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# Osteoporosis y Metabolismo Mineral

**Supplement**

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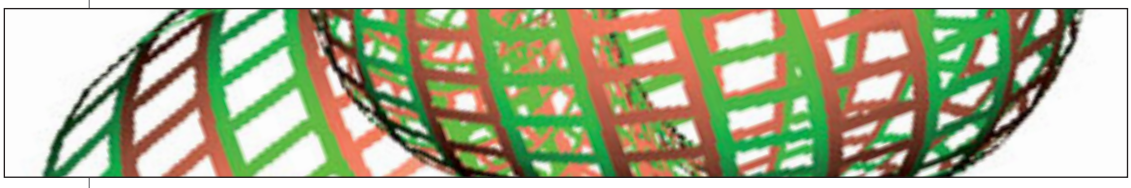

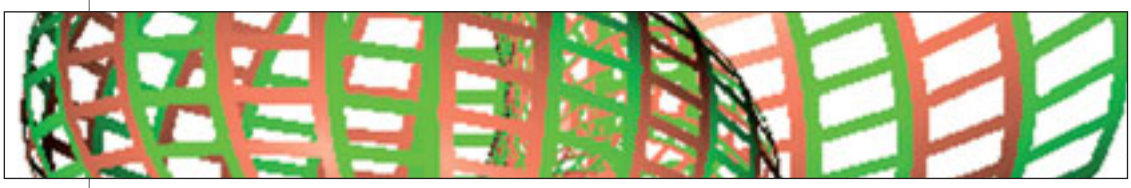


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# Osteoporosis. Definition. Importance. Physiopathology and Clinical manifestations

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## Introduction. Definition

There is no totally satisfactory definition of osteoporosis. In the 50s Fuller Albright defined it as: "too little bone"[1], a concept which is incomplete, since it only captures the quantitative, and not the qualitative, aspect of the disease. Subsequently, in 1988 the American National Institute of Health (NIH) published its first definition, in which osteoporosis is referred to as "a condition in which the bone mass diminishes, increasing susceptibility of bones to suffer fractures"[2]. Nowadays, we accept as the definition of osteoporosis that published by the NIH in the year 2001, updating the earlier definition of 1988, which considered it to be "a disease of the whole skeleton characterised by a low bone mass and an alteration in the bone microarchitecture which causes fragile bone, the consequence of which is an increased risk of fractures."[3].

Although the current definition focuses on what is the fundamental problem in osteoporosis: the existence of greater bone fragility which results in an increase in the risk of suffering fractures, and integrates the loss of quantity (bone mass), with changes in the bone quality, the alterations in microarchitecture, this definition does not have a direct clinical application, because with it we cannot identify patients who suffer from the disease. Thus, in day to day care, the definition of osteoporosis most used is that based the finding of a densitometry with a T-score lower than -2.5, although this definition has the limitation of being based exclusively on quantitative criteria.

## Importance of osteoporosis

Osteoporosis is a preventable and treatable disease, but one which lacks alert signs before the appearance of fractures, which results in many patients not being diagnosed in early phases and being treated early and effectively. Thus, some studies have found that 95% of those patients presenting with a fragility fracture did not have a previous diagnosis of osteoporosis[4].

Osteoporosis is a disease which results for those patients who suffer from it in an increase in morbidity, generating in them a deterioration in their quality of life, as well as increasing mortality, resulting in a significant consumption of social-health resources of all kinds. We discuss each of these independently.

### a) Quality of life

Numerous studies have found that those patients who suffer fragility fractures have shown a deterioration in their quality of life in[5-12]. In all of these cases there was a lower score in all the areas evaluated in the quality of life questionnaires.

Although the cause of this deterioration in quality of life is due in the main to the fractures, the feeling of having a chronic disease which requires long term treatment, and which in many cases occasions the development of a real terror of suffering a fracture[13], means that depression is more common in patients affected by osteoporosis[14-18], which in turn results in a lower score in many of the areas evaluated in the quality of life questionnaire.

Table 1. Mortality associated with the presence of fragility fractures in the Dubbo study, Australia. 1989-2004

| Type of fracture | Female | Male |
|---|---|---|
| | *Odds ratio* (IC 95%) | |
| Proximal extremity of femur | 2.18 (2.03-2.32) | 3.17 (2.90-3.44) |
| Vertebral | 1.66 (1.51-1.80) | 2.38 (2.17-2.59) |
| Other fractures ("major") | 1.92 (1.70-2.14) | 2.22 (1.91-2.52) |
| Other fractures ("minor") | 0.75 (0.66-084) | 1.45 (1.25-1.65) |

**b) Increase in morbidity**

Osteoporosis in itself does not increase the risk of suffering from other diseases, with the single exception, perhaps, of depressive syndrome, as mentioned above. On the other hand, a large number of diseases, or the medication used to treat them, are capable of producing osteoporosis and increasing the risk of fracture. In these cases the osteoporosis is considered to be secondary.

Fragility fractures increase the risk of suffering other fractures[19,20]. So, after suffering a vertebral fracture there is an increase by a factor of 7-10 of suffering new vertebral fractures, and the presence of previous vertebral deformity predicts the occurrence of a hip fracture with a risk quotient of 2.8-4.5, increasing with the number of vertebral deformities[21-23].

In the same line of argument, Lindsay et al, stated that 20% of patients who had a vertebral fracture would suffer a new fracture of this type within a year[24].

The coexistence of various types of fragility fractures is not rare in patients with osteoporosis.Thus, for example, in a national cooperative multicentric study carried out in women who had been admitted after presenting with a fracture of the proximal extremity of the femur, it was observed that there was at least one vertebral fracture in 62.6% of cases, with the notable fact that in practically all those cases there had not been, prior to the study, a diagnosis of vertebral fracture[25].

The 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 common in the perimenopause and their incidence increases rapidly after the menopause to stabilise at 65 years of age. In males the incidence stays practically constant with age. This type of fracture only requires hospitalisation in less than 20% of cases, but increases the risk of hip fracture by 50%[26,27].

**c) Increase in mortality**

Various studies have shown that those patients who suffer fragility fractures had an increase in mortality, both in descriptive studies, in which is reported the mortality associated with osteoporotic fractures, and in cohort studies, in which it is observed that fractured patients had a higher mortality compared with controls of the same age and sex who did not have fractures. In some studies the description "excess of mortality" was used, since those patients affected by osteoporosis are generally patients of advanced age, especially those with fracture of the proximal extremity of the femur, in whom mortality is naturally high[28-30].

Thus, various studies carried out in this country on the epidemiology of the fracture of the proximal extremity of the femur[31,32] have shown that the mortality of the proximal extremity of the femur in its acute phase, considered to be during the first month after fracture, varies between 6% and 10%[33], but if a follow up is made of these patients, the mortality increases up to 30% in the first year after the fracture 31 and reaches 40% at 2 years.

The Dubbo study, Table 1, carried out in Australia between 1989 and 2004 in a population of 2,413 women and 1,898 men of over 60 years of age, also observed that those patients who had suffered an osteoporotic fracture had a higher mortality in comparison with those who did not have fractures. In this cohort the males presented a mortality higher than that of the women in all fractures[33]. Similar results were obtained in a metaanalysis carried out in patients of both sexes who had suffered a fracture of the proximal extremity of the femur. It was observed that older people had an increased risk of mortality, from all causes, of between 5 and 8 times, after only 3 months having passed from the moment of the fracture, and that this increased risk was also greater in men than in women[29].

**Physiopathology[34]**

Bone is a tissue in a state of constant formation and destruction throughout life. This phenomenon is known as bone remodelling and comes about by means of bone remodelling units which consist of a combination of cells charged with destroying small pieces of bone, which are later substituted by new bone. Bone remodelling has two main functions: in the first place, to substitute old bone tissue for new, increasing the resistance of the

skeleton to fractures, and in the second place, to make available minerals such as calcium, phosphorus or magnesium, to be transported from the bone to the extracellular liquid, and vice versa, according to the needs of the organism (Figure 1).

The cells which participate in bone remodelling are of various types, but there are two principal protagonists in the process: the osteoclasts, which are macrophages specialised in destroying bone, a phenomenon called "bone resorption", and the osteoblasts, cells derived from the connective tissue which are charged with forming bone. There are other cells, such as the osteocytes, lymphocytes, macrophages and endothelial cells which lend their support to the bone remodelling process[35].

In osteoporosis there is a dysfunction in the units of bone remodelling which, in turn, is due fundamentally to two types of changes. The first consists in the establishment of a "negative balance"; the second in an increase in the number of units of bone remodelling, which gives rise to what is called " increased bone turnover".

**a) Negative balance**

In young adults there is a "zero" bone balance, since the quantity of bone which the osteoblasts form in each unit of bone remodelling is equal to that which has earlier been destroyed by the osteoclasts. However, at around 40 years of age, the quantity of bone formed by the osteoclasts begins to be slightly lower than that destroyed by the osteoclasts. This situation is described as being in "negative balance", and its consequence, logically, is the reduction in the total quantity of bone. Depending on the initial bone mass, level of negative balance, and the period during which it has been happening (ultimately, the age of the person), this loss may lead to values of bone mass which we would qualify as osteoporotic. Therefore the negative balance is a *sine qua non* for the development of osteoporosis.

The negative balance which develops with age is due fundamentally to a reduction in bone formation, probably related both to a decrease in the number of osteoblasts (due in part to a diminution in their precursors, in part to a reduction in their differentiation, and partly to a reduction in their survival) as well as in their individual activity. This is due, at least partly, to the fact that the concentration of stimulatory factors for these cells also diminishes in the bone's microenvironment, which in some cases (Wnt proteins) has been attributed to an increase in ROS radicals in aging. On occasion an increase in bone resorption contributes to the negative balance, due to an increase in osteoclastic activity. This increase may translate, also, into a greater range for the osteoclast, up to the point at which the trabecular may become perforated. On the other hand, this increase in the activity of the osteoclasts is accompanied by the birth of a greater number of units of bone remodelling, which leads to the phenomenon we know as "increased turnover". Against the reduction in the activity of the osteoblasts due to age, the increase in the activity of the osteoclasts bears a relationship with the reduction in estrogens. The lack of this hormone probably also inhibits the formative activity by favouring the apoptosis of the osteoblasts, which intensifies the negative balance.

Figure 1. Physiology of osteoporosis. Heterogeneity of remodelled bone

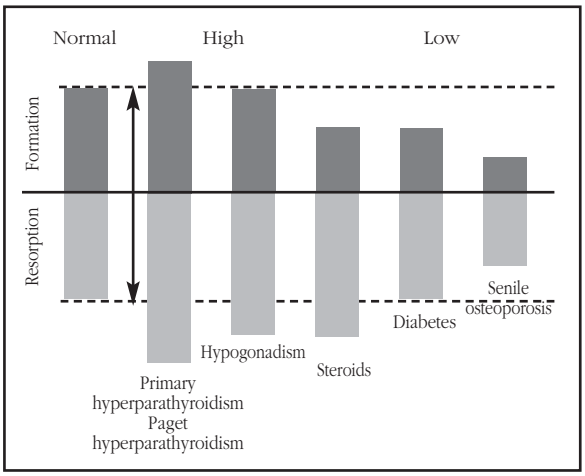


Figure 2. Lateral radiography of the spine showing a vertebral fracture

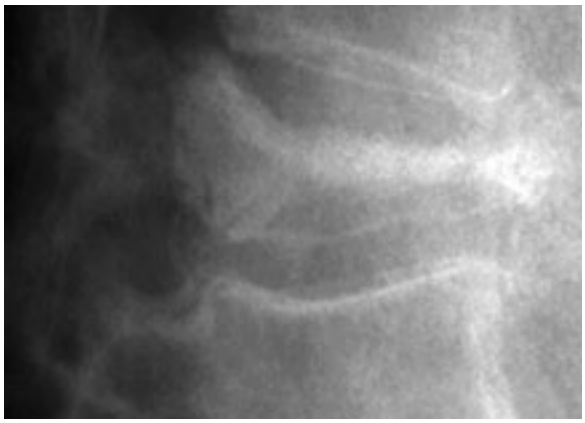

Figure 3. Measurement of the span

**b) Increase in bone turnover**

The increase in the number of units of bone remodelling when they find themselves in negative balance results in an increase in the number of

Table 2. Symptoms and signs which can be observed in patients with diseases capable of producing secondary osteoporosis.

| Disease | Symptoms | Signs |
|---|---|---|
| Rheumatoid arthritis | Pain<br>Functional impotence<br>Swelling<br>Morning stiffness | Inflammation of the joints<br>Rheumatoid nodules<br>Finger deformities |
| Cushing disease | Weight gain | "Full moon" face<br>Vinous stretch marks<br>Obesity<br>Arterial hypertension |
| Anorexia nervosa | Changes in perception of body shape<br>Bulemic behaviour | Thinness<br>Amenorrhea |
| Chronic alcoholism | Behavioural changes<br>Ethyl fetor | Parotid hypertrophy Gynecomastia<br>Hepatomegalia Spider angiomata*<br>Collateral circulation*<br>Ascitis* |

**In the presence of hepatic cirrhosis*

points in the skeleton in which bone mass is lost, and thus an acceleration in this loss. In fact, although the negative balance is an indispensible factor in the development of loss of bone mass, the factor which usually has the responsibility for the greatest quantity of loss of bone mass is the increase in turnover. The forms of osteoporosis in which this factor effectively plays a primordial role are known as "high turnover osteoporosis". The most characteristic example of increased bone turnover is the menopause, with the depletion of estrogen which it brings. It is this increase in bone turnover to which the acceleration of loss of bone mass which follows is due, and which, ultimately, is the mechanism responsible for "postmenopausal osteoporosis". In persons of an advanced age, the increase in bone turnover may be due to the development of secondary hyperparathyroidism, which in turn may lead to both a reduction in renal function as well as a reduction in blood levels of vitamin D[36].

However, it should be taken into account that the heterogeneity of osteoporosis allows that there are some cases of this disease in which bone turnover is not increased, such as occurs in idiopathic osteoporosis in males, although these clinical circumstances are certainly much less frequent[37].

## Clinical manifestations

Osteoporosis in itself does not hurt, nor does it produce any kind of symptoms. The clinical manifestations of this disease come as a result of the fractures. It is a general error to attribute to osteoporosis musculo-skeletal pain in any of its manifestations: joint discomfort, arthralgia and myalgia, general pain in the skeleton...etc. There is no clinical relationship between osteoporosis and arthrosis or fibromyalgia, and if these processes coincide in a patient, it is by chance.

Fragility fractures constitute the principal, if not the only, clinical complication of osteoporosis[38]. Although certainly almost any fracture may be observed, with the exception of that of the cranium, the bones most commonly affected are the vertebrae, (Figure 2) the distal extremity of the radius , the proximal extremity of the femur (called, incorrectly, a hip fracture) and fracture of the humerus. From a practical point of view, the fractures are usually classified as vertebral or non-vertebral. We are not, personally, in agreement with this classification, since it considers equally as "non-vertebral fractures" fracture of the rib and fracture of the proximal extremity of the femur.

Vertebral fractures usually cause back pain. In the acute phase this can be accompanied by antialgic muscular contraction. The pain often becomes chronic. In a co-operative multicentric study carried out in Spain in postmenopausal women who attended the internal medicine outpatients clinic due to chronic back pain, it was found that there was at least one vertebral fracture not previously diagnosed in 15.8% of them[39]. On the other hand, one may also observe loss of height and development of dorsal kyphosis[40]. In the aforementioned study, the women with vertebral fracture had an average of 3 cm less in height than the women in the control group, without fractures.

An approximation can be made of the loss of height which has occurred in a patient by measuring the distance between the two middle fingers, with the patient seated and their arms completely outstretched (Figure 3). In normal conditions, the distance between the ends of the two fingers

corresponds approximately to the height of the patient, a fact which has been known since Renaissance times (remember the Vitruvian Man of Leonardo da Vinci).

Finally, the clinical history and physical examination may show up symptoms and signs of other diseases capable of producing secondary osteoporosis as their complications. A non-exhaustive account of these data is shown in Table 2.

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# Epidemiology of osteoporotic fractures: vertebral and non-vertebral fractures

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Osteoporosis is a common disease, responsible for most of the fractures which occur after the age of 50 years. It is a worldwide health problem of great magnitude which increases with the aging and the lifestyles of the population, especially in Western countries. The main complication is fracture which carries with it a high health and social cost[1]. In spite of the fact that it is a preventable and treatable disease, to date, policies developed to deal with it so far have not managed to reduce the problem. Osteoporosis is defined as a general disorder of the skeleton characterised by low bone mass and deterioration in the microarchitecture of the bone tissue, which is translated into a diminution of bone resistance which predisposes it to fracture[2]. Bone resistance is made up of two components – bone density and bone quality. In turn, the concept of quality attempts to integrate all those factors, apart from bone mass, which contribute to bone fragility, and which include among others, the microarchitecture, the degree of bone turnover, the accumulation of lesions or microfractures and degree of mineralisation[2,3].

According to the definition, the most significant clinical fact is fragility fracture. The absence of manifestations of osteoporosis without fracture make diagnosis difficult. Without methods of evaluating quality, or its components, the diagnosis is based on the confirmation of low bone mineral density (BMD). Thus, in 1994 the WHO agreed an operative definition based on levels or cut-off points of BMD for white postmenopausal women[4]. Thus, it was proposed that normal levels for BMD be set at a value higher than a -1 standard deviation (SD) in relation to the average for young adults (T-Score > -1); for osteopenia, values of BMD between -1 and -2.5 SD (T-Score between -1 and -2.5); for osteoporosis, values of BMD lower than -2.5 SD (T-Score lower than -2.5) and established osteoporosis, when, along with these conditions, are associated one or more osteoporotic fractures (Table 1). It has recently been recommended that these same cut-off points be used for osteoporosis in males[5].

In the epidemiology of osteoporosis it is necessary to distinguish between the concepts of osteoporosis and osteoporotic fracture. The available data are limited by problems due to the definition of osteoporosis, diagnostic methods, the existence of asymptomatic fractures and the characteristics of the population studied.

## Epidemiology of osteoporosis

It is estimated that there are 75 million people who suffer from osteoporosis in the US, Europe and Japan[6]. In accord with the WHO criteria, it has been estimated that the prevalence of osteoporosis in white women over 50 years of age is 15% when one of the three usual locations (spine, hip or writs) is measured, and 30% when measured in all of them[7]. The prevalence increases with age from 15% for the period between 50 and 59 years of age, up to more than 80% in ages over 80 years[8]. In males, the prevalence of osteoporosis is lower, 8% according to the NHANES study[9].

Table 1. Diagnostic criteria for osteoporosis from the WHO

| Valuation | Value of BMD |
|---|---|
| Normal | T-score >-1 SD |
| Osteopenia | T-score entre -1 y -2,5 SD |
| Osteoporosis | T-score <-2,5 SD |

*T-score: value of BMD compared with the average value in a young adult expressed in terms of standard deviation*

Nearly 2 million women and 800,000 men have osteoporosis in Spain. Díaz Curriel et al. found a prevalence of densitometric osteoporosis of 26.07% (95% CI, 22.57-29.57%) in women over 50 years of age[10]. As expected, the prevalence in males was less, 8.1% in those older than 50 years[11] and 11.3% in those over 79 years of age[12].

## Epidemiology of fractures

Bone fractures have a bimodal distribution, the first stage occurring during adolescence and youth, with the second peak of frequency in old age. The first fractures are traumatic, predominantly in the large bones and affect males more. In the later stage the fractures are more frequent in women, occur with minimal trauma and are predominantly in the vertebrae, hip and wrist. These are the complications of osteoporosis and are responsible for its serious clinical consequences and socioeconomic costs. Johnell et al. studied the consequences of incapacity produced by osteoporosis in Europe which exceeds the overall impact of many cancers and other chronic diseases such as rheumatoid arthritis, asthma or the cardiac repercussions of hypertension[13].

Osteoporotic fractures are classified as vertebral or non-vertebral. Those of the hip, wrist and humerus are the most common, but many others are related to bone fragility. Only fractures of the face or the ankle have no clear relationship with a reduction in BMD, and thus are not considered as osteoporotic[14]. Neither, among vertebral fractures, are cervical or thoracic fractures above T5 considered to be osteoporotic.

It has been calculated, using data from 2000, that there were more than 9 million osteoporotic fractures worldwide, of which more than half were in Europe and the US, with the following distribution: hip, 1.6 million; forearm, 1.7 million; and clinical vertebral (symptomatic), 1.4 million[13]. The current data have been projected into the future and it is estimated that fractures will increase in the next few decades[15]. There are no direct overall data on the number of fractures in Spain, it is likely that it could amount to 25,000 fractures per year, with direct costs higher than 126 million euros and indirect costs of more than 420 million euros.

## Vertebral fracture

The prevalence of vertebral fractures is difficult to quantify. More than two thirds are asymptomatic and can only be diagnosed by imaging methods, generally lateral radiography of the lumbar and dorsal spine[16,17]. There are various methods proposed for the radiological recognition of vertebral fractures, which limits the uniformity of the results. The presence of a previous fracture in women of over 65 years of age multiplies by 7-10 times the risk of suffering another new fracture in the next 5 years[18]. It also increases the probability of suffering non-vertebral fractures, which is estimated to have a risk quotient of 2.8 – 4.5, and this increases with the number vertebral deformities.

Vertebral fractures are infrequent before the age of 50 and, as with other fractures, increase with age. Various studies have indicated that their prevalence in women over 50 years of age is between 18 and 28%[19]. In Europe, the data on prevalence come mainly from the "European Vertebral Osteoporosis Study" (EVOS), in which a prevalence of 12.2% for males, and 12% for ages between 50 and 79 years, was observed[20]. The individuals from this study were subsequently included in a prospective study "European Prospective Osteoporosis Study" (EPOS)[21]. The annual incidence is considered to be 1% in women of 65 years of age, 2% in those of 75 years and 3% on those over 85 years of age. In males over 50 years of age it is from 5.7 to 6.8/1,000 person/years, which is equivalent to approximately half that seen in women[22].

## Hip fracture

Hip fractures are considered, from the point of view of their prognosis, the most important fractures due to their associated high morbimortality. Fewer than half patients return to their previous state, with 25% requiring home care and 20% remaining in a state of dependency after the fracture.

Table 2. Risk factors for osteoporotic fractures

| | High Risk | Moderate Risk |
|---|---|---|
| Mixed (Associated with BMD + independent component) | Advanced age<br>Personal history of osteoporotic fracture<br>Maternal history of hip fracture<br>Low weight *<br>Glucocorticoids**<br>High level of remodelled bone | Diabetes mellitus<br>Smoking |
| Associated with low BMD | Hypogonadism in males<br>Primary hyperparathyroidism<br>Anorexia nervosa<br>Prolonged immobilisation<br>Anticomicials<br>Malabsorption | Female sex<br>Early menopause***<br>Amenorrhea<br>Rheumatoid arthritis<br>Hyperthyroidisms<br>Vitamin D deficit<br>Low intake of calcium**** |

*High risk: when the relative risk > 2. Moderate risk: relative risk > 1 and < 2. * Body mass index: < 20 kg/m². **Period of more than 3 months and more than 7.5 mg prednisone/day. ***Before 45 years of age. ****Lower than 500-850 mg/day. Factors related to a tendency to falls, and associated with the occurrence of fractures, are considered as independent factors. BMD: bone mineral density*

The incidence of hip fractures increases exponentially with age and in women is twice that in men[23]. The majority occur after a fall from a height equal to or lower than the patient's height. The overall risk of hip fracture from 50 years of age in the United Kingdom is 11.4% and 3.1% for women and men respectively. The incidence varies substantially from one population to another, and is usually higher in white Caucasian individuals. In Europe, the proportion of hip fractures varies by a factor of up to 7 across different countries. Spain is considered to be a low incidence zone[24], while in Norway, Sweden, Iceland, Denmark and the US, the incidence is high[25]. In this country, the annual incidence is highly variable and varies between 301/100,000 and 897/100,000 patients over 65 years of age[26].

## Wrist fracture

Distal cubital and radius fractures, or Colles fractures, have a presentation profile different from the abovementioned fractures. Data on this fracture is more scarce than with hip or vertebral fractures. Most of the incidence data comes from the Northern hemisphere, principally the Scandinavian countries, the United Kingdom and the US. There is an increase in the incidence in Caucasian women between 40 and 65 years, followed by a plateau which continues over the later years[19], which has been related with a change in neuromuscular reflexes caused by aging, and by a tendency to suffer falls, whose impact individuals automatically attempt to cushion with outstretched arms. This type of fracture appears mainly in women and, largely, after 65 years of age. In the United Kingdom, the risk of fracture over their life-time for women of 50 years of age is 16.6%, while at 70 years this risk falls to 10.4%. The incidence in males is significantly lower and does not change much with age (risk over the rest of their life-time is 2.9% at 50 years and 1.4% at 70 years)[27].

## Risk factors for fractures

There are various factors which facilitate the development of osteoporotic fractures. The most significant of all these is low BMD, which accounts for 70% of bone fragility. However, there are other factors, independent of BMD, probably related to bone quality. It should also be taken into account that the mechanism related to the mechanical impact of falls also has a role in the development of fractures. A number of these factors interact in a complex way in each individual. The principal risk factors[3] are listed and summarised in Table 2.

## Fractures and mortality

The available data indicate, without a doubt, that one of the consequences of fractures is an increase in mortality, which depends on the type of fracture. This is especially high in hip and vertebral

fractures[28]. In the cohort from Rochester, USA, it was found that the survival rate at 5 years from suffering a vertebral or hip fracture was 80% of that expected in men and women without fracture of a similar age[29]. But in more recent studies coming from the cohort from Dubbo, Australia, it has been found that there is an increase in mortality in all types of fracture, including after minor fractures in patients older than 75 years of age[30]. Mortality is higher immediately after the fracture and reduces over time. In the case of a hip fracture the increase in mortality remains high during at least 10 years, while for the remaining fractures it starts to reduce after 5 years. The causes of the mortality are not always directly related to the fractures, with associated diseases, disability, and immobility due to pain which may facilitate infections, appearing to be additional determinants.

In hip fractures mortality is higher in men than in women and increases with age. As was expected, it is higher in patients with other concurrent diseases, with worse functional capacity before the fractures and with an increase in fragility[31]. Approximately 8% of men and 3% of women over 50 years of age die during hospitalisation. In the United Kingdom, survival after suffering a hip fracture is 63.3% in men against an expected 90.0%, and 74.9% in women against an expected 91.1%[27]. The risk of death is highest immediately after the fracture and reduces gradually with time, although it remains raised for 10 years after the fracture[30]. The cause of death is not usually attributed directly to the fracture, but to other concomitant diseases and to the fragile state of the patient[31]. One of the factors which influences a poor prognosis is the period of time which passes until a surgical intervention, since mortality increases when this is delayed beyond the second day[32]. In Spain, using data from the Ministry of Health, mortality during hospital admission due to a hip fracture is 8.4% for men and 4.8% for women[33]. Curiously, the mortality is higher in regions with cold climates.

Vertebral fracture is also associated with an increase in mortality. In the American cohort of the "Study of Osteoporotic Fractures" (SOF) it was found that women with vertebral fractures were 1.26 times more likely to die[34]. In other studies such as EVOS, the risk was raised to 2.4 times, without a difference between the sexes[35]. Mortality increases with the number of crushed vertebrae by 32% for each new vertebra[36]. Mortality remains raised for at least 5 years, subsequently declining. Among the causes were pulmonary problems and cancers, especially of the breast.

In terms of the influence of other types of fractures on survival, there are contradictory results. Some authors did not find a relationship between wrist fracture and other non-vertebral fractures[29,37]. But in very recent data it has been found that those patients with any type of osteoporotic fracture had a diminished rate of survival. Non-vertebral fractures other than those of the hip are responsible for an increase in mortality, especially in patients older than 75 years of age[30].

## Conclusions

Osteoporosis is a worldwide health problem of considerable magnitude. The frequency of the disease and, above all, of fractures, has a very high socioeconomic cost. The fractures have serious consequences, with repercussions on the person who suffers them since they reduce survival and quality of life, and aggravate concurrent diseases. It is estimated that this situation will worsen in the next few years. Therefore, it is essential to design therapeutic and preventative strategies to limit their consequences.

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# Bazedoxifene. First 3rd generation SORM. Safety in endometrium and breast

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Bazedoxifene is a new drug which belongs to the group of modulators selective for oestrogen receptors (SORMS), a class of drugs which act selectively on oestrogen receptors (ORs). Recently approved in the European Union and in the regulatory review process in the United States for the prevention and treatment of postmenopausal osteoporosis[1], bazedoxifene has appeared on the market as a daily oral drug for the treatment of postmenopausal osteoporosis.

The latest clinical data on the modulators selective for oestrogen receptors has served as a base for the re-evaluation of the SORM concept. The SORMs have effects on tissues which contain ORs, such as the breast, bone, uterine and genitourinary tissue, and brain, and on markers for cardiovascular risk. The current evidence indicates that each SORM has a unique range of clinical activity. The differences in the patterns of actions of the SORMs suggest that each clinical variable should be evaluated individually, and that the conclusions around any particular SORM can only be established through appropriate clinical trials.

The action mechanism of the SORMs occurs through the bonding of two types of oestrogen receptors: alpha (OR-α) and beta (OR-β). The SORMs have agonistic and antagonistic properties at the same time, depending on the type of tissue[2,3]. This is explained, in part, by the availability of different sub-types of ORs in different tissues.

## Effects of bazedoxifene on different tissues of the body

Bazedoxifene has shown an affinity for the OR-·s and betas (OR-β), with a slightly stronger affinity for the OR-α. They act as competitive inhibitors of estradiol in the oestrogen receptors, which indicates an antagonistic effect in the presence of high levels of estradiol, whilst it has an agonistic effect at low levels of estradiol[4].

Safety of the endometrium and breast is an important consideration in evaluating therapy with SORMs[5]; the clinical development of various SORMs which have been being researched for postmenopausal osteoporosis have been suspended, in part, because of concerns about endometrial safety.

## Effect on the endometrium

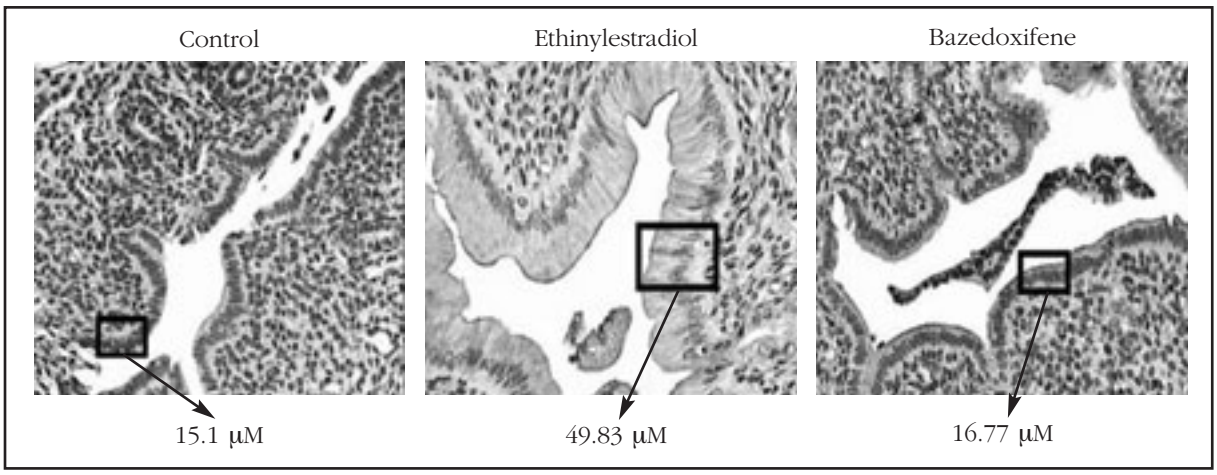
Endometrial hyperplasia is a surrogate marker for the development of endometrial cancer. The histological classification of endometrial hyperplasia shows transitions from simple hyperplasia (a benign lesion) through to adenomatose hyperplasia or atypical hyperplasia. While some SORMs such as tamoxifen clearly induce endometrial hyperplasia (an oestrogenic agonist effect), and increase the risk of developing endometrial cancer 6, others, such as raloxifene, do not appear to have an agonistic effect on the endometrium[7].

### • Preclinical data

The wet weight of the uterus of an immature rat is an accepted animal model for measuring oestrogenic effects. An increase in the wet weight of the uterus indicates a response to the oestrogen or the stimulation of the uterus.

In evaluating different doses of bazedoxifene, with a dose of 0.5 mg/kg there was an increase in wet

Figure 1. Activity on uterine tissue in immature rat model. Ethinylestradiol induces a 3-fold increase in the height of the luminal cells. This effect has been observed with raloxifene. Bazedoxifene induces a slight, non-significant increase in cellular height. Taken from: Komm BS, et al. Endocrinol 2005;146: 3999-4008




weight of the uterus of 35%, while at a dose of 5 mg/kg, paradoxically, there was no significant difference in weight[8]. It was notable that the increase in weight with the 0.5 mg/kg dose was not accompanied by hypertrophy of the luminal epithelial cells or hyperplasia, hypertrophy of the myometrium or luminal distension (Figure 1). Bazedoxifene does not stimulate the oestrogen receptors of the uterus at a dose of 0.5 mg/kg, while a dose of 5 mg/kg is antagonistic in the rat animal model[4,8].

**• Clinical data**

The effects of bazedoxifene on the endometrium were evaluated in a total of 497 healthy postmenopausal women (average age: 53 years) in a two-part study, double blind, randomised and controlled with active treatment and placebo[9]. All retained their uterus, and received at least one dose of medication, and a vaginal ultrasound was carried out at the start and at least once more during the follow up.

• In the first part of the study, 302 women received bazedoxifene daily of 2.5, 5, 10 or 20 mg, 0.625/2.5 mg of oestrogen combined with medroxyprogesterone acetate (CEO/MPA), or a placebo, for 6 months. There were no significant differences in endometrial thickness with doses of 2.5 to 20 mg/day in comparison with the placebo, while there was a small but significant increase in endometrial thickness with CEO/MPA in comparison with the placebo ($p < 0.05$). Bazedoxifene at 10 and 20 mg significantly reduces the endometrium stimulated with combined equine oestrogen (COE)[4]. Due to the first results of this study being favourable, it was broadened for a second phase.

• In the second phase of the study (N=497), bazedoxifene at doses of 30 and 40 mg/day is associated with a significantly lower change in endometrial thickness in comparison with the placebo ($p<0.001$), indicating a greater antagonism in the endometrium with the higher doses. None of the biopsies showed endometrial hyperplasia. It was concluded that bazedoxifene in doses of up to 40 mg/day is well tolerates and does not stimulate the endometrium[9]. At doses of 2.5 to 20 mg/day the average change in the endometrial thickness from the start was no different from that observed with the placebo. The average change in thickness with 30 and 40 mg/day was significantly less in comparison with those treated with the placebo, which suggests antagonistic action on the ORs of the endometrium, a feature which had not previously been reported with any other SORM.

Bazedoxifene has been evaluated in two large Phase III prospective studies, for the prevention and treatment of osteoporosis[10,11].

• In a two year study 10 of healthy postmenopausal women at risk of osteoporosis (N= 1,583; average age, 57.6 years), randomly allocated to daily treatment with bazedoxifene at 10, 20 or 40 mg, raloxifene at 60 mg, or placebo, the endometrial thickness with bazedoxifene endometrial thickness remained stable during the period of treatment of two years, without differences from the start, or compared with the placebo[10,12]. There were no diagnoses of hyperplasia or endometrial cancer with the treatment with bazedoxifene, nor were there significant differences in the incidence of endometrial polyps between the placebo (3.5%) and bazedoxifene at 10, 20 or 40 mg (2.2.%, 3.4% and 2.3% respectively) or with 60 mg of raloxifene (4.7%)[10,12].

• In the 3 year reference trial[11], in the population of postmenopausal osteoporotic women (N= 7,492); average age, 66.4 years) randomly allocated to bazedoxifene at 20 or 40 mg, raloxifene at

60 mg or a placebo, who at the start of the study presented an endometrial thickness of 5 mm or less determined by transvaginal ultrasound, the long term therapy with bazedoxifene showed it to have good levels of safety in the endometrium, ovaries and breast[13]. The changes in endometrial thickness from the start with bazedoxifene were no different from those of the placebo. The incidence of endometrial polyps was similar between the groups on bazedoxifene and the placebo[11]. There was a report of endometrial hyperplasmia in each treatment group, endometrial carcinoma was reported in two, two and three participants treated with 40 mg bazedoxifene, 60 mg of raloxifene and the placebo, respectively[11]. In general, bazedoxifene was associated with a neutral effect on the endometrium similar to that of the placebo, since the ultrasound tests did not show clinically significant changes in endometrial thickness. The incidence of endometrial hyperplasia, cancer or polyps did not increase in comparison with the placebo. A higher proportion of participants treated with raloxifene were diagnosed with endometrial polyps in comparison with those treated with bazedoxifene or the placebo in this study. The treatment with raloxifene was associated with a significant increase in endometrial thickness at 12 months in relation to the placebo (p= 0.01). A small but significant increase in endometrial thickness had already been observed in a large randomised trial in postmenopausal women treated with raloxifene[7], although the histological reviews in this and other studies did not show a higher risk of hyperpalsia or cancer of the endometrium.

## Effects in mammary tissue

Prospective studies have found that some SORMs reduce the risk of breast cancer by reducing the levels of endogenous estradiol[15]. Tamoxifen and raloxifene block the effects of endogenous oestrogens in the breast 16 and reduce the risk of breast cancer[7].

### • Preclinical data

The stimulatory effect of an agonist on the ORs induces a proliferation in the MCF-7 cell line (human cells of mammary adenocarcinoma). Bazedoxifene does not promote the proliferation of these mammary cells, and in the presence of cells treated with 17-β-stradiol, inhibits this proliferation[8]. This inhibition is dependent on the dose, and there is evidence that bazedoxifene is probably an antagonist in this tissue. The effect of raloxifene in this tissue is similar[4,8,14].

### • Effect on mammary pain

Self-referred mammary pain was evaluated in a 6 month trial in 351 postmenopausal women randomly selected to receive bazedoxifene at 2.5, 5, 10 or 20 mg, CEO+MPA or a placebo[17]. The women who received CEO+MAP reported a significant increase in mammary pain; in women who took any dose of bazedoxifene it was not significantly different from the placebo. Because of these results the study was extended to include 236 additional postmenopausal women to evaluate bazedoxifene at 20 mg and 40 mg compared with a placebo. It was confirmed that mammary pain was no different with 20 mg bazedoxifene than with the placebo, and that the 40 mg dose was associated with a significant reduction in mammary pain in comparison with the placebo (p= 0.034)[17].

### • Mammographic density

An increase in mammographic density is one of the main risk factors known for breast cancer[18], and a higher risk of breast cancer with a higher mammary density may reflect the cumulative effects of the oestrogens on mammary tissue.

The effects of the SORMs on mammary density is of clinical interest, given the continuing development of these agents for use in postmenopausal women. Studies with tamoxifen and raloxifene have provided evidence that these SORMs do not affect mammographic density[19,20].

A retrospective review of the mammograms of a subset of women who had participated in the reference trial for the treatment of osteoporosis[11] showed that treatment with bazedoxifene at 20 and 40 mg over 2 years did not affect the age-related changes in mammary density evaluated by digital mammography, and this effect was similar in those on raloxifene and the placebo[21].

The greatest reduction in mammary density normally occurs at around 45 years of age, stabilising at around 60 years of age[22]. Given that the women who participated in this study had an average age of approximately 59 years and were almost 13 years postmenopausal, it is reasonable to expect that the majority of these women would already have experienced a significant reduction in mammary density related to their age before they joined the study. Therefore, the effects of bazedoxifene on mammary density in recently menopausal women could be different to that of the older menopausal women who participated in this study, about which better information is needed.

### • Mammary pathology

As has been shown with other SORMs, in the Phase III study which compared bazedoxifene at doses of 20 or 40 mg/day, raloxifene at 60 mg/or placebo, at 3 years fewer women presented with mammary cysts and/or fibrocystic mammary disease with 20 or 40 mg of bazedoxifene (0.7 and 0.6%, respectively) in comparison with 60 mg of raloxifene (1.7%) or placebo (1.0%)[11]. No significant differences were reported in the incidence of breast cancer between the treatment groups, although there was a lower frequency in those groups treated with bazedoxifene than in the placebo or raloxifene groups[11].

In another study of similar design to study the safety of bazedoxifene in the endometrium, ovary and breast[13], there was a significantly lower incidence of fibrocystic mammary disease with bazedoxifene compared with 60 mg of raloxifene, although the

Table 1. Adverse events associated with different doses of bazedoxifene compared with a placebo

| Adverse event | Number of subjects (%) | | | | |
|---|---|---|---|---|---|
| | **BZD 10 mg (n = 321)** | **BZD 20 mg (n = 322)** | **BZD 40 mg (n = 3,191)** | **RLX 60 mg (n = 311)** | **Placebo (n = 310)** |
| Any adverse event | 306 (95.3) | 309 (96.0) | 301 (94.4) | 287 (92.3) | 297 (95.8) |
| Any adverse event arising from treatment | 299 (93.1) | 304 (94.4) | 292 (91.5) | 279 (89.7) | 289 (93.2) |
| Deaths | 2 (0.6) | 0 | 3 (0,9) | 0 | 1 (0,3) |
| Any adverse event which results in abandonment | 54 (16.8) | 55 (17.1) | 58 (18.2) | 43 (13.8) | 48 (15.5) |
| Any serious adverse event | 29 (9.0) | 37 (11.5) | 33 (10.3) | 29 (9.3) | 28 (9.0) |
| Adverse effects of special interest* | | | | | |
| • Myocardial infarction | 0 | 2 (0.6) | 1 (0.3) | 0 | 1 (0.3) |
| • Cerebral haemorrhage | 1 (0.3) | 0 | 0 | 0 | 0 |
| • Cerebral ischemia | 0 | 0 | 0 | 1 (0.3) | 0 |
| • Cerebrovascular accident | 0 | 0 | 1 (0.3) | 0 | 0 |
| • Deep vein thrombosis | 0 | 2 (0.6) | 0 | 0 | 1 (0.3) |
| • Phlebitis (superficial) | 1 (0.3) | 1 (0.3) | 3 (0.9) | 0 | 1 (0.3) |
| • Pulmonary embolism | 0 | 0 | 1 (0,3) | 0 | 0 |
| • Retinal thrombosis | 0 | 0 | 0 | 1 (0,3) | 0 |
| • Breathlessness | 63 (19.6) | 67 (20.8) | 77 (24.1) | 58 (18.6) | 44 (14.2) |
| • Cramp | 30 (9.3) | 39 (12.1) | 38 (11.9) | 37 (11.9) | 36 (11.6) |

*Data taken from: Miller PD, Chines A, Christiansen C, et al. Effects of bazedoxifene on bone mineral density and turnover in postmenopausal women: 2-year results of a randomized, double-blind, placebo- and active-controlled study. J Bone Miner Res. 2008; 23(4):525–535*

number of women and of mammary events was too small to allow definitive conclusions to be drawn. In general, the incidence of adverse events related to the breast in groups treated with bazedoxifene was similar to that reported in the placebo group. There were fewer cases of breast cancer with bazedoxifene in comparison with the placebo or raloxifene[13].

These findings suggest a possible protector effect of bazedoxifene on the breast. However, we do not have data available to calculate with precision the reduction in the risk of breast cancer attributable to bazedoxifene, or to estimate the number of women who need to be treated to prevent a single case of invasive breast cancer.

## Effects in other tissues

Bazedoxifene has been shown to be well tolerated in the population of healthy postmenopausal women at risk of osteoporosis-related fractures. The incidence of adverse events, serious adverse events and abandonment of treatment due to adverse events were similar across all the treatment groups.

• No statistically significant differences were observed between the treatment groups for cardiovascular events[10].

• In the two Phase III studies, bazedoxifene showed favourable effects on the lipid metabolism in postmenopausal women, with a reduction in total cholesterol and LDL-cholesterol, an increase in HDL-cholesterol and neutral effects on the triglycerides[10,23]. However, it is still to be determined if the changes observed in the lipid profile with the treatment with bazedoxifene have some clinical relevance.

• No adverse effects have been shown on the ovary in any of the clinical trials which evaluated the effects of bazedoxifene at 10, 20 or 40 mg, on ovarian volume, number or size of ovarian cysts or on the incidence of ovarian cancer over 24 months[12,13].

• There is no evidence of other adverse gynaecological effects, including neoplasias in the uterine neck, growth of uterine fibroids, uterine haemorrhage and vaginal bleeding[12].

## Adverse effects

As a SORM, it would be expected that bazedoxifene would have the "classic" adverse effects, including those related to hypooestrogenism (shortness of breath, mood swings and vaginal dryness); and, on the other hand, agonistic oestrogenic effects (a higher risk of thromboembolisms and thrombophlebitis, nausea, dyspepsia, peripheral oedema, migraine and arthralgia).

• Although the preclinical data suggested that bazedoxifene could not have vasomotor effects in postmenopausal women[8], the incidence of breathlessness and leg cramps in the Phase III trial was significantly higher in the bazedoxifene and raloxifene groups than in the placebo group ($p< 0.05$). However, the majority of the episodes of breathlessness were light to moderate and did not continue on discontinuation of the treatment[11].

• In the 2 year prevention study the incidence of deep vein thrombosis was low and similar among all groups (0% with bazedoxifene at 10 mg and 40 mg and raloxifene at 60 mg, 0.6% in bazedoxifene at 20 mg and 0.3% with the placebo)[10]. In the 3 year treatment study the incidence of all the venous thromboembolic events (pulmonary embolism, deep vein thrombosis and retinal vein thrombosis) was higher in the active treatment groups (raloxifene or bazedoxifene) compared with the placebo, although the incidence was generally very low (< 1%) and was not statistically significant[11]. Similar findings were observed in the extension study of 2 years.

## Adjustment of dosage with age

There are currently no data available on the use of bazedoxifene in premenopausal women. This group may need protection against osteoporosis in situations such as hypogonadism and premature ovarian insufficiency. Bazedoxifene has been studied in women during the first years of the menopause. There no data on its use in senility. However, it is not expected that the use of bazedoxifene in patients of advanced age requires an adjustment in dosage since, differently from other drugs, the way bazedoxifene is metabolised does not appear to be affected by age[24].

## Future perspectives

A new approach to therapy or the menopause is tissue selective oestrogen complex (TSEC), which associates a SORM with one or more oestrogen, this combination having the objective of achieving an optimum balance of agonist/antagonist activity on the oestrogen receptor for the treatment of menopausal symptoms and the prevention of loss of bone mass[25,26]. The first TSEC in clinical development associates bazedoxifene with combined oestrogens (CEO). Phase III clinical trials of 20 mg and 40 mg of bazedoxifene, each with a CEE of 0.45 or 0.625 mg, have shown a significant increase in bone mineral density (BMD) and an improvement in vasomotor symptoms and vulvo-vaginal atrophy, and at the same time guaranting endometrial safety in postmenopausal women[27].

## Conclusion

The available data on bazedoxifene reflect a favourable safety profile with respect to the endometrium, ovary and breast in healthy women in recent menopause at risk of osteoporosis. It is important to highlight the fact that the safety data at 5 years are, in general, similar to those at 3 years, based on the findings of a recent two year extension study[28,29].

The use of bazedoxifene to reduce the risk of fracture may contribute to the reduction in the risk of breast cancer, without risk to the uterus or ovaries. The most significant difference between bazedoxifene and raloxifene appears to be the inhibitory effect of the former on the endometrium, which allows the association of bazedoxifene with CEO. The combination of bazedoxifene and CEO has shown an improvement in BMD and in vasomotor symptoms without stimulatory effects on the endometrium or breast. The use of bazedoxifene to replace gestagen as a protector of the endometrium in hormonal therapy is a potential future application of bazedoxifene.

New clinical trials should clarify the differences between bazedoxifene and other SORMs and clinical experience will help us to define the clinical value of bazedoxifene in the treatment of osteoporosis.

**Conflict of interests**

*Dr. R Sánchez-Borrego declares his membership of the Advisory Board on Bazedoxifene of the Pfizer Laboratories, Spain.*

*Dr. F. Lugo declares that he has no conflicts of interest.*

*No person with a working relationship with the Company has been involved in the preparation of this article.*

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# Efficacy of bazedoxifene, pre-biphosphonate sequential therapy for osteoporosis and the patient profile for bazedoxifene

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## Summary
Osteoporosis is a gendered disease, being especially prevalent in postmenopausal women due to the sharp drop in levels of endogenous oestrogens. The interest in, and concern for, this pathology has resulted in the development of ever more efficacious and safe new drugs. Bazedoxifene (BZA) is a new third generation SORM, recently launched on the European Union market for the treatment of postmenopausal osteoporosis in women at high risk of fracture. BZA, at a dose of 20 mg/day, has shown a significant effect on the prevention of loss of bone mass in healthy postmenopausal women with low or normal bone mineral density. In a pivotal study aimed at osteoporotic women, BZA has reduced by 42% ($p< 0.05$) the risk of vertebral fracture at three years in comparison with a placebo; this effect is maintained over five years. In addition, it has been shown in a post hoc analysis, in a group of women at high risk of fracture, to diminish the risk of non-osteoporotic fractures by 44% more than 60 mg of raloxifene ($p= 0.05$). Its antifracture potency and its strong uterine antioestrogenic effect makes bazedoxifene especially indicated in recently postmenopausal women with osteoporosis and risk of fracture.

**Key words:** *Bazedoxifene, Antifractural potency, SORMS, Osteoporosis, Sequential therapy.*

## Introduction

The interest in, and concern about, osteoporosis has resulted in the acquisition of greater knowledge of its epidemiology, achieving advances in diagnostic tools and the discovery of ever more efficacious and safe new drugs. In terms of the drugs, there are currently multiple options, among which are included the biphosphonates and the selective oestrogen receptor modulators (SORMS: raloxifene (RLX) and bazedoxifene (BZA)), the oestrogens calcitonin, parathormone (PTH) and strontium ranelate. With the exception of the oestrogens, the antifractural effects of all these medicines has been demonstrated in women with a densitometric diagnosis of osteoporosis[1]. All this necessitates an individualised therapeutic indication depending on the benefit-risk profile of each patient.

The SORMs represent a class of drugs with ever more numerous compounds, characterised by acting as agonist/antagonist of oestrogen receptors (OR) in a tissue-specific way[2]. This pharmacological profile may offer an opportunity to obtain favourable oestrogenic effects, while avoiding any negative effects of them on breasts and endometrium. The SORMS have been shown to have great value in breast cancer. They have also been shown to be efficacious in the prevention and treatment of osteoporosis and in improving lipid metabolism, and there are other possible benefits which are being studied, such as as a treatment for vaginal atrophy[3]. This versatility of the SORMs is due to the capacity of each of them to produce a different conformational change in the oestrogen receptors $\alpha$ and $\beta$, and with this, ultimately, to stimulate or block the activity of the transcription genes for the oestrogens[2].

The different SORMs exert a different affinity and competition for the bond to the oestrogenic receptors and determine a different genetic expression. The evidence suggests that each SORM should be studied, and its clinical response evaluated, independently[4].

The two SORMs currently most used are tamoxifen, which is used for the prevention and treatment of breast cancer, and raloxifene, indicated for the treatment and prevention of postmenopausal osteoporosis, and for the prevention of breast cancer in the US. Both SORMs have positive effects on the lipids, but are associated with an increased risk of venous thromboembolism and hot flushes. In addition, tamoxifen increases the risk of cancer of the endometrium. On the other hand, none of these SORMs have shown a preventative effect on non-vertebral fractures[3,4].

Therefore, of any new SORM it is necessary to ask which has the best efficacy, or the best safety, or both, knowing that the ideal SORM is one which prevents vertebral and non-vertebral osteoporotic fractures, which serves as primary or secondary prevention of breast cancer, and which may have additional benefits regarding cardiovascular risk. This ideal SORM would not increase the risk of either hyperplasmia, or endometrial adenocarcinoma, nor venous thromboembolisms or hot flushes[4]. Although it is very difficult to find this ideal SORM, the new SORMs are a step forward, based on preclinical selection criteria and data on the clinical response in relation to efficacy and safety.

Up until now, RLX has been the only SORM in the market approved for the treatment of osteoporosis. Now we can also count on bazedoxifene (BZA), a new generation SORM, which has completed its clinical development and has been approved by the European Medicines Agency (EMEA) for the treatment of postmenopausal osteoporosis in women with a high risk of fractures[5].

## Efficacy of bazedoxifene

BZA is a SORM derived from the indoles, with phenyl rings which act as the site for bonding to the receptor. They bond strongly with both types of oestrogenic receptor, alpha and beta, but with the bond to the alpha oestrogen receptors being clearly stronger[6].

The first preclinical studies showed that they did not stimulate the proliferation of the MCF-7 mammary cell line, and even suppressed, dose-dependently, the proliferation induced by 17 beta estradiol[7]. In animal studies treatment with BZA reduced the markers for remodelled bone and prevented the loss of bone mass[7]. What appeared to be especially interesting was that it protected the increase in uterine weight produced by the oestrogens in immature rats[22]. The potency of BZA over the inhibition of uterine weight and on the stimulation of the mammary gland cells produced by the oestrogens is higher than that found with other SORMs, such as raloxifene and lasofoxifene[8].

### Pharmacokinetics and pharmacodynamics

BZA has been demonstrated in healthy postmenopausal women to have a half life of 28 hours, with a maximum blood concentration at within 1-2 hours of taking the dose[9]. The main route of excretion (85%) is through the faeces. Its administration to patients with hepatic insufficiency may elevate the drug's blood concentration, for which reason its use is not recommended in these cases, as well as in severe renal insufficiency, since, although the principal mode of excretion is through the faeces, it is also partially excreted in the urine[10].

Bazedoxifene increases concentrations of sex hormone-binding globulin SHBG and thyroxine-binding globulin TBG. It does not metabolise through cytochrome P450, which means that important this enzyme neither induces nor inhibits the activities of the isoenzymes[10]. In vitro analyses suggest that bazedoxifene does not interact with other drugs which metabolise by means of cytochrome P450, and therefore no significant pharmacological interactions have been described.

No pharmacokinetic differences have been observed in relation to race.

### The lowest efficacious dose

The two phase 2 clinical studies have shown a clearly significant reduction in markers for remodelled bone with BZA, compared with a placebo,

Table 1. Clinical characteristics of the prevention of osteoporosis at 2 years

| | |
|---|---|
| **Type of study** | Multicentric, double blind, randomised, compared with active product (raloxifene) and placebo |
| **Main selection criteria** | Healthy women ≥ 45 years and ≥ 1 year of postmenopause. Women between 1 and 5 years of postmenopause should have ≥ 1 risk factor for OP |
| **Treatment groups** | BZA 10 mg (n= 292); BZA 20 mg (n= 288), BZA 40 mg (n= 290); RLX 60 mg (n= 280), placebo (n= 284) |
| **Average age** | 58 years |
| **Half of DMO in lumbar column (T Score)** | -1,12 to -1,24 |

Table 2. Characteristics of pivotal study at 3 years

| | |
|---|---|
| **Type of study** | Multicentric, double blind, randomised, compared with active product (raloxifene) and placebo |
| **Main selection criteria** | Generally healthy women aged between 55 and 85 years and ≥ 2 years of postmenopause with OP (BMD in the range for OP or vertebral fracture confirmed by radiography) |
| **Treatment groups** | BZA 20 mg (n= 1.886); BZA 40 mg (n= 1,872), RLX 60 mg (n= 1,849); placebo (n= 1,885) |
| **Average age** | 66 years |
| **Half of DMO in lumbar column (T Score)** | -2,4 |

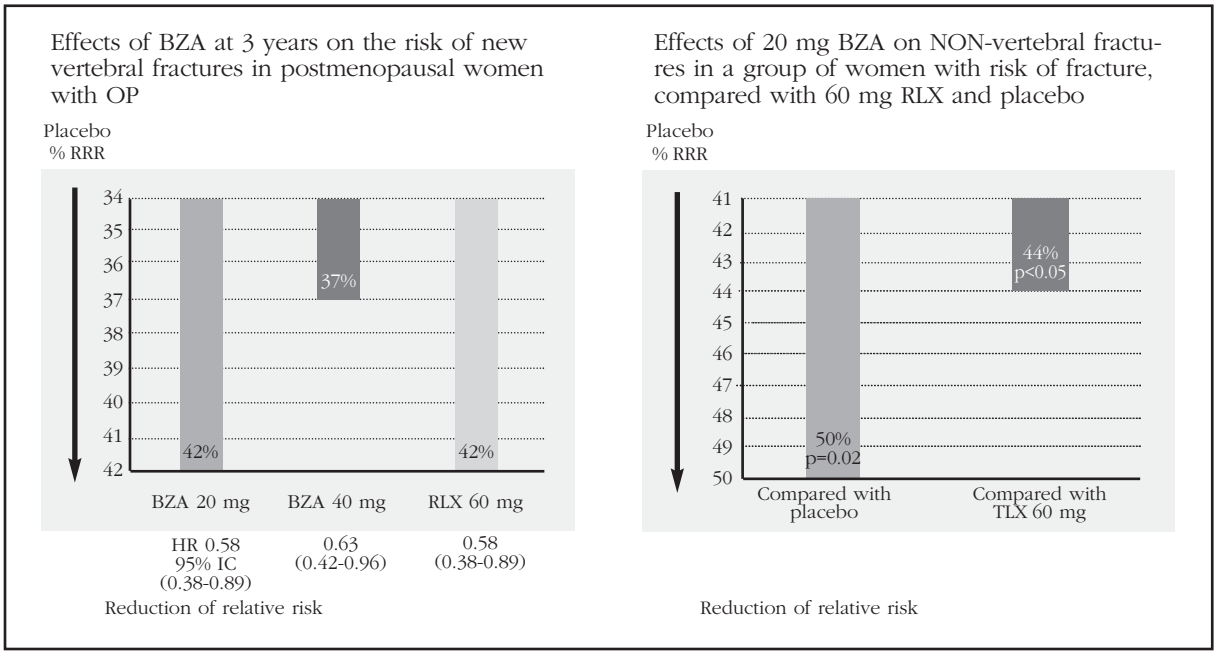
and even with a dose of only 5 mg a day of BZA, this reduction being dose-dependent[11].On the other hand, in this clinical phase it was possible to confirm that a dose of 20 mg/day of BZA was the lowest dose which provided the best efficacy profile with a good endometrial and mammary safety profile[12].

**Study of prevention**

A phase 3 clinical study of osteoporotic prevention has been carried out of two years duration[13], including 1,583 healthy postmenopausal women with low or normal bone mineral density (BMD), with the triple of objective of looking at efficacy and safety, comparing the lowest efficacious dose and comparing it with raloxifene RLX.

In this study the women received daily doses of BZA of 10, 20 and 40 mg, 60 mg of raloxifene or a placebo, and all of them took 600 mg of calcium element daily during the two years of the study (Table 1)[13]. Both the three doses of BZA and the dose of RLX had the same efficacy in the prevention of loss of bone mass measured as BMD in the lumbar spine, hip, femoral neck and femoral trochanter. Already at 6 months, the three doses of BZA demonstrated a significant preventative effect on the loss of BMD compared with the placebo. The differences in average percentages of BMD in the lumbar spine with respect to the baseline at 24 months with 10, 20 and 40 mg of BZA, in comparison with the placebo, were 1.08 ± 0.28%, 1.41 ± 0.28% and 1.49 ± 0.28% respectively (with statistical significance of $p < 0.001$ for all).

Figure 1. Effects of BZA at 3 years on vertebral and non-vertebral fractures




Other interesting data from the study were that at three months, both the women on BZA and those on RLX showed a significant reduction in levels of markers for remodelled bone (blood osteocalcin and telopeptide C), compared to those found in the placebo group ($p< 0.001$), and this effect continued during the whole study. In addition, BZA showed a positive effect on the lipid profile, with a significant reduction being found in levels of total cholesterol (-3.75%) and cLDL (-3.6%), and a significant increase in cHDL (5.10%), in comparison with the placebo[13].

**Pivotal study**

The pivotal phase 3 clinical study was designed to determine the efficacy and safety of BZA in the prevention of fractures in postmenopausal women with osteoporosis (Table 2)[14].

In this study, the women received daily treatment with BZA at 20 or 40 mg, 60mg RLX, or a placebo, all supplemented with 1,200 mg daily of calcium and 400-800 UI of vitamin D.

BZA significantly increased BMD and reduced the levels of markers for remodelled bone (osteocalcin and telopeptide C), compared with the placebo ($p< 0.001$). The incidence of new vertebral fractures at 3 years, which was the main objective of the study, saw a clearly significant reduction with 20 mg of BZA (a reduction after 3 years of 42%), with 40 mg of BZA (a reduction after 3 years of 37%) and 60 mg of RLX (a reduction after 3 years of 42%), in comparison with the placebo. All these reductions with active treatments were statistically significant ($p< 0.05$) with respect to the placebo (Figure 1). In terms of the % of fracture, at three years they were 2.3, 2.5, 2.3 and 4.1% with BZA at 20 mg, BZA at 40 mg, 60 mg of RLX and the placebo, respectively. The effect of the treatments was similar in women with or without previous fractures.

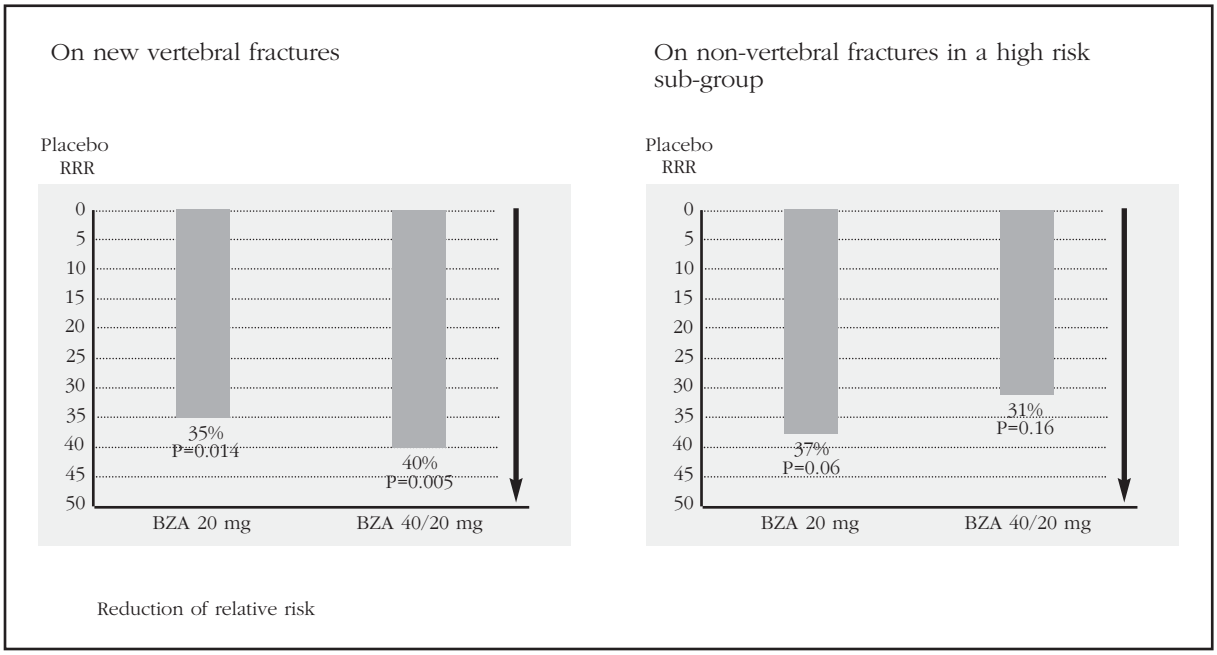
The incidence of non-vertebral fractures was similar at three years in the group with 20 mg BZA (5.7%), 40 mg BZA (5.6%), 60 mg RLX (5.9%) and the placebo (6.3%)[14]. However, in a post hoc analysis of a sub-group of women with a high risk of fracture, based on known risk factors (n=1,772), BZA at 20 mg showed a reduction in risk of non-vertebral fractures of 50% compared with the placebo ($p= 0.02$) and 44% with respect to 60 mg of RLX ($p= 0.05$) (Figure 1).

An independent reanalysis[15] has been carried out of the fracture data of the whole population, using FRAX (the Fracture Risk Assessment tool), to estimate the probability of fracture at 10 years[16,17]. The results of this analysis show that BZA reduces significantly the risk of all clinical fractures and morphometric fractures[15]. Similar results were observed regarding the effects of BZA on non-vertebral fractures[18]. Another conclusion has been that the effect of BZA increases according to an increase in the probability of fracture.

The positive effect of 20 mg of BZA in the lipid profile was of a reduction after three years from the baseline for total cholesterol of -3.8% ($p<0.001$) and of cLDL of -5.4% ($p< 0.001$), with a clear increase in cHDL of 5.1%. There were no changes in the triglycerides compared with the placebo group[19].

A total of 4,216 women were included in the extension study which lasted a further two years. The 60 mg RLX group finished at the fourth year, and the patients who were in the 40 mg BZA group

Figure 2. Effects of BZA at 5 years compared with placebo




were moved to the 20 mg group at the fourth year, constituting the 40/20 mg BZA group. The results, which were presented at 5 years, were in respect of the 20 mg BZA and 40/20 mg BZA groups, compared with the placebo group[20]. The primary objective was to look at new vertebral fractures, and secondarily, at non-vertebral fractures .

At 5 years the incidence of new vertebral fractures was significantly lower in the 20 mg BZA (4.5%) and 40/20 mg BZA (3.9%) groups, than in the placebo group (6.8%), corresponding to a relative risk of 35% less (p= 0.014) and 40% less (p= 0.005), respectively (Figure 2). There were no significant differences in the study's population in terms of non-vertebral fractures between 20 mg BZA (9.5%), 40/20 mg BZA (7.6%) or the placebo (9.0%). In the analysis of the high risk patients (T-Score in the femoral neck less than or equal to 3 and/or one or more moderate vertebral fracture or two or more light vertebral fractures; n=1,324), there was a reduction in incidence of 37% (p= 0.06) and of 31% (p= 0.16) (Figure 2) of non-vertebral fractures in the 20 mg BZA and 40/20 mg BZA groups in relation to the placebo group.

In conclusion, the values for the reduction in new fractures and, in a high risk sub-group, of non-vertebral fractures, were maintained throughout the two year extension, with the results at 5 years being similar to those at 3 years[20].

## Sequential therapy for osteoporosis

A key clinical objective consists in identifying those patients with a high risk of presenting this disease. Osteoporosis is predictable and treatable, but the lack of alert signals before the appearance of a fracture means that few patients are diagnosed in early phases of the disease and treated efficaciously[21]. Osteoporosis is the most significant risk factor, and the one with greatest predictive power, for fragility fractures (atraumatic fractures or those due to minimum trauma)[22].

Knowledge of the risk factors is important for detecting those patients in whom it is most probable that the disease will appear. But the correction of those factors that are modifiable also has notable therapeutic implications.

When the bone mineral density and those risk factors for each woman are determined doctors are in a position to answer their patients' queries about the level of risk of fracture[23]. But it will also be their obligation to promote changes in the patients' life styles, to predict the use of health resources and carry out a minimum cost benefit analysis of the possible alternative interventions for the disease. The necessity of treating osteoporosis is justified by the reduction in risk of fractures by increasing bone strength with this intervention. A systematic review of 76 clinical trials and 24 meta-analyses confirm the efficacy of the treatment in the prevention of fracture in comparison with the placebo in women with low bone mass or osteoporosis[24].

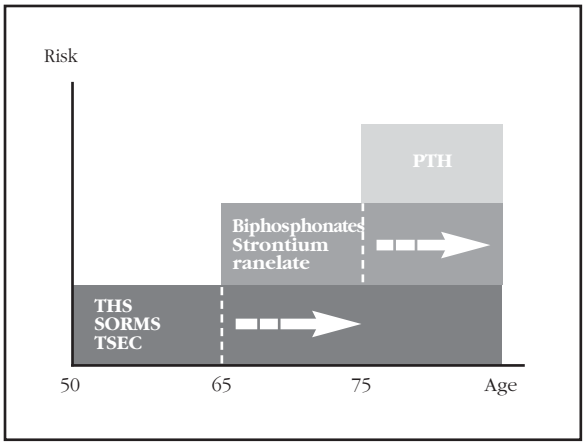
Although there is no common agreement on which women should receive drug treatment, the majority of scientific societies have suggested that it is indicated in those who have already presented with fragility fracture before the presence of densitometric osteoporosis and when there is low bone mass and associated risk factors[25].

There are no fixed rules or established protocols in terms of the drug or regime to be used. The decision to start treatment and which type should be based on the necessity to reduce the risk of

Figure 3. Phases of bone loss in menopause

| Years | Bone resorption | Bone formation |
|---|---|---|
| 50 - 59 | ↑↑↑ | ↑↑ |
| 60 - 70 | ↑ | Normal |
| > 70 | ↑ | ↓ |

Figure 4. Sequential treatment of risk of fragility fracture.




fracture, taking into account in each specific case the following factors, in addition to BMD and other major risks: renal function, drug allergies, comorbidities, earlier treatments, contraindications, secondary effects of the drugs and costs. By doing this it is possible to establish the risks and benefits of a drug for each patient. In addition, it is recommended that the importance of improving adherence be considered. Treatment for osteoporosis, it being a chronic disease, needs to be used over a long period, which makes necessary the use of individualised measures and sequential treatments.

Sequential treatment consists in designing a strategy which will sustain a drug over a sufficient period of time in order to achieve its benefits with minimum risk and maximum adherence, in order to be able to later move onto another drug, or drugs, which achieve the same results. The undesirable effects of prolonged use of some drugs, dealing with the risk of fracture which we wish to prevent and data from clinical trials which support their use, as well as efficacy in relation to the age of the patient, will have to be taken into account. Drug treatment should not be static but should change over the lifetime of the woman, thus adapting to her clinical needs and metabolism over time.

In theory, the treatments could start to be used during the first postmenopausal years using drugs aimed at the physiopathology of the rapid bone loss produced by the increase in bone resorption as a result of the reduction in oestrogen (Figures 3, 4), the most appropriate drugs being hormone replacement therapy (HRT) in symptomatic women and the SORMs in asymptomatic women. Another possibility could be HRT for two or three years and then SORMS, or a combination of oestrogens with a SORM (TSEC). Subsequently, there is a period with an increase in resorption and a reduction in formation (Figures, 3,4), coinciding with over 10 years of postmenopause and with a greater risk of hip fracture, where drugs such as biphosphonates or strontium ranelate have clearly shown their effectiveness. Finally, in women of more than 70-75 years of age, there is a significant reduction in formation (Figures 3, 4), where PTH could be indicated in cases at very high risk of fracture[4].

## Patient profile for bazedoxifene

The most common, and frequently unnoticed, consequence of osteoporosis, is an increase in the risk of fracture, and most seriously, in mortality and morbidity. For this reason, the objective of treatment in osteoporosis is the prevention of new fractures, and in patients with fractures, in minimizing the symptoms, improving functionality and optimising quality of life. The knowledge of the greatest risk factors for fracture and bone loss will help the therapeutic approach.

On the basis of the initial consideration that bazedoxifene is indicated in the treatment of osteoporosis in postmenopausal women with an increased risk of fracture, in principal, it could be indicated for all those women with this condition and in whom there is no contraindication for its use.

By assessing the specific characteristic and effects of the product, it is possible to profile those women to whom it would be expected to bring most benefit. Bazedoxifene has shown efficacy in osteopenic (average age 57.6)[13] and osteoporotic (average age 65.9)[14] women, which means that its indication could be around women with an increased risk of fracture in the first years after the menopause (natural or surgical). Taking into account the fact that the most frequently reported adverse effect is the presence of hot flushes, it does not seem sensible to indicate this treatment in their presence.

Bazedoxifene has shown efficacy both if there is a vertebral fracture, as well as in their absence. The women who get the most benefit from the drug treatment are those at risk of fracture and in whom has also been shown a reduction in fractures in any location[14].

In clinical trials bazedoxifene did not produce more adverse gastrointestinal effects than the placebo[13,14], so, another group which could benefit are patients with poor tolerance of other treatments (for example, gastrointestinal intolerance to biphosphonates), and may be taken at whatever time of day, with or without meals, which makes it somewhat easier to establish a time of taking the dosage which matches the patient's preference, avoiding the necessity of strict rules for timing, fasting or limitation of activities.

Other considerations to be taken into account are that BZA has an appropriate security and tolerance profile, a favourable lipid profile, a neutral effect on the breast and an antioestrogenic effect in the endometrium[4], which helps good compliance. Thus, in clinical trials the rate of abandonment has been similar to the placebo[13,14].

It is important to bear in mind that it is not the treatment of choice for patients with a personal history of venous thromboembolism or with a raised risk of presenting this pathology. Another indication comes from the evaluation of its cost-effectiveness. One of the most recent works has been to evaluate the binomial coefficient of the cost-efficacy of BZA vs a placebo in France, Germany, Italy, Spain, United Kingdom and Sweden[26], form the public health perspective using the FRAX index[16]. The conclusions have been that the use of BZA can be economical from the point of view of cost-effectiveness, depending, as seems logical, on how high the risk of osteoporotic fracture is according to the FRAX index.

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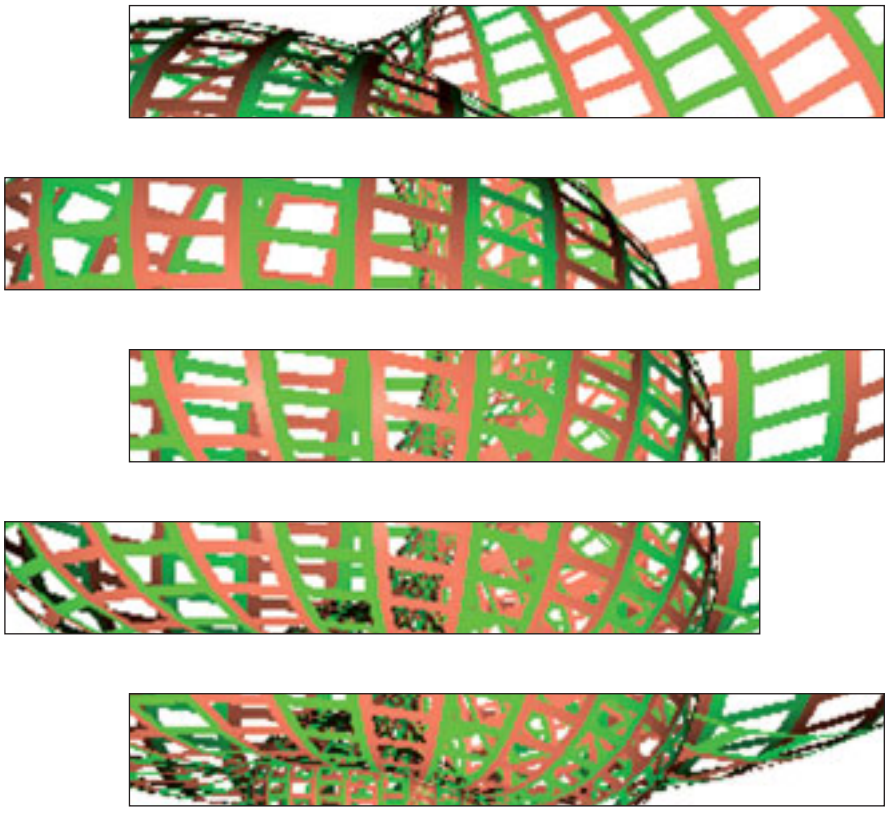

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