: 1.7-2.25), and the probability of being studied or treated after a hip fracture is lower in men (4.5%) than in women (49.5%)¹⁴⁻¹⁸. Some authors postulate that

the higher prevalence of comorbidities, and the lower level of therapeutic care observed in men with a fragility fracture could explain, in part, this extra morbimortality.

Vertebral fracture

The prevalence of vertebral fracture is difficult to establish due to there being no consensus regarding the radiological definition of the deformities, and to the fact that its presence is usually asymptomatic. Between 20 and 25% of women over 50 years of age will have a secondary vertebral fracture due to osteoporosis, according to data from European studies. Vertebral fractures are rarely present in those younger than 50 year of age but increase exponentially with age¹⁹⁻²¹. The annual incidence is considered to be 1% in women of 65 years, 2% in those of 75 years, and 3% in those over 80 years. In men over 50 years of age it is from 5.7 to 6.8/1,000 people per year, which equates to approximately half of that observed in women²². Vertebral deformities in lumbar and dorsal spinal X-rays are three time more frequent than hip fractures, and only a third of vertebral fractures require medical attention.

In European population studies such as the European Prospective Osteoporotic Study (EPOS) and the European Vertebral Osteoporotic Study (EVOS), at 75-79 years of age the incidence of vertebral fractures is 13.6/1,000 people per year for men and 29.3/1,000 people per year for women, and the global incidence by age is 10.7/1,000 people per year in women and 5.7/1,000 people per year in men²³⁻²⁴. After a vertebral deformity there is a 7- to 10-fold increase in new vertebral deformities, and the presence of a previous vertebral deformity predicts an incidence of hip fracture with a risk quotient of 2.8-4.5, and this increases with the number of vertebral deformities²⁵⁻²⁷. (Figure 1).

Proximal femoral fracture

Hip fractures are considered the most significant osteoporotic fractures due to their associated high morbimortality. In patients with this type of fracture fewer than 50% have complete recuperation, 25% go on to require home care and 20% will require continuing support after the fracture.

Hip fractures are more frequent in women, with a female/male ratio of 3 to 1. The most frequent age for their occurrence is between 75 and 80 years. The incidence of hip fracture increases with age, increasing exponentially from 50 years, their incidence in people younger than 35 years being 2/100,000 and 3,000/100,000 in those over 85 years of age²⁸.

Distal radius fracture

Fracture of the distal third of the radius is more frequent in women, with a female-male ratio of 4 to 1. In women, these fractures are more frequent in the perimenopause, and their incidence increases rapidly through menopause before stabilising at 65 years. In males the incidence remains practically constant with age.

This type of fracture only requires hospitalisation in less than 20% of cases, but increases by 50% the risk of hip fracture^{29,30}.

Conclusions

Osteoporosis should be considered as a real public health problem which justifies the implementation of preventative measures and efficacious therapies. Hence, the primary objective should be to prevent the first fracture and to preserve the integrity of the bone, increasing bone mass and improving bone quality.

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Socioeconomic impact of osteoporosis

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Introduction

Osteoporosis (OP) is included in the group of diseases which constitute the greatest health problems in the world, both for its ubiquity and for its socioeconomic consequences. In the United States of America it has been calculated that around 10 million people have OP and that nearly 34 million are at risk of suffering a fracture due to their having low bone mass¹. In Spain, it is estimated that 3 million people suffer from OP and that this would mean an incidence of hip fracture of approximately 6.94 ± 0.44 per 1,000 inhabitants per year². However, it is difficult to know exactly the global reach of OP since only data on femoral fractures is known with any exactitude, because it is the only one which always requires hospitalisation. In fact it would be possible to divide the consequences of OP into three well differentiated types of fracture: vertebral fracture (VF), femoral fracture (FF) and non-vertebral, non-hip fracture (NVF). VF has the inconvenience that it is only symptomatic in 30% of cases, and despite a third of vertebral fractures requiring specific medical attention, the rest are underestimated and remain diagnosed as back pain or arthritic lumbago³. FFs are the only truly quantifiable of these fractures, since they always require hospitalisation, at least in countries described as developed, and their costs can be assessed with greater accuracy. NVFs, which would include fractures of the forearm, humerus, clavicle, ribs, and ankle, are also very difficult to quantify, since although some cases require surgical intervention, the majority are attended to in outpatients or casualty departments of hospitals without the patient being admitted.

Vertebral fractures

Epidemiological studies such as the European Vertebral Osteoporosis Survey (EVOS)⁴ have allowed, through the systematic taking of X-rays, the realisation of an approximation of the true picture of this condition in Europe and in our country (Table 1). Naves et al.⁵ published the results of a cohort of the EVOS study followed over 6 months and observed that the incidence of vertebral fractures was 4 times greater than in those of the hip. The incidence of VF was found, according to these studies, in some 1,250 cases per 100,000 women.

All these data reflect the true situation in Europe, in which vertebral fractures have a prevalence of 12% at 60 years of age and increase progressively with age until they reach 25% at 75 years in women and 17% in men. These data confirm in VF the fact that its highest incidence occurs in a person's 60s and 70s⁶ when being active is so important, and thus its social impact and its affect on quality of life is going to be key.

The greatest impact on quality of life of the patient who has suffered a VF is that this fact alone constitutes the greatest risk factor for suffering a new fracture⁶. From the point of view of economics, VF has been estimated as having a global cost, depending on age, of between 90 and 190 million dollars in the year 2005 (Table 2)⁷. Clearly the individual costs of each fracture is going to depend on the procedures carried out, admission to hospital, vertebroplasty or kyphoplasty, etc., in addition to the indirect costs occasioned if the person affected is an active worker.

One truly important aspect is the morbidity and worsening of quality of life caused by the VF. The

Table 1. Incidence of hip, Colles and vertebral fractures in the population of Oveido (Naves et al. Med Clin (Barc) 2000)

| | Hip | Colles | Vertebral |
|-------|------------------|--------------------|----------------------|
| Women | 325 (106-757) | 793 (411-1,381) | 1,250 (648-2,173) |
| Men | 140 (17-506) | 140 (17-506) | 741 (298-1,520) |
| Total | 236 (95-486) | 477 (261-798) | 985 (594-1,534) |

Values expressed as incidence of fractures per 100,000 people-year (in brackets the 95% confidence intervals)

measurement of quality of life in osteoporosis, and essentially in fractures, is usually carried out with specific quality of life questionnaires, such as Health-Related Quality Of Life (HRQOL), QUALEFFCO or ECOS 16. The study by Hallberg et al.⁸ was able to show that a cohort of 600 consecutive women with osteoporotic fractures of between 55 and 75 years of age, worsened their quality of life, measured by means of the HRQOL, two years after the fracture. The principal and most important clinical effect of VF is the pain it causes, which provokes the immobilisation of the patient and high consumption of analgesics. In addition, the pain goes on to provoke respiratory complications, above all in patients with pulmonary diseases, with the consequent increased impact on their quality of life, and even increasing their risk of mortality. In fact, in order to quantify, in an epidemiological way, the repercussions of the fracture on an individual, the concept of loss of Disability Adjusted Life Years (DALYs) has been established. Using this concept Johnell et al.⁹ showed that in the year 2000, in which it was estimated that 9 million osteoporotic fractures occurred, 5.8 million DALYs were lost globally, which represents a greater loss than for cancer (except for lung cancer) or for arthritis.

With respect to mortality, in the Fracture Intervention Trial, Cauley et al.¹⁰ analysed the mortality data for women of between 55 and 81 years of age, with a follow up of 3.8 years. The relative risk adjusted for age of dying after a clinical vertebral fracture was 8.64 (95% CI: 4.45-16.74). Recently, the results of the Canadian Multicentre Osteoporosis Study (CAMO) have shown that in a cohort of 7,753 patients (2,187 males and 5,566 women) followed over 65 years that the mortality of those patients who had suffered a VF during the second year of follow up is increased 2.7 times at 5 years¹¹.

Femoral fracture

The incidence of FF is an index which represents the national situation with respect to the importance of osteoporosis in that country. In an epidemiological study it was estimated that in 1990 1.31 million new FFs were produced globally, of which

690,382 were in North America, Eastern Europe, Japan and Australia, and in the world there were a total of 4,481,541 people with some disability due to having suffered an FF¹².

In Spain, the incidence of femoral fractures has been known for the different regions, having a tendency to increase, probably due to the effect of the aging population (Table 3)¹³⁻¹⁷. Serra et al.¹⁸ carried out a longitudinal study of incidence in each of the regions of Spain, based on the records of the Ministry of Health and Consumption for the years 1996 to 1999. During this period, a total of 130,414 cases were recorded in patients over 65 years of age. They observed that the 89% of patients with hip fracture had an average age of 82 years, with wide variations in incidence between different parts of Spain, but approximating to 270 cases per 100,000 inhabitants in males and 695 per 100,000 in women over 64 years of age.

Recently, in the context of the Bone Ultrasound in Primary Care (Ecografía Ósea en Atención Primaria (ECOSAP)) study the incidence of femoral fractures in women older than 65 years was 360 cases per 100,000 women per year¹⁹.

In terms of the economic impact of FF, the annual cost has been estimated at 9,000 million dollars, with some 300,000 hospitalisations for this reason. In Spain, the direct costs alone of the intervention and hospitalisation could amount to 90,000 euros annually. However, what must also be considered, in addition to the costs directly related to the acute phase of the fracture, is the cost related to convalescence, rehabilitation, and indirect costs such as a personal home carer or admission to geriatric centres or residences, which represent 43% of the total cost of treatment of FF⁷. In terms of the morbimortality of FF, it is well known that the mortality in the acute phase is in the region of 8% within the first month as a consequence of immediate postoperative complications, and a mortality after a year of 30%, which reaches 38% at two years. The previous cognitive state of the patient appears to be a predictive factor of mortality. On the other hand, if there is dementia or senile involution, this is seen to be increased even more after the femoral fracture, which leads to a greater deterioration in the patient's general state²⁰.

Unfortunately, and despite all the efforts made in recent years, the mortality of FF assessed recently in countries such as Denmark, continues to be very similar at 9% at one month, 15.5% at 3 months, 26.5% at one year and 36.2% at two years²¹.

Non-vertebral fractures

Until recently NVFs excluding the hip appeared to have little importance, probably due to FF being the key objective in the treatment of OP. However, in recent years, greater importance has been granted to this type of fracture, above all because it represents 67% of all osteoporotic fractures¹. In Spain the ECOSAP study has brought this matter to light, and the incidences of each type of fracture in the Spanish population reflect their importance (Table 4)¹⁹.

Table 2. Cost in USA according to type of fracture in 2005 (Burge et al. J Bone Miner Res 2007)

| Age | Vertebra | Femur | Wrist | Pelvis | Others | Total |
|-------|----------|-------|-------|--------|--------|-------|
| 50-64 | 91 | 614 | 130 | 34 | 564 | 1,433 |
| 65-74 | 126 | 1,045 | 76 | 67 | 318 | 1,633 |
| 75-84 | 253 | 3,521 | 113 | 253 | 431 | 4,601 |
| >=85 | 193 | 4,138 | 58 | 331 | 410 | 5,129 |

However, the direct and indirect economic costs of this type of fracture is much more difficult to determine, although in some cases, such as the fracture of the forearm, or Colles fracture, some approximations have been made. Thus, Ohsfeldt et al.²², estimated the costs of forearm fractures in the USA in 2003 to be 2,688 US\$ per fracture per year. Also here, the indirect economic repercussions due, for example, to time off work or to secondary disability of movement due to poor consolidation, are more difficult to quantify.

In relation to the morbidity and mortality of NVFs, the situation is more complicated since there are no data on this matter at a global level. The repercussions most studied centre on Colles fractures or those of the forearm: those known are the complication of complex regional pain syndrome or the loss of strength of grip in the hand, post-fracture. In spite of this, their true incidence after fracture is not known with exactitude, although what is known is the necessity for early rehabilitation after immobilisation²³.

Conclusions

The socioeconomic impact of osteoporosis is truly important, from the prevention of fractures, and their treatment, to their later repercussions, the disease is one which has greater impact on the global health budget. From the data which can be obtained from the pharmaceutical companies for the sales of their products, the epidemiological data, and figures about the different fractures, above all that of the femur, is what makes osteoporosis considered to be a true social-health problem of the 21st century.

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Table 3. Incidence of hip fracture in Spain. Expressed as cases/100,000 inhabitants and women/men ratio

| | Global incidence | > 49 years | Relation |
|--------------|------------------|------------|----------|
| Alicante | 29 | | |
| Barcelona | 76.3 | 225.4 | 2.9 |
| Salamanca | 44.4 | 132.5 | 3.0 |
| Sevilla | 83 | | 4.7 |
| Madrid | 42 | | 2.9 |
| Cantabria | 60.6 | 198 | 3.4 |
| Gijón | 22.0 | | 3.4 |
| Gran Canaria | 34.9 | 161.2 | 2.8 |
| Valladolid | 72.5 | 264.7 | 3.2 |
| Asturias | 77.6 | 261.1 | 3.9 |

Table 4. Incidence of the principal non-vertebral, non-femoral fractures in the Spanish population according to the ECOSAP study

| Type of fractures | Incidence by 100,000 women/year |
|-------------------|---------------------------------|
| Forearm | 887 |
| Humerus | 333 |
| Ribs | 180 |
| Pelvis | 113 |
| Collar bone | 60 |
| Tibia | 73 |
| Fibula | 120 |

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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 clear-

ly 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 BMD¹⁻⁸.

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)^{1,5}; 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).

Table 1. Model of risk factors for fracture of the hip among 9,516 caucasian women without recorded previous history of fractures nor of bone mass (adapted from reference 5)

| Factor | Relative Risk (Confidence Interval at 95%) |
|---|--|
| Age (for each 5 years) | 1.5 (1.3-1.7) |
| Maternal history of hip fracture | 2.0 (1.4-1.9) |
| Increase in weight since age 25 (for each 20%) | 0.6 (0.5-0.7) |
| Reduction in height since age 25 (for each 6 cm) | 1.2 (1.1-1.4) |
| Own perception of state of health (for each point*) | 1.7 (1.3-2.2) |
| History of hyperthyroidism | 1.8 (1.2-2.6) |
| Use of long acting benzodiazepines | 1.6 (1.1-2.4) |
| Use of anti-epileptics | 2.8 (1.2-6.3) |
| Consumption of coffee | 1.3 (1.0-1.5) |
| Exercise (regular walking) | 0.7 (0.5-0.9) |
| Standing up < 4 hours/day (vs > 4 hours/day) | 1.7 (1.2-2.4) |
| Inability to get up out of a chair without help | 2.1 (1.3-3.2) |
| Reduction de la propriocepcion (lower quartile) | 1.5 (1.1-2.0) |
| Cardiac frequency > 80 bpm at rest | 1.8 (1.3-2.5) |

*Scored from bad (1 point) to excellent (3 excellent)

Table 2. Risk of fracture for the rest of life (A) and in the next 5 years (B) in 9,516 caucasian women (adapted from reference 4)

| A Type Frx/Age | 50 | 60 | 70 | 80 |
|-------------------|-------|-------|-------|-------|
| Hip | 14.3% | 13.8% | 13.6% | 12.3% |
| Wrist | 14.4% | 11.5% | 7.6% | 4.2% |
| Vertebral | 15.0% | 14.7% | 13.5% | 9.2% |
| Other | 31.2% | 27.9% | 22.2% | 15.6% |
| B Type Frx/age | 50 | 60 | 70 | 80 |
| Hip | 0.2% | 0.6% | 1.6% | 5.2% |
| Wrist | 1.6% | 2.8% | 2.8% | 2.0% |
| Vertebral | 0.6% | 1.5% | 2.9% | 4.7% |
| Other | 6.9% | 9.6% | 10.9% | 13.5% |

• 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^{1,4,5}, 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^{1,3-5} (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^{1,3-5}.

The National Osteoporosis Foundation⁵ 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 9 (FRAXTM), 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 (QFractureTM) developed and tested in the primary healthcare system of England and Wales 10. 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 items¹¹, and the SCORE test, with 6 items¹². The NOF also recommends assessing those patients with one of the main risk factors: age ≥ 65 , BMI < 22kg/m², personal or family history of osteoporotic fracture or smoking. In their last update, they also inclined towards the use of the FRAXTM tool for the assessment of absolute risk of fracture, especially in people without densitometric criteria for osteoporosis.

Table 3. Risk factors for fracture (adapted from references 1 and 2)

| | High Risk (Relative Risk >2) | Moderate Risk (Relative Risk 1 to 2) |
|--|--|--|
| Partially or totally independent of BMD | Age Personal history of osteoporotic fractures Family history of fracture of the femur Low body weight (BMI < 20) Glucocorticoids (≥ 3 months with ≥ 7.5 mg/day of prednisone) High bone turnover | Diabetes Smoking Inability to get up out of a chair High intake of alcohol (≥ 3 units a day) Hyperthyroidism |
| Dependent on BMD | Hypogonadism in males Primary hyperparathyroidism Anorexia nervosa Prolonged immobilisation Malabsorption syndrome | Feminine sex Menopausia precoz (<45 años) Primary and secondary amenorrhea Rheumatoid arthritis Vitamin D deficiency Low intake of calcium (< 500-850 mg/day) |

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)¹³ 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

Table 4. Risk factors for falls (adapted from reference 6)

| Factors |
|---|
| Changes in mobility |
| Changes in balance |
| Neuromuscular or musculoskeletal diseases |
| Age |
| Changes in vision |
| Neurological or cardiac diseases |
| History of falls |
| Medications |
| Cognitive change |

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 FRAXTM or QFRACTURETM 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**¹⁴ (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)

| | |
|--------------------------------|--|
| Age | 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 |
| Sex | Man or woman. Enter that which corresponds |
| Weight | Should be entered in kg |
| Height | Should be entered in cm |
| Previous fracture | 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 |
| Parents with hip fracture | Questions about the history of hip fracture in mother or father of the patient. Enter yes or no |
| Active Smoker | Enter yes or no, depending on whether the patient currently smokes tobacco |
| Glucocorticoids | 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) |
| Rheumatoid arthritis | Enter yes in cases in which the patient has a confirmed diagnosis of rheumatoid arthritis. If not, enter no |
| Secondary osteoporosis | 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 (<45 years), chronic malnutrition or malabsorption and chronic liver disease |
| Alcohol, 3 or more doses a day | 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) |
| Bone Mineral Density (BMD) | 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) |

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/>)

| Variable | For both sexes |
|--|---|
| Age | 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 |
| Body Mass Index | Expressed as kg/m ² |
| Smoking | Non-smoker, ex-smoker, light, moderate or heavy smoker |
| Consumption of alcohol | Trivial (<1 measure a day), low (2-3 measures a day), moderate (4-6 measures a day), significant (7-9 measures a day), very significant (>9 measures a day) |
| Rheumatoid arthritis | Yes/no |
| Cardiovascular disease | Yes/no |
| Diabetes type 2 | Yes/no |
| Asthma | Yes/no |
| Use of tricyclic anti-depressants | Positive if more than 2 prescriptions in last 2 months |
| Use of corticosteroids | Positive if more than 2 prescriptions in last 2 months |
| History of falls | Yes/no |
| Chronic hepatopathy | Yes/no |
| Variable | Only in women |
| Use of hormone replacement therapy | Equine or not, balanced with progestagens or not, continuous or intermittent, high or low doses, tibolone |
| Parental history of hip fracture | Yes/no |
| Clinical climacteric symptoms (vaginal dryness, sofocos – flushing, discharge) | Yes/no |
| Intestinal malabsorption (including Crohn Disease, ulcerous colitis, celiac disease, steatorrhea, blind loop syndrome) | Yes/no |
| Other endocrinopathies (thyrotoxicosis, hyperparathyroidism, Cushing syndrome) | Yes/no |

68-70%); also, from the cohort of the study of osteoporotic fractures (SOF), the FRACTURE¹⁵ 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 Study⁸ identified independent predictors of **osteoporotic fractures** in (672)

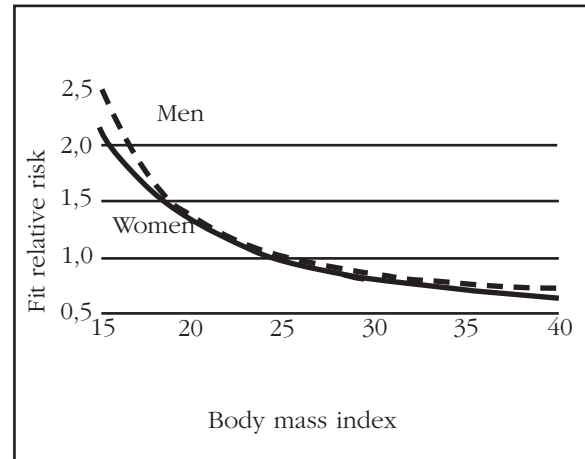
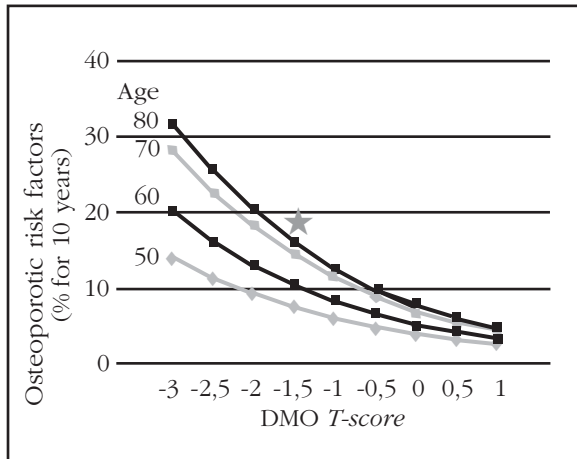
healthy postmenopausal women (age ≥ 65 years, previous falls, BMD of total hip ≤ 0.736 g/cm², force of the left hand ≤ 0,6 bar, maternal history of fracture, low levels of physical activity and history of fragility fracture).

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)¹⁵.

To calculate the risk of **non-vertebral fracture** (hip, leg, pelvis, humerus, clavicle), in 2,546 postmenopausal women with osteoporosis and

Figure 1. Upper panel. The influence of age as a risk factor independent of bone mineral density (BMD) on the risk of fracture. The star shows the raised risk which the presence of a fracture confers (patient of 60 years of age with a T-score -1.5 – osteopenia and previous fracture). Modified from Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B, et al. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. *Osteoporos Int.* 2001;12: 989-995

Lower panel. The influence of the body mass index (BMI) on the risk of fracture in both sexes. Low BMI is associated with risk of fracture in a clearly independent way. Modified from Hippisley-Cox J, Coupland C. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores. *BMJ* 2009; 339: b4229



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)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 women¹⁷. 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 by 68,132 women who participated in the clinical trial and tested in 10,750 women in the same study who had measurements of BMD, although it should be mentioned that osteoporosis was not one of the entry criteria for this study. The predictive variables were age (the majority of the women were between 60 and 69 years of age when they entered the study), their self-perception of state of health, weight, height, ethnicity or race, self-reported level of exercise, personal and family history of fracture, smoking, use of corticosteroids and diabetes in treatment¹⁸.

From data from the EPIDOS prospective study¹⁹, 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 al⁴ 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 Kuopio²⁰ of 11,798 perimenopausal 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

Fractures²¹. 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^{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 chosen²². 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^{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 risk⁹.

The FRAX™ 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 years⁹ (FRAX™) has been created based

Lower panel: QFracture™ tool developed in the United Kingdom for the estimation of the individual risk of hip or major osteoporotic fracture (hip, vertebral, distal radius) in the following 5 or 10 years. (Available at: <http://www.clinrisk.co.uk/qfracture/>)

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 years⁹ (FRAX™) has been created based

Table 7. Scales for the detection of patients with high risk of osteoporosis

| Scale | Cut-of point | Risk factors/Scoring |
|--|---------------------------------|---|
| NOF (National Osteoporosis Foundation) | ≥ 1 | One point per: age > 65, BMI < 22, Family history, Personal history, Smoking |
| SCORE (Simple Calculated Osteoporosis Risk Estimation) | ≥ 6 | +5 for non-african-americans, +4 if RA, +4 for each OP Frx (maximum 12 points), +1st digit of age x 3, +1 if NO HRT, -weight in pounds/10 (rounded to a whole number) |
| ORAI (Osteoporosis Risk Assessment Instrument) | ≥ 9 | Age: ≥ 75 : +15, 65-75: +9, 55-65: +5; Weight < 60 kg: +9; NO HRT: +2 |
| ABONE (Age, Body Size, No Estrogen) | ≥ 2 | One point per: age >65, weight <63.5 kg, NO HRT or OCC |
| OST-T (Osteoporosis Self-assessment Tool) | Medium (>-9) or high (>20) risk | Age (years) – weight (kg) |
| ORACLE | 0,27 | Phalangeal USQ, Age, BMI, Use of HRT, Frx from 45 years |
| OSIRIS | ≥ 1 | Age: Years x -2 (drop last digit) Weight: Kilos x +2 (drop last digit) Use of HRT/ +2 Low energy Frx/ -2 |

BMI: Body Mass Index; RA: Rheumatoid Arthritis; Frx: Fracture; OP: Osteoporosis, HRT: Hormone Replacement Therapy. SOT: Sustitutive Oestrogen Therapy . OCC: Oral Contraceptives

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^{24,26}.

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 risk which is 8.75% in men and 8.75% in women.

In conclusion, as is stated in SEIOMM's Guide to Clinical Practice^{1,2} or the European Guide⁶, the strategy of searching for cases of osteoporosis recommended continues to be an opportunistic search, in that also this can collaborate²⁵, although some authors^{24,26} 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.

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PTH 1-84 in the treatment of osteoporosis

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Introduction: Physiopathological basis for the anabolic treatment of osteoporosis

The treatment of osteoporosis in postmenopausal women consists initially of a series of non-pharmacological measures which can be applied to all patients, such as increasing where possible physical exercise, especially that which applies load, a balanced diet with sufficient calcium and vitamin D, exposure to sun for 10 minutes a day at a time when is it less strong, in addition to suppressing smoking and preventing falls^{1,2}. However, in postmenopausal women with osteoporosis, or at high risk of developing it, to these should be added pharmacological measures.

Chronologically, the first drugs developed for the treatment of osteoporosis were the antiresorptives, among which were the oestrogens^{3,6}, calcitonin⁷ and the first biphosphonates, such as etidronate^{8,9}. All these drugs had a plausible physiopathological basis, and were the confirmation that osteoporosis produces an increase in bone resorption, checked both by the biochemical markers for bone remodelling and by bone biopsies¹⁰. Studies carried out with these drugs, as later with other antiresorptive drugs, confirmed that they produced a small increase in bone mineral density which was not related to a reduction in risk of fracture¹¹.

In the last few years a series of drugs have been developed whose action mechanism is based on the direct stimulation of bone formation, and which, together, are called anabolic bone therapies. The objective which all these treatments pursue is the formation of new bone, the restoration of bone microarchitecture, to increase bone

mineral density, and thus reduce the risk of fracture. Among these compounds are included fluorine, growth hormone (GH), insulin-related growth hormone type 1 (IGF-1), the statins, and above all, two agents which show the greatest evidence of efficacy: strontium ranelate and parathyroid hormone (PTH) and its active fragments. We focus our review on the whole molecule of PTH, known also as PTH 1-84.

Physiopathological basis for the treatment of osteoporosis with PTH

Bone remodelling is the term with which we refer to a constant process of renewal to which bone is subject. It takes place simultaneously in multiple microscopic well defined units, dispersed throughout the whole skeleton. In each of these units the bone is destroyed and then replaced by newly formed bone. By means of bone remodelling, the organism replaces aged or damaged bone by new tissue, and at the same time contributing to mineral homeostasis¹².

In osteoporosis a change in bone remodelling is produced. For reasons not yet completely known, an imbalance is produced between bone formation carried out by the osteoblasts, and the resorption or destruction of bone, for which the osteoclasts are responsible. In postmenopausal osteoporosis, there is typically an increase in bone resorption, with formation remaining steady or slightly reduced^{13,14}. As a consequence of this, a negative balance results, which drives loss of bone mass. It is precisely the low mineral density which is the most significant risk factor for osteoporotic fractures¹⁵⁻¹⁸.

In the physiopathology of osteoporosis there is also a quantitative factor, which is the change in the microarchitecture in which the increase in bone turnover takes place, producing instability in the skeleton, microperforations and microfractures^{19,21}. Even more, in practically all the clinical trials in which antiresorptive drugs, such as calcitonin, oestrogens, selective inhibitors of oestrogenic receptors (SERMs) and biphosphonates have been used, a reduction in the risk of fracture has been observed, which bears no relationship to the increase in bone mineral density^{11,17}.

On the other hand, in diseases in which there is an excess of PTH, such as in primary hyperparathyroidism (HPT), PTH exerts a powerful anabolic effect on the bone, increasing bone formation. A group of studies has shown that treatment with PTH brings significant increases in BMD, fundamentally in the trabecular zone, as well as a reduction in the risk of both vertebral and non-vertebral fractures²². The continuous secretion of PTH, such as occurs in hyperparathyroidism, produces an increase in bone turnover, with a hyperstimulation of the osteoclasts and a net balance in favour of bone resorption. However, the intermittent administration of PTH at low doses provokes an increase in bone mass²³, since it produces a stimulation of growth factors and reduces osteoblastic apoptosis, resulting in an increase in bone mass²⁴. This dual action is what is known as the paradoxical effect²⁵. On the other hand, to confirm this fact, Silverberg et al, have published data which shows that in asymptomatic forms of HPTP conservation of trabecular bone occurs, which results, qualitatively, in being of better quality than bone in controls of the same age and sex²⁶⁻³¹. Similar results have been published by other authors^{30,32}.

Taking into account these facts, it is easy to understand that treatment of osteoporosis with PTH implies a different approach to those therapies normally used up to now. PTH acts directly on the osteoblasts, given that these bone-forming cells have specific receptors for this hormone³³, producing bone formation by a dual mechanism: on one hand, by the increase in the index of remodelled bone, and on the other, by obtaining a positive balance in the quantity of bone deposited in each unit of bone remodelling, as confirmed by biopsy in the increase in the trabecular thickness in the osteones. This differentiates the effect of treatment with PTH from other clinical forms with high levels of remodelling, such as occurs with oestrogen deficiency, which has a negative effect on the bone. The result is the direct production of new bone with the consequent gain in bone mineral density and reduction in risk of fracture.

Historical view of treatment with PTH

In reality, treatment of osteoporosis with PTH is not new. Already, more than 30 years ago, Reeves et al, in a preliminary study, published for the first time in the 70s a series of 4 patients to whom PTH had been administered, (the fragment 1-34) at dif-

ferent doses (between 100 and 400 mg/day in cycles of 8 days). As a parameter to assess the effectiveness of treatment the calcium balance was used, which returned to positive in all the cases, allowing the authors to calculate the quality of the mineral deposited in the skeleton^{34,35}. In those days densitometry was not yet available.

The same research group presented other publications, following up the same patients^{36,37}. In spite of promising results, this research group abandoned this line of investigation. Almost a decade later, Slovik et al.³⁸ presented a series of 8 patients treated with PTH over 12 months in whom an increase in bone mineral density (BMD) was obtained, determined through computerised axial tomography (CAT). There was also another therapeutic initiative with PTH with what is called sequential treatment, or ADFR (Activate, Depress, Free period and Repeat), proposed by Frost³⁹. The activation phase was carried out with phosphorus, and sought the indirect release of endogenous PTH. This treatment was also abandoned.

The effects of PTH 1-84 in vertebral fractures and bone mineral density in postmenopausal women with osteoporosis. The TOP study

This reference study for PTH 1-84 is called the TOP (Treatment for Osteoporosis) study, published by Greenspan et al.⁴⁰. This study, which included 2,532 postmenopausal women, was carried out over 18 months in 168 centres in 9 countries. It consists of a randomised double blind clinical trial in which the women in the treatment group were administered 100 micrograms of PTH 1-84 subcutaneously, with this and the control group receiving supplements of 700 mg/day of calcium and 400 U/day of vitamin D. The baseline characteristics of this population are set out in Table 1.

The main objective was the reduction in the risk of vertebral fractures. After 18 months of treatment a decrease of 66% in the risk of new vertebral fractures was observed in the group who received treatment with PTH, a decrease which was observed both in women who had at least one previous vertebral fracture and in those who had none. Table 2 shows a summary of these results.

In the TOP study, at 18 months, the BMD increased in the lumbar spinal column by 6.9% in patients who received PTH compared to the women in the control group. The increase in BMD in the spine occurred independently of baseline BMD, age, number of years in menopause, previous treatment for osteoporosis and country. At the end of the study after 18 months, the BMD had increased in the hip by an average of 2.1% in the total hip, by 2.5% in the femoral neck and by 1.6% in the trochanter ($p < 0.001$ in all cases). The BMD was reduced in the extreme distal radius by 3.4% in the group treated with PTH.

Other studies

Hodsman et al.⁴¹ carried out a study in 217 postmenopausal women affected by osteoporosis,

Table 1. Baseline characteristics of patients included in the TOP study

| | Placebo | | | Treated with PTH 1-84 | | |
|--------------------------------------|--------------|-------------------|--------------|-----------------------|-------------------|--------------|
| | All | Started treatment | Abandoned | All | Started treatment | Abandoned |
| Age (years) | 64.5 (7.9) | 64.3 (7.8) | 64.8 (8.3) | 64.4 (7.4) | 64.0 (7.4) | 65.1 (7.9) |
| BMI (Kg/m ²) | 25.7 (4.4) | 25.7 (4.27) | 25.5 (4.8) | 25.6 (4.6) | 25.6 (4.34) | 25.8 (4.9) |
| Without fractures | 1011 (81.1) | 733 (83.6) | 275 (74.5) | 1050 (81.6) | 680 (82.5) | 368 (79.7) |
| With at least one fracture | 235 (18.9) | 144 (16.4) | 94 (25.5) | 236 (18.4) | 144 (17.5) | 94 (20.3) |
| With one earlier fracture | 184 (14.8) | 117 (13.3) | 67 (18.2) | 165 (12.9) | 101 (12.3) | 64 (13.9) |
| With two earlier fractures | 27 (2.2) | 15 (1.7) | 12 (3.3) | 48 (3.7) | 30 (3.6) | 18 (2.9) |
| With more than two earlier fractures | 24 (1.9) | 12 (1.4) | 12 (3.3) | 23 (1.8) | 13 (1.6) | 10 (2.2) |
| BMD. T-score | | | | | | |
| Lumbar spine | -2.96 (0.77) | -2.97 (0.74) | -2.93 (0.86) | -3.02 (0.79) | -3.04 (0.78) | -2.97 (0.81) |
| Femoral neck | -2.21 (0.72) | -2.17 (0.71) | -2.31 (0.72) | -2.25 (0.70) | -2.23 (0.71) | -2.30 (0.68) |
| Total hip | -1.89 (0.78) | -1.84 (0.77) | -2.00 (0.81) | -1.92 (0.80) | -1.89 (0.81) | -1.97 (0.78) |

with an average age of 64.5 years, to whom had been randomly administered either a placebo or PTH 1-84 at doses of 50, 75 or 100 µg. This study was intended to establish the safety of treatment with PTH 1-84 and to assess changes in BMD, depending on the doses of PTH used. The study was extended for one year, at the end of which the average increase in BMD was 3.0, 5.1 and 7.8% in the groups whose doses were 50, 75 and 100 µg/day, respectively, all of which were statistically significant and clearly dose dependent, whilst in the control group, which received calcium and vitamin D, an increase of 0.9% was observed, which was not statistically significant. The increase in BMD seen in the group receiving 100 µg was statistically significant with respect to the two other groups which received PTH, the T-score of -3.2 at the start of the study moving to -2.8 at the end of it. On the other hand no statistically significant differences were seen in the BMD of the hip.

Modification of the bone cytoarchitecture after treatment with PTH 1-84

In 2005, in the absence of data in humans, with a view to studying the changes PTH 1-84 generates

in bone architecture, a study was planned and carried out as randomised double blind treatment versus placebo study of biopsies of the iliac crest in postmenopausal women with osteoporosis who received daily injections of placebo or 100 µg PTH over 18 months. All the subjects received at the same time treatment with calcium (700 mg) and vitamin D (400 UI), with no significant differences between the two groups in terms of age, weight, markers for bone turnover, or BMD in vertebral column or hip.

Before being selected for the histomorphometric study, the biopsies were submitted to micro-computerised tomography to quantify the 3-D and 2-D structure of the trabecular and cortical bone, respectively. After 18 months biopsies were obtained from 8 women treated with placebo and 8 treated with PTH 1-84⁴².

In the group treated with PTH 1-84 an increase in the formation of spongy bone was observed, and in the volume of bone measured in the iliac crest, without significantly affecting bone resorption. In addition, PTH 1-84 improved trabecular connectivity and restored the trabecular architecture in such a way that it changed to having a "plate" structure instead of a "rod" structure, these

Table 2. Impact on fractures. TOP study

| | Vertebral fractures n (%) | | Reduction in absolute risk 95% | Value of p | Relative risk 95% |
|--|---------------------------|---------------------|--|-----------------------|--|
| | Placebo | Treated with PTH | | | |
| New or worsened vertebral fracture (treated with placebo, n=1246; with PTH, n=1266) 3.37% of the patients who completed the study 4.52% of the patients who completed the study | 42 (3.4) | 18 (1.4) | -2.0 (from -3.2 to -0.8) | 0.001 0.05 0.07 | 0.42 (from 0.24 to 0.72) 0.60 (from 0.36 to 1.00) 0.62 (from 0.37 to 1.04) |
| New vertebral fracture (placebo, n=1246; with PTH, n=1286) Without base fracture (placebo, n=1011; with PTH, n=1050) With base fracture (placebo, n=235; with PTH n=236) | 21 (2.1) 21 (8.9) | 7 (0.7) 10 (4.2) | -1.4 (from -2.4 to -0.4) -4.7 (from -9.2 to -0.2) | 0.006 0.04 | 0.32 (from 0.14 to 0.75) 0.47 (from 0.22 to 0.98) |
| New non-vertebral fracture (treated with placebo, n=1246; with PTH, n=1286) | 72 (5.8) | 72 (5.6) | -0.2 (from -2.0 to 1.6) | 0.85 | 0.97 (from 0.71 to 1.33) |

changes resulting from a new mechanism in which the trabeculars are first thickened and then divided by tunnels by the osteoclasts. This trabecular improvement is compatible with the marked reduction in the incidence of vertebral fractures in women treated with PTH 1-84 over 18 months. The values of the structure obtained for trabecular and cortical bone were very similar between those obtained by histomorphometry and by microcomputerised tomography.

This study was carried out in 2008, lengthening the period of treatment to 24 months instead of 18 months and adding on the way a more exhaustive study of bone cytoarchitecture. For this, joining the patients of the earlier study were a sample of 7 patients, also postmenopausal women with osteoporosis who were treated with the drug in the same conditions over 24 months, and who were studied in a similar way⁴², evaluating the formation and structure of trabecular and cortical bone after treatment.

At 24 months, the volume of trabecular bone measured by microcomputerised tomography and histomorphometry was 45-48% higher in those subjects treated with PTH 1-84 in contrast with the placebo, associated with a higher number of trabeculae and higher trabecular tunnelling and thickness. In addition, a more connected, "plate" trabecular architecture was revealed.

The index of trabecular formation (BFR) was 2 times higher in those patients treated with PTH given the greater surface of mineralisation. The osteoblastic and osteoclastic surfaces were 58% and 35% higher, although these parameters did not end up being significant, whereas neither the surface of osteoclasts nor the cortical, endocortical or periostic thickness, were modified with PTH treatment, even though cortical porosity was higher.

It was observed also that, although the formation of trabecular bone was lower after the 24 months of treatment, the measures of the structure of the trabecular and cortical bone were the same in both periods. The bone formed as a result of the treatment with PTH 1-84 had a normal lamellar structure and mineralisation, without any signs of abnormal histology.

As a conclusion, coinciding with that stated earlier, treatment with PTH increases the volume of trabecular bone, as well as its "plate" structure, and this is related with a lower incidence of fractures⁴³.

Biochemical markers for remodelled bone

Due to its anabolic action, the administration of PTH 1-84 produced in the TOP study an increase in the biochemical markers for remodelled bone, specifically bone alkaline phosphatase, barely a

month after the start of treatment. The markers for bone resorption were not modified at the start and only modified after at least 6 months had passed from the start of treatment, at which point an increase in urinary collagen type 1 N-telepeptide was observed. This suggests that PTH 1-84 produces an increase in osteoblastic activity at the start, which, at a later stage increases bone resorption. The markers for remodelled bone remain increased after 18 months of treatment, findings which were consistent with those seen in the bone biopsies obtained from the iliac crests of those patients, in which were observed an approximate doubling in the indices of bone formation⁴⁰. In the PaTH study, to which we refer later, it was observed that the administration of PTH 1-84 produced an increase in biochemical markers for bone formation, specifically of PINP, in months 1, 3 and 12 of 80, 140 and 157%, while blood levels of bone alkaline phosphatase, another marker for bone formation, increased by 22, 46 and 63% over the same period of time. On the other hand, the increase observed in the biochemical markers for bone resorption, specifically blood CTX was 5, 64 and 109% respectively⁴⁴. The point in time at which these changes happen reinforce the hypothesis that the action of PTH is initially anabolic to start with and that later, after approximately 6 months, it produces an activation of the osteoclasts as part of the cycle of remodelled bone.

PTH 1-84 in combined therapy

In the PaTH study, Black et al.⁴⁵ analysed the effect that PTH 1-84 had on BMD, alone, combined with alendronate and with alendronate alone. After a year of follow up, it was found that BMD increased in the lumbar spine in the three groups treated, without statistically significant differences between the group on PTH alone and that which combined PTH and alendronate, and the volumetric density, measured by computerised axial tomography, also increased significantly in the two groups which received PTH. However, the markers for bone formation did not increase in the group which combined PTH with alendronate. When the markers for bone resorption were analysed they were reduced in those to whom alendronate was administered. The authors concluded that the combine treatment with PTH 1-84 with alendronate did not have a synergistic effect, a point which was commented on in detail in an editorial by Khosla⁴⁶, and which, at the time generated considerable controversy.

Another similar study was carried out by Fogelman et al.⁴⁷, who combined PTH 1-84 in postmenopausal women who were receiving hormone replacement therapy. It is a study in which few women participated (only 187 patients were randomised). However, at its conclusion after 2 years the authors found that the women who had received HRT and PTH had obtained higher increases in BMD than those who had received HRT and placebo. However, subsequently, Vestergaard et al.⁴⁸ published a meta-analysis in which the effect

of PTH alone or in combination with other drugs was studied, both on bone mineral density and in the reduction in risk of fracture. The authors reached the conclusion that, although the number of studies on non-vertebral fractures is limited, the aggregated data indicated that PTH administered alone or in combination with antiresorptive drugs would be capable of reducing the risk of vertebral and non-vertebral fractures and of increasing the BMD in the lumbar spine and perhaps in the hip. However, the authors indicated that the results had been obtained on the basis of transversal studies and that more studies are necessary to be able to a definitive conclusion to be reached, and that the superiority of PTH combined with an antiresorptive as opposed to PTH alone with respect to BMD and a reduction in the risk of fracture could not be established.

But, on the other hand, in addition to the combined therapy which we have just analysed (which consists of administering both drugs at the same time), sequential therapy was tried, in which first PTH 1-84 is administered as an anabolic drug, attempting to obtain the maximum gain possible, for a subsequent second phase after suspending the PTH, of administering an antiresorptive. Thus, a study carried out by Rittmaster et al.⁴⁹, studied a group of 66 women who had received PTH 1-84 at doses of 50, 75, and 100 µg /day over one year and after suspending this treatment, were then administered 10 mg/day of alendronate for one more year. During the first year the BMD in all the women (at all the different doses of PTH) increased by $7.1 \pm 5.6\%$ in the lumbar spine, by $0.3 \pm 6.2\%$ in the femoral neck and by $22.3 \pm 3.3\%$ in the whole body. After moving on to the alendronate, at the end of one year the changes in bone mineral density were $13.4 \pm 6.4\%$ in the lumbar spine, $4.4 \pm 7.2\%$ in the femoral neck and $2.6 \pm 3.1\%$ in the whole body. In the subgroup of patients who received the highest dose of PTH, the average increase in BMD in the lumbar spine was $14.6 \pm 7.9\%$. While the treatment with PTH was maintained the biochemical markers for remodelled bone remained at increased levels and decreased to below the initial value after the year on alendronate.

Efficacy and safety of PTH 1-84 in prolonged therapy

We have seen, to this point, that therapy with PTH 1-84, both on its own and combined, is efficacious. However, there is still argument about for how long a period it can be administered with safety and efficacy for the treatment of osteoporosis. Studies such as TOP⁴⁰, talk of a proven efficacy at 18 months, although there is discussion of whether at 24 or even 36 months PTH 1-84 still maintains its efficacy, without causing serious consequences which impede the use of the drug. In fact in our country, PTH 1-84 is approved for use for 24 months. The parameters most often used to measure the efficacy of the drug over the period of treatment has been, on the one hand, the determination of the markers for remodelled bone,

whose changes are correlated with expected action of this type of bone-forming agent, of which the most important is the elevation in bone alkaline phosphatase and the N telopeptides of collagen type 1. The other parameter for the evaluation of efficacy is the reduction in risk of fracture after treatment. On the other hand, to evaluate safety, reference has been made both to the reasons for the rejection of treatment as well as histological studies obtained through trabecular and cortical bone biopsy in long term treatments.

Recalling the conclusions of the TOP study⁴⁰, it could be demonstrated that the administration of 100 micrograms of PTH daily over 18 months, resulted in a therapy efficacious both in the prevention of new fractures and in preventing the worsening of existing fractures in postmenopausal women with osteoporosis. The raised levels of markers for remodelled bone, more specifically bone alkaline phosphatase, was already evident from the first month of treatment, and this elevation was significant in comparison with the placebo group. This did not happen in the same way with the N telopeptides of collagen type 1, although at 6 months levels of both were significantly raised. The most important point is that at the end of 18 months, levels of these markers remained elevated, which perhaps suggests that the drug could continue to act beyond the period covered in the study.

It is for this reason that, subsequently, it was decided to carry out a prolongation of this study, with women who had participated in it, in whom treatment with PTH was extended until they had completed 24 months of treatment. Reference is made here to the OLES study⁵⁰, in which subjects whose adherence to treatment had been 80% were compared with those who had presented less than 80% adherence to treatment. It was observed that at 24 months that the BMD in the lumbar spine those whose adherence was over 80%, was 8.4% higher than that achieved after 18 months of treatment, recorded at the end of the TOP study, and that those subjects with less than 80% adherence succeeded in surpassing those in the TOP study by 4.5%. In the femoral neck, levels 2.6% and 1.5% higher respectively were attained. In terms of the markers for remodelled bone, while a decrease in its levels from months 12-18 could be seen, it could also be observed that in month 24 they would remain raised, or even become higher than those recorded at the end of the TOP study, showing that PTH 1-84 continues to maintain its efficacy after 24 months.

The TRES study (Treatment Extension Study), gathered data from the extension of this treatment, two months after the OLES study in women in whom treatment with PTH 1-84 was prolonged at the same dose, for a total of 36 months. Although it should be noted that in this period of two months between studies there was a slight reduction in BMD, which it is thought could be due to the interruption in treatment, the results obtained after 36 months showed an increase of 8.5% above

the levels of BMD measured in the lumbar spine in the OLES study, as well as a 3.2% increase in the hip and 3.4% in the femoral neck, with the conclusion that the BMD continues to increase, even after 36 months of treatment with PTH 1-84.

With regard to the safety of the drug at 36 months in terms of bone histomorphology, the results obtained in the TRES study were collated by the group led by Recker et al.⁵¹, concluding that the treatment with PTH 1-84 of postmenopausal women with osteoporosis was generally well tolerated, with the biopsies obtained from the trabecular and cortical bone not being pathological. This all suggests that even at 36 months of treatment PTH 1-84 continues to be beneficial in the treatment of osteoporosis.

Adverse effects of treatment with PTH 1-84

While the efficacy of treatment with PTH 1-84 as an alternative to antiresorptive agents used until now against osteoporosis has been proven, it is worth mentioning that there is in turn, a series of frequent adverse effects, which, although on occasion have meant withdrawal the subjects studied which may result in modifying the results, can be resolved.

The adverse physical effects produced due to treatment with the drug are mostly mild^{40,45}, the most common being hypercalcemia, present in 28% of women treated as opposed to 4.6% in the placebo group, and hypercalciuria in 46% and 23% respectively. However, the number of withdrawals from treatment for this reason was small in the clinical trials published (two patients in the PaTH study and six patients in the TOP study) and generally the effect is controlled by withdrawing the calcium and vitamin D supplements which the patients are receiving without requiring a reduction in the dose or withdrawing treatment.

The electrocardiographic studies give similar results in both groups with no significant variation observed in relation to studies carried out at the start of the period of treatment, although it is thought that hypercalcemia may slightly modify these results by diminishing the QT interval, without significant changes, or minimal variations, in cardiac frequency, the PR interval or the duration and axis of the QRS. Other adverse effects described, although infrequent and not of equal importance to those mentioned earlier, were nausea and vomiting.

The reason for which the period of use of PTH is limited was the appearance of a few cases of osteosarcoma in rats, at doses much higher than those used for treatment. These occurred only in rats (Table 3). No increase in the incidence of osteosarcoma, or any other type of tumour, have been detected in humans. Recently Tashjian et al. reported that they have not recorded a single case of osteosarcoma in humans, after the prescription of more than 250,000 treatments with PTH, both 1-34 and 1-84 intact, or even after following up the patients who participated in studies with PTH 1-84 in the 1980s⁵²⁻⁵⁴.

Table 3. Incidence of osteosarcoma in rats treated both with teriparatide and with PTH 1-84 over 24 months. Data obtained from Vahle et al.⁵⁶ for the teriparatide and from Wilker et al.⁵⁷ for the PTH 1-84.

| Doses | Low | Medium | High |
|---------------------------|-----|--------|------|
| Teriparatide (µg/kg) | 5 | 30 | 75 |
| PTH 1.84 (µg/kg) | 10 | 50 | 150 |
| Incidence of osteosarcoma | | | |
| Males (number) | 60 | 60 | 60 |
| Teriparatide | 3 | 21 | 31 |
| PTH 1-84 | 1 | 13 | 27 |
| Females (number) | 60 | 60 | 60 |
| Teriparatide | 4 | 12 | 23 |
| PTH 1-84 | 0 | 5 | 13 |

What is the role of PTH 1-84 in the treatment of osteoporosis?

PTH 1-84 reduces the risk of vertebral fracture, both in patients who had a previous vertebral fracture and in those who did not. Given its price, and the necessity of daily parenteral administration, it is a drug which should be used in patients with a high risk of fracture or when there is no possibility of using the drug of first choice, such as alendronate, risedronate or zoledronate, in accordance with SEIOMM's clinical guides of⁵⁵.

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