"IBEROAMERICAN CONSENSUS ON OSTEOPOROSIS SIBOMM 2009"
Osteoporosis: Prevention, Diagnosis, and Treatment

Iberoamerican Society of Osteology and Mineral Metabolism
(SIBOMM)

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1. **ABSTRACT**

Objective: To present the Iberoamerican Consensus on Osteoporosis 2009 as a guideline and recommendation for the management of osteoporosis in the Iberoamerican region.
Methods: The Iberoamerican Society of Osteology and Mineral Metabolism **(**SIBOMM) based this Consensus on the contributions made in the Consensuses achieved by the Member Societies of SIBOMM in the last five years and on the Guidelines on Osteoporosis issued by the said societies. It followed principles and advances in the world literature and the contributions or observations made by the representatives of the Societies participating in the Consensus, and by professionals and experts who are members of the Consensus Panel.
The mentioned recommendations were presented and discussed in the 8th SIBOMM Congress/ 3rd BRADOO, held in Foz do Iguaçu, Brazil, on October 1-3, 2009.
Results: The major problem of osteoporosis, which is highly prevalent particularly in the elderly population, is the risk of bone fractures. Such fractures, especially hip and spinal fractures, cause important morbidity and mortality in that population. Because of the high economic costs of osteoporotic fractures, the main objective of treatment is the prevention of fractures. Prevention is achieved when loss of bone mass is stopped, bone strength is maintained, and risk factors for fractures such as falls are minimized or eliminated. Assessment of the risk for osteoporosis should be based on a correct and complete medical history and the necessary diagnostic tests, the most important of which is bone densitometry. The main risk factors for osteoporosis are: aging, previous fractures, family history, low calcium intake, low levels of vitamin D, smoking, low body weight, menopause, low bone density, and low mineral density, among others. Aging, low bone mineral density, fragility fractures, and parental history of fragility fractures are the most common risk factors for osteoporotic fractures. There are many therapeutic and preventive measures, such as a balanced diet with an adequate intake of calcium and vitamin D, physical activity, no smoking and moderate alcohol intake, fall prevention, and use of approved drugs. There are several such drugs: bisphosphonates, strontium ranelate, selective estrogen receptor modulators, parathormone, estrogens, calcitonin, calcium, and vitamin D, among others.
Conclusions: Management strategies for patients with osteoporosis consist in: A) Identifying those are at risk of developing osteoporosis and of suffering one or future fractures caused by bone fragility. B) Establishing the necessary measures to achieve a reduction in modifiable risk factors, to administer drug treatment, and to carry out the corresponding follow-up with the adequate use of diagnostic resources.

Key words: consensus, osteoporosis, fractures, menopause, bone mineral density, hormone therapy, bisphosphonates, selective estrogen receptor modulators, calcitonin, parathormone, calcium, vitamin D, SIBOMM.

2. INTRODUCTION

The participants of and those responsible for this Consensus document wish to point out that any scientific investigation, professional activity, and health care assistance should be based on basic principles of bioethics, especially equity and justice. This will guarantee that the Iberoamerican population will have a decent and appropriate access to benefits of scientific investigation and technological development. In this manner, the dignity and autonomy of the decisions of the mentioned population will be respected and the establishment of rules and regulations that preserve the basic human values for peaceful coexistence will be favored.

The Iberoamerican region is a vast and heterogeneous area of 21,652,281 km^2 and has a population of 621,244,725 people. In this area, there is an increasing incidence of osteoporosis, which is a pathology associated with rates of fragility fractures relatively similar to the rest of the world. Osteoporosis has serious consequences, and constitutes a major public health problem in the region and the whole world. Osteoporotic fractures frequently cause significant disability, high costs for the patients and its family, high socioeconomic costs, and an increase in morbidity and mortality (Cole *et al*, 2008). Thus, physicians and health authorities should develop guidelines for the diagnosis, prevention, and treatment of osteoporosis in order to improve its management and more efficiently handle the effects caused by the disease on public health, from a medical, social and economic point of view (Brown *et al*, 2002; Melton, 2003; AACE Osteoporosis Task Force, 2003).
As a consequence of this, the **Iberoamerican Consensus of Osteoporosis 2009** emerges. It is encouraged by the Iberoamerican Society of Osteology and Bone and Mineral (SIBOMM) together with its member societies. Its objective is to provide guidelines and recommendations regarding diagnosis, prevention, and treatment of osteoporosis. It should not be considered as a rigid rule applicable in individual patients. It intends to help reduce the risk and frequency of osteoporotic fractures and to contribute to good medical praxis and an adequate use of available diagnostic and therapeutic resources.

SIBOMM acknowledges the participation of the member societies and professionals who are members of the Consensus Panel who have directly or indirectly contributed to the Consensus with their valuable papers and opinions. Their contributions have made it possible to create this tool. It expects to be enriched by its future application and to be renewed in future meetings.

3. METHODS

This document was produced and/or revised by a multidisciplinary working group formed by SIBOMM members. It was presented in the Consensus Session carried out during the 8th SIBOMM Congress/3rd BRADOO. For writing the document, the last Consensuses achieved by the SIBOMM Member Societies and the Guidelines on Osteoporosis issued by the said societies were taken into account, as well as the advances registered in the highest impact literature, the recommendations, contributions, and observations made by experts especially invited. The present health conditions of the different regions of Iberoamerica, which are very heterogeneous and show special characteristics, were also considered.

Aspects related to the definition of osteoporosis, its epidemiological relevance, the risk factors for developing osteoporosis, osteoporotic fractures, FRAX, diagnostic evaluation, prevention, and treatment will be developed.

The Consensuses achieved by the SIBOMM Member Societies and the Guidelines issued by the said societies, on which the document was based, are the following:
-"Posições Oficiais 2008 da Sociedade Brazileira de Densitometria Clínica" Sociedade Brazileira de Densitometria Clínica (SBDens) [Brandão *et al,* 2009].
-" Apuntes Relativos a Osteoporosis en Cuba", 1998-2009. Actividades de la Sociedad Cubana de Endocrinología y la Sección de Climaterio y Osteoporosis (CLIMOS) de la Sociedad Cubana de Ginecología y Obstetricia [Navarro Despaigne, 2009].
-"Guías de Práctica Clínica en la Osteoporosis Posmenopáusica, Glucocorticoidea y del Varón", 2008. Sociedad Española de Investigación Ósea y del Metabolismo Mineral (SEIOMM) [González Macías *et al,* 2008].
-"Guías Para Diagnóstico, Prevención y Tratamiento de la Osteoporosis 2007". Consenso de la Sociedad Argentina de Osteoporosis (SAO) y la Asociación Argentina de Osteología y Metabolismo Mineral (AAOMM) [Schurman *et al,* 2007].
-"Posiciones Oficiales de la ISCD 2005. Revisión del Panel Iberoamericano 2006" [Ragi *et al,* 2007].
-"Consenso Ecuatoriano de Osteoporosis 2007. Guías y Recomendaciones de Manejo Diagnóstico y Terapéutico de la Osteoporosis" [Jervis *et al,* 2007].
-"Recomendações para o Diagnóstico e Terapêutica da Osteoporose", 2007. Sociedade Portuguesa de Reumatologia e Sociedade Portuguesa de Doenças Ósseas Metabólicas (SPODOM) [Tavares *et al,* 2007].
-"Guías para diagnóstico, prevención y tratamiento de la osteoporosis inducida por corticoides, 2005" Sociedad Argentina de Osteoporosis [Messina *et al,* 2006]
-"Guías de diagnóstico, prevención y tratamiento de la osteoporosis", 2006. Sociedad Chilena de Reumatología (SOCHIRE) y Sociedad Chilena de Osteología y Metabolismo Mineral (SCHOMM) [Arriagada *et al,* 2006].
-"Guía Práctica de Diagnóstico, Prevención y Tratamiento de la Osteoporosis", 2006. Grupo de Estudio de Osteopatías de la Sociedad Uruguaya de Reumatología (GEOSUR).

The present SIBOMM Member Societies are: Asociación Argentina de Osteología y Metabolismo Mineral; Sociedad Argentina de Osteoporosis; Asociación Boliviana de Osteología y Metabolismo Mineral; Sociedade Brazileira do Densitometria Clínica; Sociedade Brazileira do Osteoporosis; Sociedade Brazileira para o Estudo do Metabolismo Ósseo e Mineral; Fundación Costarricense de Osteoporosis; Sociedad Cubana de Reumatología; Grupo de Climaterio y Osteoporosis (Sociedad Cubana de Ginecología y Obstetricia); Sociedad Chilena de Osteología y Metabolismo Mineral; Fundación Chilena de Osteoporosis; Asociación Colombiana de Osteología y Metabolismo Mineral; Asociación Colombiana de Endocrinología; Sociedad Dominicana de Osteoporosis; Sociedad Ecuatoriana de Metabolismo Mineral; Sociedad Española de Investigaciones Óseas y Metabolismo Mineral; Fundación Hispana de Osteoporosis y Enfermedades Metabólicas Óseas; Asociación Mexicana de Metabolismo Óseo y Mineral; Consejo Panameño de Osteoporosis; Sociedad Peruana de Climaterio; Sociedad Peruana de Reumatología; Sociedad Peruana de Osteoporosis y Enfermedades Óseas; Sociedad Puertorriqueña de Endocrinología y Diabetología; Sociedad Puertorriqueña de Endocrinología; Sociedade Portuguesa das Doenças Ósseas Metabólicas; Sociedad Uruguaya de Osteoporosis y Metabolismo Mineral; Sociedad

Uruguaya de Reumatología; Fundación Venezolana de Menopausia y Osteoporosis; Sociedad Venezolana de Menopausia y Osteoporosis.

More than 5,000 professionals are members of SIBOMM societies.

4. EPIDEMIOLOGY

Osteoporosis is a major public health problem that affects more than 200 million people worldwide and it is estimated that 30-50% postmenopausal women will suffer from it.
Every year, there is an increase of 1% of the population aged 65 years and more and a 20% mortality rate, on average, in the year following a hip fracture. After a hip fracture, it is estimated that around 10% of the patients become dependent; 19% of them require home care and between 30% and 50% of such patients can return to their daily activities (Brown *et al,* 2002; Melton, 2003; Fortes *et al,* 2008; Tosteson *et al,* 2009). Recent studies reveal that mortality after hip fracture slightly decreases after the first year, but remains high even after 5 and 10 years (Bliuc *et al,* 2009).
In Latin America, the most frequent fracture suffered by osteoporotic patients is vertebral fracture. The prevalence of such fracture is 11.2% (95% CI: 9.23-13.4), according to LAVOS, *Latin American Vertebral Osteoporosis Study* (Clark *et al,* 2009). These results are similar to those in studies carried out in Beijing (China), and in some European regions. These results are not so similar to the ones found in the USA, considering that the same methods were used in all cases. In the LAVOS study, 1,922 women of 50 years of age or more, coming from Argentina, Brazil, Colombia, Mexico, and Puerto Rico, were evaluated. The prevalence of spinal fracture was similar in the 5 mentioned countries and it considerably increases with age from 6.9% (95% CI: 4.6-9.1), in women of 50 to 59 years old, to 27.8% (95% CI: 23.1-32.4) in those of 80 years old or more ($p < 0.001$). One out of four hip fractures worldwide occur in Latin America and Asia. This figure will increase to one out of two fractures in the year 2050 causing expenditures of around 13,000,000,000 USD per year.
In Argentina, prevalence of spinal fractures in women of 50 years of age and more is estimated at 17% (Clark *et al,* 2009). According to different studies, on average, 320 hip fractures occur annually every 100,000 women of 50 years of age and more and 125 hip fractures occur every 100,000 men of 50 years of age and more. The female-to-male ratio is 2.56 (Bagur *et al,* 1994; Mosquera *et al,* 1998; Somma *et al,* 2000; Wittich *et al,* 2003; Morosano *et al,* 2005; Claus-Hermberg *et al,* 2008; Bagur *et al,* 2009).
In Brazil, 33% of women and 16% of men aged 65 years or more suffer from osteoporosis in all skeletal areas analyzed according to BMD test (Camargo *et al,* 2005). In the above mentioned country, prevalence of spinal fractures in women of 50 years of age and more, is estimated at 14.8% (Clark *et al,* 2009). BRAZOS study, *The Brazilian Osteoporosis Study,* estimated that 12.8% of men and 15.1% of women had a history of fractures after osteoporosis. To calculate this, a representative sample of over 2,400 Brazilian people aged 40 and older was used, of which 70% were women (Pinheiro *et al,* 2009).
In Chile, according to the Fundación Chilena de Osteoporosis (FUNDOP), the pertinent data are (Arriagada, 2009): 10,350 people of 56.6 years old on average (SD 15.7) were evaluated (81% women). It was found out that 5.1% of the women suffered from osteoporosis (T-*score*? -2.5) and 43.3% suffered from osteopenia (T-*score* -2.49 to -1.0) respectively, while among men, 2.4% developed osteoporosis and 28.0% osteopenia. Official data provided by the Ministry of Health indicates that femoral neck fractures in

Chile accounted for 3,953 hospital discharges in 2001, and 5,350 in 2006. The hip fracture rate in women of 65 years old and more, was 278/100,000 per year. In an investigation (unpublished) carried out in the Instituto Traumatológico (Traumatological Institute) in Santiago de Chile, between the years 1997 and 2005, 2,157 hip fracture patients (75% women) were reported. The 2-year follow-up of post hip fracture reported a mortality rate of around 24% in the first year of follow-up, and 48% in the second year.

In Colombia, prevalence of vertebral fractures in women of 50 years old and more is 17.8% (Clark *et al,* 2009).

In Cuba, 9,370 hip fractures in people aged 60 years or more occurred during 2007, affecting 68.9% of women (the F/M ratio was 2.2:1). Seventy-four percent of such fractures occurred while the patients were at home and 3% while they were in institutions (Navarro Despaigne, 2009).

In Ecuador, where life expectancy is over 70 years old, the incidence of femoral fracture in subjects of 45 years of age and more was 54.7 and 82.7 per 100,000 in men and women, respectively (Bracho *et al,* 2009; INEC, 2001).

In Mexico, in women of 50 years old and more, prevalence of vertebral fractures is 19.5% (Clark *et al,* 2009). In that country, one out of 12 women and one out of 20 men will suffer a hip fracture after age 50, with a possible lifetime fracture risk of 8.5% in women and 3.8% in men (Clark *et al,* 2005). The annual cost for the assistance provided during acute hip fracture was estimated at more than 97 millon dollars in 2006. This expense is equivalent to the insulin consumed by all Mexican diabetic patients who were insulin-dependent in that same year (Clark *et al,* 2008).

In Uruguay, in the year 1993, the rate of global incidence of hip fractures was 53.2 per 100,000 people and in the year 1999, it was 67 per 100,000 people. By the year 2010, it is estimated that the global incidence rate of hip fractures willd be 98.5 per 100,000 people (Chijani *et al,* 2006).

5. DEFINITION AND CONCEPTUAL ASPECTS

Osteoporosis is a skeletal disorder characterized by a compromise of bone strength, low bone mass and deterioration of the microarchitecture, with a consequent reduction in bone resistance, increase in bone fragility, and increase in the risk of bone fractures (Consensus Development Conference, 1993; NIH Consensus Development Panel, 2001).

The World Health Organization (WHO) defines osteoporotic fracture (fragility fracture) as the fracture caused by a trauma suffered by a strength or torsion performed on the bone (such strength would be insufficient to fracture a normal bone). This trauma, called minimal trauma, occurs, for example, when falling from a standing position (Kanis *et al,* 1994).

The concept of bone strength includes integrity of bone density and quality. Bone density, expressed in terms of grams of mineral per area or volume, is determined by the peak bone mass reached and by the balance between gain in bone mass and bone loss produced afterwards.

Bone quality is determined by bone architecture, bone turnover, accumulation of damage (e.g.: microfracture), and mineralization. Assessments of bone quality (determination of its architecture, porosity, size, and geometry, among other factors) are carried out for clinical investigation (Ferretti, 2009) but are not available for massive use.

Therefore, for the diagnosis of osteoporosis, the measurement of bone mineral density (BMD), **e**specially with central DXA devices, is still an unanimously accepted method.
In general, the WHO criteria of 1994 is still accepted for the classification of osteoporosis based on the comparison between the BMD values of the patient and the mean young adult normal population of the same gender and race – postmenopausal white women (Kanis *et al,* 1994). In this classification, the *T-score* or T value is considered, that is, the number of standard deviations above or below the mean BMD of the young normal population of the same gender studied with central DXA technique. See Table 1.

Table 1: CLASSIFICATION OF OSTEOPOROSIS ACCORDING TO BONE MINERAL DENSITY BY THE WHO SCIENTIFIC GROUP
(WHO Scientific Group, 2004)

DIAGNOSIS	**BMD T-*score***
Normal	T > -1.0
Osteopenia (low bone mass)	T < -1.0 y > -2.49
Osteoporosis	T < -2.5
Severe or established osteoporosis	T < -2.5 + fragility fracture

In men of more than 50 years of age, T-*score* is also considered, and the previous WHO classification is applied (Binkley *et al,* 2006; Ragi *et al,* 2007). In premenopausal women and men less than 50 years of age, Z-*score* is considered (in relation to normal subjects of the same age and gender); normal, up to -2.0.
In children, bone mineral content (BMC) and BMD are assessed by considering Z-*score* for lumbar spine and total body assessment (the hip should be considered only if the other two areas cannot be measured); normal, up to -2.0.
Z-*score* is not used to define osteoporosis. However, a low value of Z-*score* identifies individuals with a lower BMD than the expected one for that age (WHO Scientific Group, 2004).
These cut-offs were established to be able to compare the prevalence of osteoporosis in different populations. These should not be considered as the only diagnostic criterion for administering treatment.

6. RISK FACTORS FOR DEVELOPING OSTEOPOROSIS

Because osteoporosis is a silent disease (in most cases), risk factors need to be detected early.
Prevention should be recommended at all ages; a complete medical history constitutes an important tool for starting preventive measures.
All physicians should know how to manage the risk factors for osteoporosis. This constitutes a key element for prevention, as well as the organization of massive health campaigns aimed at the population in general and, especially, to educate children from school age to be conscious about the importance of having “healthy and strong bones” in their adulthood.
To determine the existence of the risk factors for osteoporosis in each patient is very important in order to prevent and interfere, whenever possible, with the natural evolution of the disease.

Among others, there are numerous risk factors for osteoporosis that have been studied:

6.1- Gender

Women are more exposed than men to the disease because of several reasons, such as their skeletal size, total mineral bone content, bone quantity, and muscle mass, which are lower than men's.

In general, it is established that the relation of affected men and women is 1.5/1 in Colles' fracture, 7/1 in vertebral fracture, and 2/1 in hip fracture**.**

6.2- Age

With aging, the rate of loss of bone mass in men and women older than 35 years is about 0.3-0.5% per year, which increases to 2-5% in women 4-6 years inmediately after menopause, and becomes stable afterwards. Hip fractures after osteoporosis are more frequent in old age, generally, in people of over 80 years of age, on average, according to the locations. According to age, people of 50 years of age are more prone to suffer wrist fracture; people of 60 years of age are prone to suffer vertebral fractures, and those of 70-80 years of age are more likely to suffer hip fractures.

6.3- Race

BMD presents lower values in the white and Asian population. Black people have higher BMD values than white people of the same age and gender. Something similar occurs in mixed populations. In black adolescents, BMD is higher than in white adolescents (Melton, 2003).

6.4- Early menopause and estrogen deficiency during premenopause

Estrogen deficiency, when it occurs before a woman is 40 years old (early menopause), and even more when the cessation of the ovarian function is abrupt (bilateral oophorectomy), is associated with a significant loss of bone mass. Long-term amenorrhea has a negative effect on bone status, which requires evaluation; treatment of the cause of hypoestrogenism has a positive effect on the bone of female patients.

6.5- Weight and nutritional status

Low weight represents a risk factor for osteoporosis, mainly when body mass index (BMI, kg/m^2) descends below 20. A history of eating disorder also represents a potential risk. Usually, they occur together with hypoestrogenism, other hormonal disorders, alterations in the body composition (a sharp decrease in fat mass, a moderated decrease in lean mass) and a lower provision of nutrients. All this has a negative effect on the bone.

6.7- History of previous fractures after minor traumas

The history of prior fractures caused by bone fragility increases twice or three times the risk of suffering future fractures (Krall & Dawson-Hughes, 1999; Melton *et al,* 1999; Klotzbuecher *et al,* 2000). The presence of vertebral compression fractures increases the risk for future fractures (Melton *et al,* 1999), which can better predict the risk than measuring bone mineral density alone (National Osteoporosis Foundation, 2008). Non-vertebral fractures also represent an important indicator of the increase of the risk after the fracture. The risk of the first and second hip fracture can increase from 1.6 to 15 per 1,000 men and from 3.6 to 22 per 1,000 women respectively (Schrøder *et al,* 1993).

Fractures of the wrist or Colles' fractures can also be indicators of significant risk for low bone mass in the hip or future fractures (Earnshaw *et al,* 1998; Schousboe *et al,*

2005). The odds ratio for hip fracture risk after an ankle fracture was 1.6 (95% CI: 1.1-2.3) and after a humerus fracture was 3.0 (95% CI: 2.4-5.0) (Gunnes *et al*, 1998).
The loss of 3 cm (1.18 inches) or more in a person's height as well as a significant acquired kyphosis can be caused by vertebral fractures (Arriagada, 2009).

6.8- Family history of osteoporosis
Several studies have shown a genetic component to BMD. Family history is a predictor of fracture independent of peak bone mass, and the history of osteoporosis in first-degree relatives is related to decreased peak BMD. Women whose mothers or grandmothers have suffered fractures before age 70, mainly hip fractures, vertebral fractures or wrist fractures, have a higher risk of having low BMD and of suffering fractures (National Osteoporosis Foundation, 2008).

6.9- Sedentary lifestyle
Sedentary lifestyle is associated with osteoporosis. Adequate physical activity correlates with less complications caused by osteoporosis. If it is performed during growth and development, bone mass can be increased, which results in a higher peak bone mass; exercise also maintains bone mass in young adults. Women who lead a sedentary lifestyle and who remain seated for more than 9 hours per day have 43% higher risk of hip fractures than those who remain seated for less than 6 hours per day (Gregg *et al*, 1998).
Women who go for a walk for 4 hours per week *versus* those who do so for less than 1 hour per week have 45% less risk of hip fracture. In a sample of 61,200 women, the risk of hip fracture was increased when the lowest level of physical exercise was performed (Feskanich *et al*, 2002).
Adequate physical exercise, which is an important stimulus for muscle and tendons, stimulates bone formation and remodeling; it also helps the person maintain an adequate neuromusculoskeletal coordination, which decreases the risk and seriousness of falls that make people prone to suffer fractures. Young people who do physical exercise have higher BMD than those who do not, and a lack of physical activity results in decreased bone mass. Several studies agree on the fact that athletes have a 25% greater BMD than active people and that the latter have a 30% higher BMD than inactive people. Increased physical activity can be protective against fractures independent of BMD (Bemben, 1999; Branca, 1999).

6.10- Tobacco
Tobacco smoking can cause a decrease in bone mass, an increase in the risk of fracture, an alteration in the healing of bone fractures (Slemenda, 1994), and a deterioration in the reaction to bone grafts (Lee *et al*, 2002). For these reasons, tobacco smoking is considered a risk factor for osteoporosis in both genders (Compston, 2001).
There is a dose-time relationship between cigarette smoking and its effects on bone, with cummulative effects (Schuller & Holst, 2001; Szulc *et al*, 2002). Its clinical manifestations usually appear in people of 50-60 years of age with fractures at any skeletal site (spinal and hip fractures are the most frequent). The pathophysiological pathways of tobacco-induced osteoporosis are multiple and complex, and in general, they act in addition to other events or factors, pathological or not (Salica, 2003). When people breathe in cigarette smoke, they breathe in free radicals which are liberated in the body. These have negative effects on the metabolism of bone cells, impair cell function, and significantly increase resorption.

BMD measurements with X-rays or ultrasound give variable results according to the cases (Amin *et al,* 1999, Sedlinsky *et al,* 2001). Numerous epidemiological papers agree on the significant decrease of BMD values due to smoking, and includ passive smoking in this effect (Egger *et al,* 1996). With time, the rate of bone loss in the femoral neck of smokers is two times greater than for non-smokers (Law & Hackshaw, 1997).
In spite of the differences found in the Framingham study (Amin *et al,* 1999), smokers are at an increased risk of suffering fractures and future fractures in comparison to non-smokers (Cornuz, 1999). The risk of vertebral fractures is doubled and the risk of hip fractures is increased in proportion to aging: at the age of 60, 70, and 80, the risk is 17%, 41%, and 71%, respectively (Law & Hackshaw, 1997). In more than 9,500 women, during a follow-up of more than four years, it has been demonstrated that the global incidence of hip fractures is twice among smokers (Cummings *et al,* 1995). Ten years after smoking cessation, there is a decline in the risk.

6.11.-Alcohol

It has been demonstrated that alcohol consumption can affect bone formation. Even at moderate levels of 1-2 drinks/day, it has a direct, antiproliferative effect on osteoblasts and also a dose-dependent suppressive effect on osteocalcin levels. Women consuming more than 25 g of alcohol per day have higher levels of estrone, estradiol, and dehydroepiandrosterone, but do not present changes in levels of androstenedione, testosterone or SHBG, with no difference in the levels of free androgens or the in the relationship between estradiol and testosterone (Onland-Moret *et al,* 2005).
Alcohol also has an impact on levels of PTH, calcitonin, and vitamin D (Klein, 1997). It is agreed that a high level of alcohol intake is associated with decreased BMD. This does not occur at moderate levels, which show disparate results. Nevertheless, 30 g of alcohol intake per day was associated with a decreased BMD (only in women), according to the *Framingham Osteoporosis Study* (Hannan *et al,* 2000). According to the *Nurses' Health Study,* individuals of 35-64 years of age consuming more than 25 g of alcohol per day (one drink) had an increased risk of hip and forearm fracture (Hannan *et al,* 2000).

6.12- High bone turnover

Increased levels of bone turnover markers are predictors of increased future fractures independent of BMD results (Lewiecki *et al,* 2009).

6.13- Corticoids

Glucocorticoid therapy reduces intestinal absorption of calcium and increases urinary calcium loss. Glucocorticoids also reduce the activity of osteoblasts, resulting in apoptosis and reduction of bone collagen synthesis. Osteoclasts are more active during the early phase of glucocorticoid therapy by mechanisms that are still unclear. Osteocyte apoptosis is also increased by glucocorticoids, which worsens the repair of microfractures and bone damage. Glucocorticoids may also reduce testosterone levels and estrogen levels by a decrease of the pituitary secretion of FSH and LH, and a decrease of adrenal androgens in postmenopausal women (Weinstein *et al,* 1998).
Glucocorticoid therapy increases the risk of fracture, independent of BMD values. With higher doses of glucocorticoids and longer administration time, higher are the risks of osteoporotic fractures.
Doses of >7.5 mg prednisone/day or equivalent, determine a 5.2 relative risk reduction (RR) in vertebral fracture. People receiving 2.5 mg prednisone have an increased risk of fracture if compared with subjects who do not receive corticoids. After discontinuation

of the corticosteroids, the risk of fracture is gradually reduced with longer time of interruption; however, the risk remains high, to a certain extent, if populations who received corticoids are compared with those which did not receive corticoids (van Staa *et al,* 2002; Kanis *et al,* 2004; Messina *et al,* 2006).

6.14- Organ transplantation and loss of bone mass

Solid organ transplantation of all types and allogeneic bone marrow transplantation are associated with rapid bone loss after transplantation. On several occassions, patients can develop bone loss even before transplantation (Maalouf & Shane, 2005) and also suffer fragility fractures while they wait for transplantation (Hamdy, 2007).

After transplantation, the rapid loss of bone mass is caused by multiple factors but mainly due to high doses of corticosteroids. Other worsening factors are immunosuppressive drugs, particularly cyclosporine and tacrolimus, persistent hypogonadism, and immobilization early after transplantation. Without a specific treatment for osteoporosis after transplantation, 8-10% loss of BMD is produced, which is more significant in hip than in spine (Tauchmanová *et al,* 2007). BMD typically stabilizes during the second year after transplantation. Fragility fractures occur frequently in patients after transplantation, typically in the first months after transplantation (Fleischer *et al,* 2008). Other characteristic of these fractures is that they usually occur at uncommon skeletal sites.

It is recommended that all patients have a baseline bone mineral density test and that follow-up bone mineral density testing be performed yearly prior to transplantation. But if they receive corticoids, they should have a BMD repeated every 6-12 months.

6.15- Diabetes

The complex relationship between diabetes and fractures is of recent interest since fractures in women with diabetes type 2 treated with glitazones were reported.

Diabetes type 1 is more recognized as a risk factor for osteopenia/osteoporosis than diabetes type 2. In diabetes type 1, BMD is usually low and is accompanied by an increase of 9 to 12 times the risk of fracture (especially hip fracture) as regards the general population (Meyer *et al,* 1993; Forsen *et al,* 1999; Nicodemus & Folsom, 2001; Janghorbani *et al,* 2007).

BMD results in patients with diabetes type 2 are conflicting. Several studies indicate that bone mass is high (Barrett-Connor & Holbrook, 1992; van Daele *et al,* 1995; Schwartz *et al,* 2001) or normal when compared with a control group (Hampson *et al,* 1998; Hirano *et al,* 1999) and in a few cases, that it is low (Tuominen *et al,* 1999). Nevertheless, in this paradoxical case of a normal or high BMD in diabetes type 2, an increase in fracture risk, especially at skeletal sites such as feet, knees (Schwartz *et al,* 2001; Luetters *et al,* 2004;), hip (Meyer *et al,* 1993; Forsen *et al,* 1999; Nicodemus & Folsom, 2001; Ottenbacher *et al,* 2002; Strotmeyer *et al,* 2005), and forearm (Schwartz *et al,* 2001; Ivers *et al,* 2001) has been found. The studies that support that patients with diabetes type 2 have a higher risk of fracture than the general population are the following: a) The *Study of Osteoporotic Fractures* (RR 1.7 for hip, humerus, and foot fractures) (SOF, 1992); b) Janghorbani *et al* in Medline (836.941 participants; increase of hip fracture risk in both genders, RR 1.7, 95% CI: 1.3-2.2) (Janghorbani *et al,* 2006); c) the study from Ontario, Canada (people older than 66 years with diabetes have a significant increase of hip fracture risk) (Lipscombe *et al,* 2007), d) the WHI study which makes reference to patients with diabetes type 2 (29% more probability of fracture than patients who do not suffer diabetes) (Bonds *et al,* 2006).

In different studies, an increased fracture risk is shown in patients under treatment with insulin but, in fact, it is related to the level of severity of the disease and possible secondary effects, such as severe hypoglycemia and falls (Kelsey *et al,* 1992; Schwartz *et al,* 2002).

Recent evidences show that thiazolidinediones (TZDs or glitazones), PPAR-gamma agonists, cause the tissues to respond more appropriately to insulin. It has been found that TZDs cause an increase in the risk of fracture in women with diabetes type 2. Women with diabetes type 2 treated with rosiglitazone or pioglitazone have an increase in fracture risk in the upper and lower limbs (feet, hands, arms) (Bodmer *et al,* 2009; Meier *et al,* 2009).

Present evidence allows to consider that the relationship between diabetes and fragility fractures is an actual health problem. Assessment of the fracture risk in patients with diabetes should always be carried out even in cases with type 2 diabetes; and in particular, in order to decide whether treatment with thiazolidinediones should be started; if the patient is taking the drugs, in order to monitor the impact on bone (Salica, 2007).

6.16- Entities associated to low bone mass

The history of certain pathological entities listed in Table 2, or the history of having taken some of the drugs detailed in Table 3 are risk factors for developing osteoporosis.

In these situations, whenever possible and depending on the cases, it is recommended to correct the original disease, replace or reduce the dose of the drug that produces the negative impact on bone, and consider a preventive treatment in order to reduce the risk of fracture.

Tabla 2. ENTITIES ASSOCIATED WITH LOW BONE MASS

Eating disorders
Osteomalacia
Hyperparathyroidism
Hyperthyroidism
Hypogonadism
Cushing's syndrome
Hyperprolactinemia with menstrual cycle disorders
Chronic kidney failure
Renal lithiasis, hypercalciuria
Chronic hepatic diseases (primary biliary cirrhosis, chronic hepatitis)
Malabsorption syndrome
Celiac disease
Gastrectomy; bariatric surgery
Chronic inflammatory arthropathy
Diabetes type 1
Osteogenesis imperfecta
Tobacco smoking
Alcoholism

Prolonged immovilization (more than 3 months)
Chronic hematologic diseases
Multiple myeloma
Hematologic neoplasias
Breast cancer
Prostate cancer
Neoplasias
AIDS

Tabla 3. PHARMACOLOGIC AGENTS ASSOCIATED WITH DECREASED BONE DENSITY OR GREATER BONE FRAGILITY

Corticoids (>2.5 mg prednisone/day or equivalent)
Thyroid hormone at TSH suppresive doses
GnRH analogues
Antiandrogens
Aromatase inhibitors
Anticonvulsants
Anticoagulants
Furosemide
Thiazolidinediones
Proton-pump inhibitors: ranitidine, omeprazole, and others
Lithium

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7. RISK FACTORS FOR FRACTURES

There is agreement on the fact that BMD measurement predicts fracture risk especially in untreated and elderly patients. To make this prediction, risk factors such as age above 60- 65 years, history of fragility fractures (from age 50), family history (history of fragility fractures in first-degree relatives –especially mother– with hip fracture), tobacco smoking, low weight (BMI < 20 kg/m^2), corticosteroid intake, and falls are taken into consideration. Regarding age, from 65 years onwards there is an increase in the risk of fracture every 5 years of 20-40% (Bagger *et al*, 2006; Siris *et al*, 2006). According to the Chilean Osteoporosis Foundation (FUNDOP), in epidemiological studies of 10,350 evaluated individuals, the history of a previous fracture was 1.7 times more frequent among those who had osteopenia *vs.* those who had normal BMD values (95% CI: 1.6-1.95) and 3.2 times more frequent (95% CI: 2.65-3.88) among the ones who had osteoporosis *vs.* the ones who had normal BMD values (Arriagada, 2009).

7.1- FRAX™

This method was developed by Kanis *et al*, WHO experts, and has been registered with the name of FRAX™, which is available on a free webpage at www.shef.ac.uk/frax (Kanis, 2008).
FRAX is a fracture risk assessment tool combining clinical risk factors with or without BMD, which is useful in:

A) The **health area:** Primary healthcare to identify high risk patients and optimize the available diagnostic resources and treatment.
B) **Clinical practice:** To help physicians make decisions about the treatment.

FRAX is not a diagnostic tool*;* it calculates the 10-year probability of any of the 4 most frequent osteoporotic fractures *(major osteoporotic fractures)* at the following skeletal sites: hip; clinical spine; wrist; proximal humerus.
FRAX recognizes certain risk factors and does not recognize others (see Table 4). It uses risk factors which are calculated considering patients in general and not particular patients but also uses rates of fractures and mortality which are country-specific. For the countries that do not have Frax country models available yet, it is recommended that they use FRAX with the epidemiologic data of the country which they find most similar to theirs.
Among other countries of the world, Spain and Argentina can use this algorithm to assess the 10-year fracture risk in individual patients.
However, in other Latin American countries more representative epidemiologic data is considered necessary before using FRAX (Pinheiro *et al,* 2009; Claus-Hermberg *et al,* 2009). Moreover, in each country more data will be necessary to validate the FRAX calculator in the corresponding population. It will also be necessary to gather local information on pharmacological economy in order to better define thresholds for intervention.
The majority of the countries included in the FRAX have provided only data on hip fractures; in the FRAX US, data was used on the incidence of the 4 main types of fractures in Olmstead county, MN (Melton *et al,* 1999).
FRAX is a work in progress that uses a beta test version since February, 2008, which appears on the Internet; since February, 2009, it changed the way of entering BMD: BMD and the brand of the densitometer is entered. Corrections were implemented in the algorithm for the 4 fractures with double-counted hip fractures since October, 2008 (Watts, 2009). By using FRAX, it has recently been proved that there is a reasonable concordance among the expected and observed rates of fractures; e.g., evaluation of the Framingham cohorts (Samelson *et al,* 2009).
It should be taken into account that the *National Osteoporosis Foundation* recommended updating the incidence of fractures and mortality in USA to be able to use FRAX, since the rate of hip fractures has decreased in that country from 1989-1991. The NOF also states that the estimation of fractures using FRAX-US is lower than expected (Melton *et al,* 2009).
Among FRAX limitations (Watts *et al,* 2009), there are some risk factors for fractures that are not included in the model, such as vitamin D deficiency, falls, physical activity, markers of remodeling, previous treatments for osteoporosis, drugs such as anticonvulsants, aromatase inhibitors, androgen deprivation, among others. When FRAX calculator gives a yes answer to secondary osteoporosis, the risk of fracture does not change when BMD values are entered. The FRAX calculator does not allow combinations of secondary risk factors; for instance, patients with hyperthyroidism and diabetes mellitus type 1 have the same risk as if they suffered from only one of these diseases. FRAX calculator does not consider low lumbar spine BMD (it only accepts femoral neck). As regards vertebral fractures, it considers neither their number nor their severity. Moreover, it does not consider the high risk that the history of prior vertebral fractures represents.
Furthermore, FRAX considers neither the dose nor the duration of treatment with corticosteroids, current tobacco smoking, and alcohol intake. A regards body weight,

low weight, an established and recognized risk factor of fractures, does not contribute to the risk if BMD is known.
T-*score* values given by the FRAX calculator may differ from the ones calculated by other densitometers, 20% in average. This may cause the estimated absolute risk of fractures to vary (Claus-Hermberg *et al,* 2009).

Table 4. RISK FACTORS CONSIDERED IN THE FRAX

- Country of residence
- Argentina, Austria, Belgium, China, Finland, France, Germany, Hong Kong, Italy, Japan, the Lebanon, New Zealand, Sweden, Swiss, , Turkey, the United States of America, United Kingdom
- Race: (only in the USA model: White, Hispanic, Afroamerican, Asian)
- Age: ages between 40 and 90 years old are accepted.
- Gender: men - women
- Body weight (kg) and height (cm): used to calculate the BMI
- Prior fracture: during adulthood, occurring spontaneously or with low-intensity trauma
- Family history: parents with hip fracture
- Corticoids: 5 mg prednisone/day during 3 months in the past or presently
- Rheumatoid arthritis (confirmed diagnosis)
- Tobacco smoking (presently)
- Alcohol intake: 3 measures/day
- Secondary osteoporosis
    - Type 1 diabetes mellitus
    - Osteogenesis imperfecta in adults
    - Prolonged untreated hyperparathyroidism
    - Hypogonadism or early menopause (<45 years of age)
    - Chronic nutritional deficiency or intestinal malabsorption
    - Chronic hepatic disease
- BMD: femoral neck T-*score* or absolute value in g/cm^2

8. DIAGNOSTIC EVALUATION

Medical history is an important tool for the diagnosis and study of osteoporosis in a particular patient.
Among the complementary methods for the diagnosis of osteoporosis, we should mention: bone densitometry, X-ray and laboratory tests.

8.1.-Bone Mineral Density

Axial densitometry is considered to be the best method providing data on the patient's bone mineral density. The skeletal sites that are recomended for bone density testing are PA_ lumbar spine and proximal femur. In the cases of scoliosis, severe osteoarthrosis, multiple vertebral fractures, all metal overlying the scan area or any other artifact invalidating measurement, the assessment of both hips is recommended.

8.1.1- Bone Mineral Density Measurement Techniques

Until now, it is not possible to clinically assess bone resistance in a direct manner. In an indirect manner, it is possible to do so by BMD test which can assess 70% of bone

resistance (Eriksson *et al*, 1989). The devices used to assess BMD can be classified according to the technique used or the skeletal area measured (Bonnick, 2004).
The most commonly used and accepted BMD measurement devices worldwide are the so-called DXA *(dual energy x-ray absorptiometry),* due to their accuracy and precision, the reproducibility achieved, and the low doses of radiation used. The data they provide is expressed in g/cm^2.
Measurements of BMD results obtained by using devices of different brands or of the same brand but of different models usually do not coincide. Therefore, when monitoring or following-up particular patients, measurement carried out with the same device or at least of the same brand and model is recommended.
QCT *(quantitative computerized tomography)* also allows for assessment of BMD per unit volume (g/cm^3). This technique uses a monoenergetic beam which is influenced by the amount of fat within the bone marrow. The amount of fat increases with the patient's age. QCT selects a region of interest (ROI) within the bone to be measured and compares radiological density with the standard phantoms which are simultaneously scanned with the patient when performing the QCT. One of the disadvantages of QCT is that there is a higher amount of radiation exposure than in DXA. The advantage of QCT is that those cases with a calcified abdominal aorta can be better examined. QCT allows for measurement of lumbar spine exclusively; however, there are techniques that can evaluate other areas.
QUS *(quantitative ultrasound)* also can study bone quality. QUS can evaluate bone mineralization and/or the microarchitecture and/or the biomechanical features of bone tissue. QUS can determine the speed of sound *(SOS),* broadband attenuation *(BA),* and the index which is obtained by the combination of the two parameters *(Stiffness*).
The devices, according to their features, are equipped to measure the axial (or central) skeleton and the peripheral skeleton. In the first case, vertebral spine and proximal femur are evaluated and in the second case, any of the following bones are evaluated: radio, metacarpals, phalanges, distal femur, tibial diaphysis, and calcaneous.
Proximal spine and femur can be determined by central DXA or axial QCT. The peripheral skeleton can be measured by any of the following devices: peripheral DXA, peripheral QCT (pQCT), tibial QUS or calcaneal QUS.
Among others, the advantages of the peripheral devices are: cheaper costs (in comparison with central measuring devices), portability, low radiation (or no radiation in the case of the QUS).
Peripheral BMD measurement is useful to evaluate the risk of fracture and to screen patients in whom axial BMD should be performed. If a peripheral study provides low results, these should be confirmed by an axial BMD. Among the limits of the peripheral measurement devices, are: the different criteria for the diagnosis of osteoporosis. Peripheral densitometry is not useful to monitor the response to treatment because the evaluated bone usually does not show big changes, which can overlap with the precision error of these devices (Bonnick, 2004).
It is recommended that the BMD test is performed and informed by ISCD-certified technicians and physicians or by technicians and physicians who have taken and approved mastery courses in BMD offered by scientific societies.

8.1.2- Indications for bone density test

This consensus recommends and agrees, in general, with the recommendations given by the Official Positions, 2007 and the Pediatric Official Positions of the International Society for Clinical Densitometry (The Official Positions of ISCD, 2007). Such positions were also ratified by the following international societies: *The American*

Association of Clinical Endocrinologists (AACE), *The American Society for Bone and Mineral Research* (ASBMR), *The Endocrine Society*, *The North American Menopause Society* (NAMS) (supports the section referring to postmenopausal women) and the *National Osteoporosis Foundation* (NOF). See Table 5.

It has been demonstrated that there are subjects without detectable risk factors, with densitometric values which in 50% and 30% of the cases correspond to osteopenia or osteoporosis, respectively (Miller *et al,* 1999; Melton, 2000; Cummings *et al,* 2002; Kanis *et al,* 2005).

The performance of a BMD test in women older than 65 years of age and in men of 70 years of age or more is recommended almost universally by the different Societies and Guidelines.

DXA is recommended to assess central skeletal sites in order to follow-up the status of the patient. Repetition of this test will be determined by the situation of the patient and the expected change, which equals or exceeds the minimal significant change that the device can detect. In patients who do not need treatment for osteoporosis, BMD can be performed every two years or more; in patients who begin treatment, BMD should be performed in one or two years; and in future controls, BMD should be performed every 2 years. In especial situations (corticosteroid treatment, trasplantation, hip fracture), the test can be repeated in six to twelve months.

Peripheral skeletal sites are not recommended, either for diagnosis or to monitor response to treatment (Binkley *et al,* 2006).

Table 5: INDICATIONS FOR BMD MEASUREMENT

Women aged 65 or older
Posmenopausal women under age 65 with risk factors for fracture
Women during the menopausal transition with risk factors for fracture such as low body weight, previous fracture, or high-risk medication use
Men aged 70 or older
Men under age 70 with risk factors for fracture
Adults with a fragility fracture
Adults with a disease or condition associated to low bone mass or bone mass losses
Adults with medication which can be associated with low bone mass or bone loss
Anyone being considered for pharmacologic therapy
Anyone being treated, to monitor treatment effect
Anyone not receiving treatment, in whom evidence of bone loss would lead to treatment
Women discontinuing estrogen should be considered for BMD testing according to the indications mentioned above.

Monoenergetic QCT of the lumbar spine has a high coefficient of variation and it is a highly operator-dependent method; thus, it is not a good means for monitoring treatment.

In therapeutic monitoring, there are drugs which can reduce the risk of fracture with no significant increases in BMD, as occurs with raloxifene.

8.2.- X-rays

X-rays are useful when osteoporosis is suspected, and mandatory when fractures at any skeletal site are likely to occur. X-rays are an uncertain method to detect osteopenia because it is affected by several factors such as radiographic exposure, film quality, *quantum* of soft tissues, among others. It is estimated that a bone loss higher than 10-40% (according to the sensibility of the device used) is necessary before it can be detected by lateral spine radiographs.

X-rays of thoracid and lumbar spine (PA and lateral views) are recommended because they are useful for the diagnosis of vertebral fracture, spondylosis, aortic atheromatosis, or other pathologies.

8.3- Laboratory

The basic and general laboratory tests and the specific laboratory tests related to phosphocalcic metabolism will be required according to the history and need of the patient being studied. Laboratory tests are useful for the differential diagnosis of the several systemic diseases which can negatively affect bone.

8.3.1- Bone and mineral laboratory

Bone and mineral laboratory involves the following analyses: serum calcium, phosphorus, creatinine, magnesium, urine calcium, magnesium, creatinine, tubular reabsorption of phosphate. Measurement of PTH and 25-hydroxyvitamin D will be required according to the particular situation of the patient.

As regards the values of serum creatinine obtained, the calculation the glomerular filtration rate is recommended, using the formula: [(140 – age) × weight] ÷ (72 × serum creatinine), corrected × 0.85 for women, described by Cockcroft and Gault (1976). It enables to know the renal function with great accuracy, which is essential for the clinical and therapeutic management of the patient with osteoporosis.

8.3.2- Bone remodeling laboratory

These markers are not useful to make the diagnosis, but they are useful to orient physicians about the dynamics of bone turnover in a particular patient. This will help physicians to identify patients with a higher fracture risk. These markers are also useful to make an early evaluation of the response to treatment. The systematic determination of bone markers is not recommended in the evaluation of every patient with osteoporosis.

Among the bone turnover markers, there are formation markers and bone resorption markers. Among the bone formation markers, the ones that have been proven useful are: total alkaline phosphatase and its bone isoenzyme, osteocalcin, and aminoterminal propeptide of type 1 collagen (P1NP). The bone resorption markers that stand out are: Urinary deoxypyridinoline and type 1 collagen telopeptides: C-terminal (CTX) or N-terminal (NTX) –serum or urinary–. When markers are used, it is recommended to order only one formation marker and only one resorption marker.

In Table 6 biochemical tests are listed.

Table 6. LABORATORY TESTS FOR OSTEOPOROSIS

- **General laboratory**
  - Complete blood cell count
  - Red cell sedimentation rate
  - Blood urea nitrogen
  - Serum glucose
  - Electrophoretic proteinogram
  - Liver function tests
  - Urinalysis
- **Especific laboratory**
  - Serum thyrotrofin
  - Serum and/or urinary cortisol
  - Testosterone (total and/or bioavailable) in men
- **Mineral metabolism laboratory**
  - Serum calcium
  - Serum phosphate
  - Serum creatinine
  - Serum magnesium
  - Tubular reabsorption of phosphate
  - Urine calcium
  - Urine creatinine
  - Urine magnesium
  - Serum PTH
  - Serum 25-hydroxyvitamin D
- **Bone remodeling laboratory**
  - Bone formation:
    - Alkaline phosphatase or its bone isoenzyme
    - Osteocalcin
    - P1NP
  - Bone resorption:
    - Deoxypiridinoline
    - Collagen telopeptides: NTX, CTX

With antiresorptive treatment, a 70% reduction of the resorption markers is correlated with 40% reduction in the risk of fracture, while a decrease in the formation markers is correlated with 44% reduction in the risk of fracture (Hochberg *et al*, 2002).

9. PREVENTION OF OSTEOPOROSIS AND FRACTURES

The adoption of general measures has proven to be efficient in the prevention of osteoporosis and fractures. Such measures include healthy dietary habits and a healthy lifestyle.

9.1- Dairy products

The benefit of a diet with an adequate amount of calcium has been established. Dairy products are considered to be the most important nutritional sources of calcium.

Since age 50, diet should provide about 1,200 mg of calcium per day. This amount can be provided mainly by dairy products and it is preferred to include/choose calcium-fortified dairy products since they contain between 40 % and 100% more calcium than non-fortified foods. In case dairy products are not tolerated, patients can be advised to drink lactose-free milk or to take calcium supplements.

9.2- Other nutrients

A good intake of proteins (1 g protein/kg.day) is important; other nutrients (vitamins and minerals) should be present in the diet. According to an important paper, elderly women should include in their diet an adequate amount of proteins, which can be found in low-fat meat, chicken, fish, and eggs (Smith *et al*, 2008).

9.3- Physical activity

Physical activity, especially resistance exercise, provides an important load stimulus which maintains and improves the muscular-skeletal health. Physical activity has proved to have a significant positive effect on osteoporosis risk reduction, independently of drug therapy (Layne & Nelson, 1999; Sinaki *et al*,, 2005).

High-impact physical activity stimulates the mineral content in the skeleton and low impact physical activity, such as walking, has beneficial effects on other aspects of health and function, although their effects on BMD have been minimal. Any type of physical activity is good; combating sedentary lifestyle contributes to prevention. Walking is an aerobic activity which is performed by many people and is beneficiary for elderly people. Better results are obtained when people walk distances of more than 20 blocks per day for which it is recommended to start with short distances and short steps and increase them according to the tolerance and adaptation of the person to it (Berard *et al*, 1997).

Up to 19 years of age, a person performing active physical activity (resistance exercises) can increase axial mineral density from 1% to 3% per year (Sinaki & Mikkelsen, 1984; Sinaki *et al*, 1986). Exercises which strengthen extensor muscles of the spine or muscles of the lower limbs, reduce the risk of falls and fractures (Sinaki *et al*, 1993; Mosekilde, 1995); it should be remembered that 25% of falls end in fractures.

However, exercises that incurvate the spine ventrally increase the risk of vertebral fractures (NIH Consensus Development Panel, 2001; Sinaki *et al*, 2002; Sinaki *et al*, 2005).

In these cases, the main elements of an exercise plan for bone health are: impact exercise such as jogging, rapid and energetic walk, climbing stairs; exercises involving strengthening, coordination, and equilibrium can be performed when practicing tango, salsa, and other dancing activities (Hackney *et al*, 2007).

9.4- Sun exposure

Vitamin D, which is necessary not only for bone health, is found in a few foodstuffs. The main source of vitamin D is the skin exposed to ultraviolet rays. In spring/summer, sun exposures of 15-20 minutes suffices, while in fall and winter a longer exposure may be necessary. However, for people with certain skin pathologies or other pathologies the risk involved should be taken into consideration. It is also important to take into account the hours of higher risk of sun exposure, especially when there is more heliophany, as occurs in summer.

In teenagers and young adults, sun exposure of hands, face, arms, or legs is recommended which causes a "suberitemal" state equivalent to 25% of the amount of sunlight that causes a light pink colour on the skin. Such exposure should be repeated 2 to 3 times a week (Holick, 2007). In numerous cases, the intake of supplements of vitamin D is necessary, especially in people older than 60-65 years of age who expose themselves to sunlight for short periods of time. The ideal serum level of 25-hydroxyvitamin D should be higher than 30 ng/ml (Holick, 2007).

9.5- Tobacco smoking cessation

It is important to avoid tobacco smoking because of the known negative effects on bone and mineral metabolism, and because of the other known negative effects on general health.

In spite of uncertain results obtained, the use of antioxidants for a certain period of time can be considered to counteract one of the physiopathogenic effects of tobacco on bone. After years of having stopped smoking, risks are reduced.

9.6- Fall prevention

A considerable number of osteoporotic fractures occur after falls; thus, prevention of falls should be an aim to achieve when attempting to prevent osteoporotic fractures. People are more likely to fall down with advanced age.

Non vertebral fractures are usually associated with falls caused by preventable factors such as: A) Medication: tranquilizers, drugs to lower blood pressure, oral hypoglycemic agents; B) Visual problems; C) Obstacles in pathways or at home: uneven floors, carpets, loose wires, lack of bath handles and banister stairs, inadequate light, among other factors; D) Domestic animals (Sánchez, 1997; Gass & Dawson-Hughes, 2006).

Performing entertaining and coordination exercises can be of interest and have proved to have a positive effect on balance and muscular strength of the limbs, which improves. Short repetition of a series of simple exercises 3 times weekly helps prevent falls and fractures (Kita *et al,* 2007).

9.7- Hip protectors

Hip protectors to reduce the risk of hip fractures consist of a pair of plastic shields along the external aspect of each hip, which are fitted in pockets within special underwear anatomically designed to absorb the impact of a fall and reduce the risk of fractures of the proximal femur. Hip protectors, which have proved to be effective in reducing the risk of fractures, should be used the whole day especially by elderly people with a high risk of falls and hip fractures (Kannus *et al,* 2000).

10. TREATMENT OF OSTEOPOROSIS

Treatment of osteoporosis should be aimed at reducing the incidence of fractures. For this purpose, it is important to take into consideration that the risk factors strongly related with the incidence of fractures are the following: a) age of the patient; b) history of fractures (vertebral or non vertebral); c) low BMD d) family history of hip fractures in first-degree relatives.

Regarding BMD results, there is no evidence of an absolute value of BMD which indicates the need of treatment in each particular situation; data guiding decisions about drug intervention result from population studies. Information resulting from BMD tests should be taken into account together with that related to other risk factors, to effectiveness, safety, risks, adverse effects, and costs of treatment (Bocanera & Puche, 2006).
In order to decide when to begin treatment for osteoporosis, it is essential to establish the risks and benefits for the individual patien; important clinical papers are useful to consider facts or general situations, but they alone do not constitute a factor determining the need for treatment (Bukhari, 2009).

The patients for whom treatment of osteoporosis should be recommended have some of the following characteristics:

- Postmenopausal women with at least one fragility fracture
- Postmenopausal women with no prior fractures but with one or more risk factors (besides menopause), with a BMD T-*score* of less than or equal to -2.0 by DXA at the spine or hip
- Postmenopausal women with no prior fractures or detectable risk factors, provided that they have a BMD T-*score* less than or iqual to -2.5 by DXA in at least one of the main axial skeletal sites
- Postmenopausal women with osteoporosis
- Men with osteoporosis
- Patients receiving chronic corticosteroid therapy
- Patients receiving treatment with doses >5 mg of prednisone per day (or equivalent) for more than 3 months with a BMD T-*score* less than or equal to -1.0
- In people older than 80 years of age with a BMD Z-*score* less than -1.5
- Patients with breast cancer who receive therapy with drugs capable of inducing bone loss
- Patients with prostate cancer who receive therapy with drugs inducing bone loss

The decision to begin treatment and the choice of drug will depend on the need to reduce the risk of fracture. For this decision, several factors should be taken into account such as age, gender, renal function, drug allergy, other comorbidities, previous treatments, adverse effects and costs, among others. The problem of poor adherence to treatment should also be considered, and measures to improve compliance should be implemented. Regarding compliance, in some evaluations drugs administered weekly or monthly fare better than those administered daily.

On the basis of their effects, drugs used for treatment are classified into: a) antiresorptives or anticatabolics; b) bone formers or anabolics; c) drugs of complex mechanism (Lewiecki *et al*, 2009).

10.1- Bisphosphonates

The oral bisphosphonates most commonly used in the Iberoamerican countries are: alendronate, risedronate, and ibandronate, which constitute the first treatment option for postmenopausal women with osteoporosis, especially if they have previous fractures (Black & Cliff, 2006). Alendronate and risedronate have proved to be useful in the

treatment of osteoporosis induced by corticosteroids, and male osteoporosis (Black & Cliff, 2006).
Treatment with bisphosphonates in fertile women with osteoporosis with no proven secondary causes is not recommended; however, it can be taken into consideration according to the cases. Alterations have not been demonstrated in those women who have taken bisphosphonates for a long period of time and have become pregnant during or after treatment.
Such drugs should be administered only if renal function is preserved (glomerular filtration rate >30 ml/min).
In several Latin American countries there are copies of bisphosphonates produced by national laboratories which have not been certified as generics by any regulatory agency. In the Argentine Republic, there is only one (Marvil – alendronate by Gador S. A.) which is a generic since it has the same pharmacokinesis and bioavailability as the original alendronate (Fosamax by MSD) (Roldán *et al,* 2005). Due to the lower costs in some countries, local copies are sold more than the original drugs.

10.1.1- Alendronate
Alendronate administered in doses of 10 mg per day or 70 mg per week for 3 years reduces the incidence of vertebral fractures, hip and wrist fractures by 50% in patients with a previous vertebral fracture. The incidence of vertebral fractures, in 4 years, in patients with no previous vertebral fractures can also be reduced by 48% (Liberman *et al,* 1995; Black *et al,* 1996; Cummings *et al,* 1998; Black *et al,* 2000). Alendronate constitutes one of the recommended treatments for osteoporosis in men (Orwoll *et al,* 2000) as well as for glucocorticoid-induced osteoporosis (Saag *et al,* 2007).

10.1.2.-Risedronate
Risedronate, in doses of 5 mg per day or 35 mg per week, administered for 3 years, reduced the incidence of vertebral fractures by 49%, and that of non vertebral fractures by 33% in patients with a previous vertebral fracture (Reginster *et al,* 2000). It significantly reduced hip fractures in elderly women with confirmed osteoporosis but it did not do so in elderly women whose BMD had not been taken into consideration (McClung *et al,* 2001).
Risedronate has proved to be effective in the treatment of osteoporosis in men, causing an increase in BMD and a reduction of the risk of fractures. So, risedronate constitutes another treatment option for this type of osteoporosis (Ringe *et al,* 2006) as well as for corticosteroid osteoporosis (Cohen *et al,* 1999).
Similar effects on BMD and on the reduction of fracture risk can be seen in recent clinical studies of risedronate in doses of 75 mg/day, two consecutive days a month, or 150 mg only one day per month, for two years (Delmas *et al,* 2008, McClung *et al,* 2009).

10.1.3- Ibandronate
The antifracture effect of oral ibandronate has been demonstrated in women with postmenopausal osteoporosis.
Studies on patients' preference regarding the administration of bisphosphonates showed that monthly ibandronate was preferable compared with weekly bisphosphonates.
A recent study carried out in Germany in 13,000 postmenopausal women with osteoporosis showed that, after a year, 90% of the women kept taking ibandronate and 77% of them were satisfied with treatment at monthly intervals. Tolerance to treatment was good or very good in 95% of treated female patients (Börst *et al,* 2009).

Ibandronate can be administered in doses of 2 mg every 2 months or of 3 mg every three months via intravenous injection (IV) without dilution, administered over 15-30 seconds. According to the DIVA study, 3 mg of ibandronate IV every 3 months showed a better response in terms of BMD and bone turnover markers (and probably a greater reduction in the risk for fracture) than the oral dose of 2.5 mg per day (Delmas *et al*, 2006).
Intravenous bisphosphonates are recommended in patients with digestive intolerance to oral bisphosphonates or in those who cannot receive other type of medication. Moreover, in those patients, the administration of bisphosphonates should be via intravenous injection and not via endoarterial or paravenous injection due to their adverse effect on the tissues. Therefore, the administration by a competent professional is recommended.

10.1.4.-Pamidronate
The dose of pamidronate via endovenous injection is 30-60 mg every 3 months and is administered diluted in 250 cc of isotonic fluid over 2-3 hours. The frequency of severe adverse effects of pamidronate every three months is rare (Sarli *et al*, 2007).

10.1.5- Zoledronate
Zoledronate or zoledronic acid administered via endovenous infusion has proved to reduce 70% of the incidence of vertebral fractures after 3 years, 41% that of hip fractures and 25% that of non vertebral fractures (Black *et al*, 2007). When zoledronate is administered after 90 days of having performed an osteoporotic hip replacement surgery for a hip fracture, the incidence of new clinical fractures decreases 35% and all-cause mortality also decreases by 28% (Lyles *et al*, 2007; Deeks & Perry, 2008).
Zoledronate has also proved effective in male osteoporosis (Piper & Gruntmanis, 2009) and in pediatrics, it is comparable in effectiveness and safety to intravenous pamidronate (Brown & Zacharin, 2009).
Recent evaluations have shown that it can prevent bone loss after organ transplantation (Crawford *et al*, 2006; Yao *et al*, 2008).
Furthermore, it has recently been approved by the FDA for the prevention of postmenopausal osteoporosis, using an intravenous infusion of 5 mg annually for two years.
There are several recommendations for the use of intravenous infusion of zoledronate: the time of the infusion should not be less than 15 minutes; it should be infused at a constant rate; the infusion solution should not be in contact with solutions containing calcium or divalent cations; and it should be administered as the only intravenous solution via a separate air intake infusion pump. If previously cooled, the solution should be left to achieve room temperature before administration.

10.1.6- Bisphosphonates and the risk of maxillary osteonecrosis
The risk of developing mandibular osteonecrosis or osteonecrosis of the jaw (ONJ) in postmenopausal women with osteoporosis treated with oral or IV bisphosphonates seems to be low. Some references suggest this possibility which varies from 1/10,000 to less than 1/100,000 patients treated per year (Khosla *et al*, 2007); other references suggest that its incidence might be higher and the corresponding diagnostic tests should be done (Escobar López *et al*, 2007; Nathaniel *et al*, 2008; Mavrokokki *et al*, 2007).
This seems to be rare in patients with postmenopausal osteoporosis or male osteoporosis treated with oral bisphosphonates. It is more likely to occur in patients with multiple myeloma or breast cancer, prostate cancer or other cancer metastatic to the skeleton and

in those who frequently receive intravenous infusions of strong nitrogenated bisphosphonates. ONJ in 94% of the cases occurs in patients with cancer treated with zoledronic acid or pamidronate (Woo *et al*, 2006).
The pathophysiologey of ONM is still unknown, but it can be associated with excessive suppresion of bone turnover, decrease of angiogenesis, dental infection, traumas, or repeated traumas, or radiation therapy to head and neck.
Risk factors to develop ONM include cancer, frequent IV infusions of nitrogenated bisphosphonates, and traumatic or infectious mouth and dental injuries. Therefore, before starting therapy with IV bisphosphonates, patients should be evaluated by a dentist. It is recommended that treatment with bisphosphonates should not be started until the dental problem is solved (if there is one).
In the cases of ONJ, systemic and local therapy with antibiotics can help reduce pain and eventually cure the disease. Bisphosphonates should be discontinued. Local surgical treatment of the ONJ should be avoided.

10.1.7- Bisphosphonates and risk of atrial fibrillation

Recent publications show that some postmenopausal patients treated with oral or IV bisphosphonates for osteoporosis could have higher risk of atrial fibrillation.
According to the HORIZON study, an unexpected increase of the risk of atrial fibrillation was demonstrated (Black *et al*, 2007) although this evidence was not confirmed in further evaluations even in populations with similar risk factors for atrial fibrillation (Lyles *et al*, 2007), nor in the reanalysis of the FIT study *(Fracture Intervention Trial)* and in other reviews of studies with risedronate (Black *et al*, 1996; Cummings *et al*, 2007). However, there are two recent papers which demonstrate a possible relationship between this medication and atrial fibrillation (Heckbert *et al*, 2008; Sørensen *et al*, 2008). It might be premature to decide, according to the available evidence, the contraindication or discontinuation of oral or IV bisphosphonates in patients with osteoporosis who present risk of atrial fibrillation; however, physicians should be aware of this possibility and, according to the case, they may decide on the convenience of maintaining treatment.

10.1.8- Duration of treatment with bisphosphonates

Regarding the duration of treatment with bisphosphonates, it has been proved that the presence of such drugs in the bone lasts for more than a decade; thus, the safety of such prolonged treatment should be controlled. Nevertheless, the studies with alendronate for 10 years do not show a loss in the antifracture effect (Bone *et al*, 2004); it is also known that the positive effect of bisphosphonates persists even after having been suspended following 3-6 years of continuous treatment (Black *et al*, 2006). Therefore, it is possible to interrupt continuous treatment with bisphosphonates in patients with low or moderate risk of fracture (Sánchez, 2006).

10.2- Calcitonin

The PROOF study is the only one to have shown that nasal salmon calcitonin, in doses of 200 UI per day, significantly reduces the rate of vertebral fractures by 33% in patients with severe osteoporosis (Chestnut *et al*, 2000) –in patients with a history of previous fractures– and by 50% in women of 70-75 years of age after 5 years of treatment (Muñoz-Torres *et al*, 2004).
With doses of 100 or 400 UI/day, no significant reduction of fractures was found.

This drug should not be used as the first treatment option for postmenopausal osteoporosis. It can be used in certain situations for the treatment of osteoporosis in men and in premenopausal women, as well as for corticosteroid-induced osteoporosis.
Calcitonin acts as an efficient painkiller especially in the cases of pain associated to acute vertebral fracture. Nevertheless, it should not be considered the first analgesic option in such cases, due to its high cost.

10.3- Hormone Replacement Therapy

In several Latin American countries, there are copies of different estrogens, tibolone, raloxifene, produced by national laboratories, which have not proven to be generic drugs before any regulatory entity. Due to the lower costs in some countries, local copies are sold more than the original drugs.

10.3.1- Estrogens

Since menarche, bone formation is regulated by multiple hormones; estrogens play an essential role during the whole lifespan of women.
The evaluation of the estrogen levels of female patients during their adolescence, mature age, and climactery should be thoroughly carried out by physicians.
Situations such as oligo-amenorrheas (hypothalamic, hypophyseal, ovarian), hyperprolactinemias, surgical amenorrheas, genetic, early menopause, are usually accompanied by a large decrease of estrogen levels. Estrogen levels lower than 50 pg/ml which are maintained for 6 months or longer inhibit bone formation and allow higher bone resorption, and meet the diagnostic criteria for such situations.
In the case of adolescents or women in fertile age with hypoestrogenism, replacement treatment is recommended in order to reach levels of estradiol between 50 and 80 pg/ml.
There are several hormone replacement therapy preparations which can be used in young women: transdermal estradiol gel or oral estradiol, (standard dose of estradiol: 2 pulses - 2 mg of micronized estradiol); natural micronized progesterone (200 mg for 10 to 14 days/month); or oral contraceptives. Low doses should always be avoided.
Contraception in teenage girls treated with ultralow doses of estrogen show a significant decrease in BMD of lumbar spine, total body, and hip in relation to groups of teenagers who do not take contraceptives or teenagers who take low or conventional doses of contraceptives (Shoepe & Snow, 2005).
Extremely low doses of contraceptives do not reduce BMD in groups of women older than 25 years of age (Nappi, 2007).
At all ages, it is recommended to control the secondary factors such as symptoms, hormonal profile (E_2-FSH-TSH); evaluation of habits such as smoking, drug and alcohol intake, drugs, and major risk factor for fractures.
During menopause, hormone replacement therapy (HRT) is still the first treatment option for osteoporosis in postmenopausal young women (Bilezikian, 1998). The meta-analysis carried out by the “Osteoporosis Research and Advisory Group” reported a decrease in the risk of vertebral and non-vertebral fractures in 50% of the cases. (Osteoporosis Research and Advisory Group, 2002).
For HRT, the choice of a lowest dose of natural estrogen according to each patient’s need and response is always recommended.
Estrogen replacement therapy, or estrogen therapy associated with progesterone during menopause has the following indications: climacteric syndrome, vulvovaginal atrophy, osteopenia, osteoporosis, and early menopause. The *North American Menopause*

Society approves such therapy for the prevention of osteoporosis (North American Menopause Society, 2007). In hysterectomized women, the replacement with estrogens alone (with no progestagens) is effective and safe (Anderson *et al,* 2004).

The contraindications which should be taken into account are the following: vaginal blood loss of unknown origin, breast or endometrial cancer, thromboflebitis, serious hepatic or renal disease, systemic eritematous lupus.

There are several ways of administering estrogens: oral, percutaneous, transdermal, intravenous, vaginal, nasal, and subcutaneous implants.

Oral estrogen has micronized estradiol; the standard dose is 2 mg. There are oral estrogens alone, oral estrogens in combination with progestagens, and estradiol in combination with drospirenone.

For percutaneous administration of estrogen, there is estradiol gel (standard dose, 1.5 mg/day, equivalent to two pulses per day). For transdermal administration, there are estradiol patches, (standard dose, 50 mcg; there are other presentations which will be detailed later, as well as its association with norethisterone acetate –cyclic or continuous–).

For vaginal administration, there is the estriol vaginal cream and promestriene cream. These compounds are not systemically useful; thus, they are not indicated for osteoporosis.

For intravenous administration, estradiol valerate (4 mg) associated with prasterone enanthate (200 mg) is used.

The other ways of administering estrogens are used neither in Latin America nor in the Iberian Peninsula.

First hepatic passage: Oral estrogens have an hepatic first-pass effect. Oral estrogens can be absorbed via the portal vein through the hepatic sinusoids reaching the liver; this situation is beneficial in some aspects, since it increases HDL cholesterol, plasma proteins, plasminogen, and reduces PAI-1 (plasminogen activator inhibitor), but it is negative in others such as increased triglycerides, renin substrate (angiotensinogen), plasma renin activity, and coagulation factors.

Transdermal or percutaneous estrogen administration is suggested in the following cases: A) Gastrointestinal disorders: gastritis, ulcer, malabsorption. B) Hepatic, gallbladder and pancreas diseases. C) Hypertension. D) Personal or family history of thrombosis or embolism; risk factors for thromboembolic disease. E) History of cerebral vascular accidents. F) Hypertriglyceridemia. G) Thyroid pathology. H) Epilepsy. I) Tobacco smoking (smoking cessation should be suggested before starting HRT). J) Diabetes.

Recent studies suggest that the dose/response curve of estrogens in different tissues is equally efficient with low doses of estrogens especially when they are associated with progestins. This could limit the untoward effects such as the risk of breast cancer in women who take them for a long period of time, etc. (Genant *et al,* 1997; Pines *et al,* 2009).

Low doses of different estrogen compounds depend on the way of administration and on the type of estrogen used (see Table 7).

Table 7. LOW DOSES OF SOME ESTROGEN COMPOUNDS

Oral estrogen: conjugated equine estrogens	0.3 mg/day
micronized estradiol	0.5 mg/day
Transdermal estrogen: 17 beta-estradiol	0.025 mg/day

Low doses improve the continuity of treatment due to a decrease of adverse effects allowing a higher number of postmenopausal women to benefit from the effects of the HRT in the short and long-term.
The HOPE study *(Women's Health, Osteoporosis, Progestin, Estrogen)* (Lindsay *et al*, 2002), which examined the efficacy of low doses of conjugated equine estrogens (CEE) associated with medroxyprogesterone acetate (MPA) in 2,673 healthy postmenopausal women, showed that low doses of such combination can be better than the same low doses of CEE with no progestogenic opposition when the vasomotor symptoms improve. An improvement in the percentage of vaginal superficial cells has been reported when the level of vaginal maturity was measured, after treatment with low doses of CEE alone and CEE plus MPA (Utian *et al*, 2001).
As regards the efficiency of low doses of estrogen as an antiresorptive, physicians should wait for the long-term results of the HOPE study and other studies which are still under way. However, in 1998, a meta-analysis carried out with 31 studies of low-dose estrogen showed the importance of the addition of calcium since the increase in the BMD of lumbar spine with estrogen was only 1.3%, while it doubled with the addition of 1.200 mg calcium /day (Nieves *et al*, 1998).
According to a case/control study of hip fractures in women of 65 years of age and more (all without hormonal treatment) carried out by Cummings *et al*, basal levels of estradiol were registered in women who later had hip fracture; in a control group of the same cohort, it was found out that women with low but detectable estradiol (5-25 pg/ml) had a significant lower risk of hip and vertebral fracture than the ones who had no detectable levels of estradiol (below 5 pg/ml) (Cummings *et al*, 1998). In other randomized groups of the same cohort, experts reported that the women with estradiol levels below 5 pg/ml had less bone mass than those with levels of 10 to 25 pg/ml (Ettinger *et al*, 1998) and that the rate of bone loss was higher in those women with lower estrogen levels (Stone *et al*, 1998).
Epidemiological studies such as the *Nurses' Health Study* with more than 70,000 postmenopausal women followed for 20 years, indicate that low doses of estrogen decrease the risk of coronary disease as efficaciously as standard doses (RR 0.58 for the former *vs.* 0.54 for the latter). Besides, the RR of thromboembolic accident was 0.54 with 0.3 mg/day CEE *vs.* 1.35 with 0.625 mg and 1.63 with 1.25 mg. Vaginal bleeding with CEE 0.3 mg/día in association with progesterone disappeared after 6 months in 53% of women and in 93% at 12 months.
Gambacciani y col. published in Maturitas (2008) a study that followed bone mass in young postmenopausal women treated with low dose combined estrogen-progestagen during two years; end points were symptoms and BMD. There were 3 groups: low dose HRT: 1 mg estradiol + 0.5 mg norethisterone acetate/day for 28 days + 1,000 mg Ca/day; another group with ultralow dose HRT: 0.5 mg 17beta-estradiol + 0.25 mg norethisterone acetate/day for 28 days + 1,000 mg Ca/day; women in the control group received only 1,000 mg Ca/day. Both low- and ultralow-dose estrogen can alleviate sumptoms and provide an adequate protection against bone loss.
Present day evidence open possibilities for the use of very low doses of estrogen, but further demonstration of their impact on BMD and fracture rates is needed.

10.3.2- Tibolone

Tibolone has proved, in some studies, to increase BMD in postmenopausal women with and without osteoporosis.

According to the LIFT study *(Long-Term Intervention on Fractures with Tibolone)* [Cummings *et al,* 2008], tibolone has proved effective to reduce the risk of fractures in three years in patients with or with no prevalent fractures. It significantly reduces 45% of the relative risk (RR) of vertebral fractures and 26% of non vertebral fractures. According to the same study, in female patients with previous vertebral fractures, the tibolone reduced 61% of the RR of vertebral fractures; and 47% of non vertebral fractures. The LIFT study also shows a 68% reduction in the RR of invasive ductal breast cancer.
Safety data show: a) 2.2 times increase in the risk of CVA in treated older women (> 70 years) compared to those taking placebo (Cummings *et al,* 2008), but without increment in the risk of thromboembolism; b) increment in the risk of breast cáncer recurrence (Kenemans *et al,* 2009).

10.3.3- Selective Estrogen Receptor Modulators (SERM): Raloxifene

The only SERM approved for the prevention and treatment of postmenopausal osteoporosis is raloxifene, which causes a significant reduction in the risk of vertebral fractures.
According to the MORE study, a 3-year clinical study, raloxifene can reduce the risk of vertebral fracture, but not of other types of fracture. An increase in the risk of venous thromboembolism was also found (RR 3.1, 95% CI: 1.5-6.2) (Ettinger *et al,* 1999). According to CORE, a 4-year clinical study, no differences were shown in mortality rates, cardiovascular events, cancer or non vertebral fractures (Ensrud *et al,* 2006). According to the STAR study, raloxifene was found similar to tamoxifene in the prevention of invasive breast cancer (Vogel *et al,* 2006).
Raloxifene can be considered for the prevention or treatment of osteoporosis in women with risk of vertebral fracture and an elevated breast cancer risk.

10.4- Fluoride

Although fluoride is on the market in many Latin American countries, present evidences do not recommend its use for osteoporosis.
Sodium fluoride or sodium monofluorophosphate (MFP), through the fluoride ion, produce an anabolic stimulus to osteoblasts inducing an increase of the trabecular bone mass. Such effect can be seen in 6 to 12 months in 60% of treated patients. A 10% increase of the lumbar BMD can be seen, but usually there is no response at the hip. Therefore, it is not recommended in patients with low hip BMD or previous fracture at this skeletal site, or in older people. Treatment with fluoride salts has not shown a significant decrease in the risk of fracture (Puche & Rigalli, 2007).

10.5- Recombinant parathormone

10.5.1- PTH (1-34) or Teriparatide

$PTHrh_{1\text{-}34}$ or teriparatide consists of the first 34 aminoacids of the PTH human molecule obtained by the recombinant DNA technique (Trivedi *et al,* 2009).
Used every day in patients with osteoporosis with doses of 20 mcg, $PTH_{1\text{-}34}$ showed a 65% reduction in the risk of vertebral fractures and a 53% reduction in the risk of non vertebral fractures after one and a half year treatment (Neer *et al,* 2004; Gallagher *et al,* 2006).

Teriparatide is especially recommended for the treatment of patients of both genders with severe osteoporosis and in postmenopausal women older than 65 years with confirmed osteoporosis and prevalent vertebral fracture (Geusens *et al,* 2009).
Due to the high cost of teriparatide, its use is restricted to the treatment of patients with more than one fragility fracture and low BMD, with T-*score* < -3.5, and to patients with new fractures after two years or more of treatment with bisphosphonates (Hodsman *et al,* 2005; Mueller *et al,* 2009).
Treatment should not exceed two years. During treatment patients should take about 1.5 g/day of calcium as well as adequate vitamin D supplements. Serum calcium should be monitored 30 days after the beginning of treatment, and unire calcium should be measured at 90 days. A small increase of calcium levels in blood and or urine can be controlled by slightly reducing calcium intake.

10.5.2- PTH (1-84)

After one year of treatment, PTH_{1-84} reduces the risk of vertebral fracture, increases lumbar BMD, and markers of bone formation. PTH_{1-84} does not cause significant modifications in hip BMD (Greenspan *et al,* 2007).

10.5.3- Combination or sequential therapy with PTH

The use of teriparatide or PTH 1-84 together with bisphosphonates has not shown to be better than either treatment alone. But after treatment with teriparatide or PTH 1-84, treatment can be continued with bisphosphonates or other antiresorptives (e.g.: raloxifene). This strategy maintains the positive effects of PTH on BMD (Finkelstein *et al,* 2006; Greenspan *et al,* 2007; Dobnig *et al,* 2009).

10.6- Strontium ranelate

It functions *in vivo* mainly as an antiresorptive although it can also act as a bone former, especially *in vitro* (Marie *et al,* 1993; Blake *et al,* 2009). However, vertebral spine and hip BMD increase due to, in part, the deposit of strontium in bones (Meunier *et al,* 2004).
Oral doses of strontium ranelate (2 g/day) are administered, preferably before going to bed at night, and two hours after having dinner. Following one year of treatment, 50% the incidence of vertebral fractures decreases by 50% and the incidence of non vertebral fractures decreases by 16%. In older people with established osteoporosis, the incidence of hip fracture decreases by 36% (Reginster *et al,* 2005; Ortolani & Vai, 2006). In women over 80 years of age, the incidence of vertebral and non vertebral fractures decreased by 32% and 31%, respectively (Seeman *et al,* 2006).
In some Latin American countries, there are copies of strontium ranelate produced by national laboratories, which have not been certified as a generi drug by regulatory agencies. Due to lower costs, in some countries, local copies are sold more than the original drugs.

10.7- Calcium

In case patients cannot take obtain enough amounts of calcium from natural sources, they should include pharmacological supplements of calcium salts.
Normal individuals of 19 to 50 years of age should take 1,000 mg of calcium per day; people older than 50 years of age should take 1,200 mg of calcium per day with a maximum recommended limit of 2,150 mg of calcium per day (Tang *et al,* 2007).

For patients with osteoporosis undergoing treatment with corticosteroids, subjects living in institutions, and subjects older than 65 years of age, and during pregnancy, an intake of 1,500 mg calcium/day is recommended (Institute of Medicine, 1997).
Calcium oversupplementation (considered to be an inadequate intake due to excess) can be associated with a higher risk of renal lithiasis and vascular calcification, and can increase mortality due to cardiovascular events (Bolland *et al,* 2008; Maziak 2009).
Foods containing oxalic acid reduce calcium absorption. This occurs with many vegetables except for soybean. The bioavailability of calcium supplements can be compromised by foods, doses, and pill disintegration. Calcium absorption is reduced when doses are higher than 600 mg; thus, supplements can be administered during meals and in divided doses. Intake of calcium carbonate supplements on an empty stomach can increase the risk of renal lithiasis. Intestinal absorption of calcium carbonate can be reduced in people treated with proton pump inhibitors (Institute of Medicine, 1997; O'Connell *et al,* 2005); when such strong antacids are used chronically, the risk of fractures can increase (Sánchez, 2009).

10.8- Vitamin D

Adequate levels of vitamin D are essential for several bodily functions, for instance, facilitating an adequate intestinal absorption of calcium, achieving an effective suppresion of the serum PTH, reducing the rate of bone loss, reducing 22% of the risk of falls and improving the function of the inferior limbs, among others. Since it is known that sun exposure may not be enough to meet vitamin D requirements, natural and pharmacological sources are essential to reinforce the diet (Dawson-Hughes *et al,* 2005).
Vitamin D, 700-800 international units (IU) has proved, according to relevant studies, to reduce 26% of the risk of hip fracture and 23% of the risk of non vertebral fracture in older people (Bischoff-Ferrari *et al,* 2005).
Optimum serum levels of 25-hydroxyvitamin D (25OHD) should be higher than 30 ng/ml (80 nmol/l) and, usually, in order to achieve such levels, intake of oral supplements of 700 to 1.000 IU is required. However, it is important to point out that the majority of the dietary supplements in pills or blisters contain less than 400 IU vitamin D, which is an inadequate dose (National Osteoporosis Foundation, 2008).
Although vitamin D_2 (ergocalciferol) is usually considered less strong than vitamin D_3 (cholecalciferol), both vitamin D_2 and D_3 are equally effective in maintaining adequate serum levels of 25OHD when administered in doses of 1.000 IU/day (Holick *et al,* 2008).
Surprising findings show that low levels of 25OHD are relatively common in the general population, not only among the elderly (Oliveri *et al,* 2004), but also among children and adolescents (Holick, 2007; Reis *et al,* 2009; Kumar *et al,* 2009).
In a few countries of the region, adequate formulations of vitamin D_2 and D_3 have been put on the market last year. In most countries, vitamin D is available only in combined formulations with calcium or is added to multivitamins in doses of 200-1,000 IU, in pills or packs of soluble powder.

10.9.-Treatment of osteoporosis in especial situations

10.9.1- Prevention and treatment of osteoporosis in men

Drugs usually chosen for the treatment of osteoporosis in men are the bisphosphonates: alendronate, risedronate, and zoledronate. An adequate intake of calcium and vitamin D

should always be considered. Supplements should be administered when the diet is considered insufficient. In cases of severe osteoporosis with high risk of fracture, or if there is no response, if there is intolerance or contraindication to the treatment with bisphosphonates, treatment with PTH is recommended. In the countries where etidronate is available, such drug can be an alternative to situations when alendronate, risedronate or PTH cannot be administered. Calcitonin can also be administered.
Loss of bone mass associated with hypogonadism can be reversed, to a certain extent, through treatment with testosterone via the aromatization to estrogens (Ilangovan, 2009). Androgens can be used for osteoporosis in men if there is hypogonadism and if there are no contraindications (Behre *et al,* 1997). Nevertheless, if the risk of fracture is very high, some of the above mentioned bisphosphonates associated with testosterone or PTH is recommended.

10.9.2- Glucocorticosteroid-induced osteoporosis
Patients on therapy with corticosteroids should have 24-hour urine calcium measured and be started on an adequate intake of calcium and vitamin D in all cases.
In people older than 65 years of age, of both genders, and in those people who have previous fractures, treatment with bisphosphonates or other antiosteoporotic drugs is recommended, independently of T-*score* values. Likewise, in men younger than 65 years of age who will receive treatment with corticosteroids for more than three months and who have a BMD T-*score* < -1.0, the prescription of bisphosphonates is suggested (van Staa *et al,* 2002; Reid *et al,* 2009).

10.9.3- Organ transplantation
Antiresorptive drugs and calcitriol can effectively prevent bone loss after organ transplantation. Similarly to what is recommended in cases of corticosteroid-induced osteoporosis, the determination of BMD every 6-12 months should be taken into account, and acccording to its results, treatment should be administered. Intake of calcium and vitamin D supplements do not prevent people from suffering bone loss after transplantation. According to several studies, analogs of vitamin D, or IV and oral bisphosphonates (alendronate, risedronate, pamidronate, zoledronate) can be effective in preventing loss of bone after transplantation (El-Agroudy *et al,* 2005; Ebeling, 2009; Walsh *et al,* 2009).

10.10- Available effecttive antifracture treatment
Treatment of osteoporosis has proved to be efficient in the reduction of fracture risk in patients.
The most effective pharmacological therapies can reduce between 25% and 50% of the risk of vertebral fractures in patients treated for 3 years (antiresorptives) and between 60% and 70% in patients treated for 18 months (bone anabolics) (Sánchez, 2007).
On average, 40-50% of the reduction in the risk of hip fracture has been shown in primary analysis to be achieved only with alendronate, risedronate, zoledronate, and HRT (Black *et al,* 2000; Reginster *et al,* 2000; Delmas *et al,* 2006; WHI, 2002; Deeks & Perry, 2008).
The following drugs have been shown to reduce the risk of non vertebral fractures by 20-50% (in average) in primary analysis: alendronate, risedronate, zoledronate, strontium ranelate, and human recombinant parathyroid hormone (Black, 2000; Reginster *et al,* 2000; Neer *et al,* 2004; Reginster *et al,* 2005; Greenspan *et al,* 2007, Deeks & Perry, 2008). The effects of the different antiosteoporotic treatments are summarized in Table 8.

Table 8. TREATMENT OF OSTEOPOROSIS. EFFECTS ON BMD AND REDUCTION OF THE RATES OF FRACTURE (according to Schurman *et al*, 2007).
(The approximate percentage of the reduction of fractures is indicated in numbers)

Drug:	**HRT**	**RLX**	**CT**	**ALN**	**RIS**	**IBN**	**ZOL**	**Sr**	**$PTH_{(1-34)}$**
BMD Lumbar spine	?	?	?	?	?	?	?	?	?
Femur BMD	?	?	?	?	?	?	?	?	?
Bone markers	?	?	?	?	?	?	?	? ?	?
Vertebral fractures	33	50	36	47	41	50	70	65	65
Femoral fractures	27	?	?	50	40-60	?	41	36*	?
Non vertebral fractures	?	47**	?	48	27	69***	25	16	53

HRT: hormone replacement therapy. RLX: raloxifene. CT: calcitonin. ALN: alendronate. RIS: risedronate. IBN: ibandronate. $PTH_{(1-34)}$: theriparatide. Sr: strontium ranelate. ? : Increase. ? : Decrease. ? No significant variation.
(*) In patients older than 74 years of age with femoral neck *T-score* < -3.0; TROPOS study (Reginster *et al*, 2005).
(**) In patients with severe prevalent vertebral fractures; MORE study (Delmas *et al*, 2003).
(***) In patients with femoral neck *T-score* <-3.0; BONE study (Chesnut *et al*, 2004).

Women with previous fractures and low bone mass have a better response to antiresorptive treatment. Important studies on this type of medication indicate that this population of women with previous fractures can reduce around 30-50% of the risk of new fractures. This has been reported by the FDA when approving therapies for osteoporosis.

12. CONCLUSIONS

Management strategies for patients with osteoporosis consist in:

1- Identifying those patients who are at risk of suffering osteoporosis or having one or new fragility fractures.
2- Establishing the corresponding measures to achieve the reduction of the modifiable risk factors.
3- Administering pharmacological treatment and carrying out the corresponding follow-up with the adequate use of diagnostic resources.

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