1. INTRODUCTION

The *Consensus Development Conference* has defined osteoporosis as "… a skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in the risk of fractures" (1). According to the Pubmed, osteoporosis is the "Reduction of bone mass without alteration in the composition of bone, leading to fractures. Primary osteoporosis can be of two major types: postmenopausal osteoporosis and age-related or senile osteoporosis." The definition of postmenopausal osteoporosis first appeared in Pubmed in 1990; it is a "Metabolic disorder associated with fractures of the femoral neck, vertebrae, and distal forearm. It occurs commonly in women within 15-20 years after menopause, and is caused by factors associated with menopause including estrogen deficiency." A PubMed search reveals as many as 53169 hits with the term osteoporosis and 13711 hits with the term postmenopausal osteoporosis. The large number of recent publications reflects the magnitude of the problem. The aim of these recommendations is to provide evidence-based advice on the management of fragility fracture risk in women younger than 70 years through literature review and consensus of expert opinion.

2. MAGNITUDE OF THE PROBLEM

Using the World Health Organization (WHO) osteoporosis definition, which is based on bone mineral density (BMD) assessment, 30% of postmenopausal Caucasian women in the USA (i.e.; 9.4 million women) are affected. At the age of 80 years, almost two thirds of women are affected (2). Accordingly, osteoporosis is estimated to affect 200 million women worldwide, 75 million in Europe, USA and Japan alone (3, 4). For the year 2000, there were an estimated 9 million new osteoporotic fractures, of which 1.6 million were at the hip, 1.7 million were at the forearm and 1.4 million were clinical vertebral fractures. Europe and the Americas accounted for 51% of all these fractures, while most of the remainder occurred in the Western Pacific region and Southeast Asia (4). Osteoporosis affects mostly postmenopausal women: 80%, 75%, 70% and 58% of forearm, humerus, hip and spine fractures, respectively, occur in women. Overall, 61% of osteoporotic fractures occur in women, with a female-to-male ratio of 1.6 (4). Nearly 75% of hip, spine and distal forearm fractures occur among patients aged 65 years or older (4). Hip fractures are extremely serious and are responsible for substantial mortality: it has been reported that more than 20% of hip fracture patients will die during the first year after a hip fracture. Of those who will survive, almost half will lose their independence (5). Vertebral fractures are often not diagnosed and often not treated, although they are common osteoporosis fractures: a 50 year old woman has a 16% lifetime risk of experiencing a vertebral fracture and it is estimated that only about a fifth to half of them are diagnosed and treated (6). Vertebral fractures can lead to back pain, loss of height, deformity, immobility, reduced cardiac and pulmonary function and ultimately increased mortality. Once a patient has suffered from a vertebral fracture, she is at increased risk of both further vertebral and non-vertebral fractures (7). It is estimated that only a fraction of women who are at increased risk of vertebral fractures benefit from sufficient information and preventive measures.

3. SEQUELAE AND RISKS INVOLVED IN FRACTURES

Fragility fractures, the consequence of osteoporosis, are as stated above responsible for excess mortality, morbidity, chronic pain, admission to institutions and economic costs. Since patients with osteoporosis usually have no symptoms before fracture, early diagnosis and treatment of the disease are of great importance to the quality of life of these patients. Thus, increased knowledge about how to prevent and to treat osteoporosis is critical in order to change care practice (8).

3.1. Mortality

The influence of osteoporotic fractures on survival varies with the type of fracture. Following a fragility fracture, the excess mortality appears to increase progressively after diagnosis of the fracture. It has been estimated that 8% of men and 3% of women over 50 years of age die while hospitalized for their hip fracture (9) .While this may represent complications of the fracture, such as infection and thromboembolism and subsequent surgery for hip fractures, it is likely to reflect coexisting co-morbidity in individuals sustaining a vertebral fracture (9). The four main predictors for higher mortality appear to be male sex, increasing age, coexisting illness, and poor pre-fracture functional status.

These data have led to public health measures such as the addition by the World Health Organization of fracture prevention to the list of public health priorities. Interestingly, it is now hypothesized that optimal osteoporosis management may affect the risk of death (10).

3.2. Morbidity

Some have tried to weigh osteoporotic fractures according to their morbidity in relation to hip fractures to try and obtain a definition of the true burden of osteoporotic fracture (11). To obtain the true morbidity of hip fractures, the incidence of hip fractures should be multiplied by a specific *factor*. Thus for women between the ages of 50 and 54 years, the disability caused is 6.07 times that accounted for by fracture alone, therefore, the incidence of hip fractures should be multiplied by a factor of 6.07 (11). Hip fracture invariably requires hospitalization, where patients are prone to developing acute complications such as pressure sores, bronchopneumonia, and urinary tract infections. The degree of functional recovery and the length of stay after this injury are age-dependent. Premorbid status and malnutrition are also strong predictors of outcome.

Vertebral fractures provide a significant warning of subsequent osteoporotic fracture, as they tend to occur more frequently and earlier than other osteoporosis-related fractures. The overall risk of further vertebral fracture is 20% in the year following incident fracture, with relative risk being 4 times greater in those with severe rather than mild fractures and 3 times greater in those with multiple (>3) rather than single vertebral fractures (12).This process,

referred to as the vertebral fracture *cascade*, is likely to be multifactorial in origin, related in part to poor bone quality, disordered spine biomechanics, and neuromuscular dysfunction (13).

Fractures other than those at the spine and hip make an important contribution to the overall morbidity associated with osteoporosis. These include fractures of the wrist, humerus, pelvis, ribs, clavicle, and lower leg.

3.3. Sequelae

Overall, after any type of fracture, there is a chance of experiencing functional decline. The impact of a single vertebral fracture can often be low, but multiple fractures have several consequences: a progressive loss of height and kyphosis and the corresponding alterations in body shape including protuberance of the abdomen and loss of normal body contours, and severe back pain in both the acute and chronic stages. Due to the anterior compression of the vertebral body, the centre of gravity moves forward, thereby creating a large bending moment. This results in muscle fatigue and pain, gait abnormalities, decrease in gait velocity, reduced pulmonary function, and consequently an increased risk of falls and additional fractures. Furthermore, the associated decrease in activity leads to a worsening of the osteoporosis (3). These changes commonly are associated with loss of self-confidence and self-esteem, difficulty with daily activities, and increased social isolation (11). The clinical impact of vertebral fractures is thus substantial, although often underestimated.

Wrist fractures cause considerable inconvenience, usually requiring 4 to 6 weeks in plaster, and long-term adverse sequels occur in up to one third of patients. These include pain, sympathetic algodystrophy, deformity, and functional impairment. Only a minority requires hospitalization.

In a recent study, hip fracture also had a significant effect on mobility.1 year after hip fracture, 40% were unable to walk independently, 60% required assistance with at least one essential activity of daily living (e.g., dressing, bathing), and 80% were unable to perform at least one instrumental activity of daily living (e.g., driving, shopping) (14).

3.4. Disabilities incurred by the disease

In Europe, the disability due to osteoporosis is greater than that caused by cancers (with the exception of lung cancer) and is comparable to that from the combined effects of a variety of chronic non-communicable diseases, such as rheumatoid arthritis, asthma, and high blood pressure–related heart disease (14). Osteoporotic fractures account for 0.83% of the global burden of non-communicable disease worldwide, and 1.75% in Europe where fragility fractures account for more *disability-adjusted life years* (DALYs) than many other chronic, non-communicable diseases (14).

3.5. Costs to society

The rapid increase in health-care expenditure in all countries has increased interest in the economic impact of individual diseases or disease categories. The economic burden of osteoporosis fracture is thought to be substantial for both the person with the disease and the health services.

The economic costs of osteoporotic fractures include both the direct costs of hospitalization and aftercare, as well as the indirect costs attributable to the impact of fracture on daily life activities including working days. Together, these costs impose a huge financial burden on health care and social services. In the United States, the direct costs of osteoporotic fractures are estimated at around $18 billion annually; while in Europe the corresponding figure is around €36 billion (15) In the absence of a significant treatment impact on the global burden of fractures, these costs are set to increase two-fold or more by 2050.

Falls are a relevant economic burden to society. Efforts should be directed to economic evaluations of fall-prevention programmes aiming at reducing fall-related fractures, which contribute substantially to fall-related costs (16).

Poor persistence to treatment of osteoporosis should consequently be acknowledged as an important and costly health problem, and be taken into account when evaluating osteoporosis interventions (17). Prevention of fractures through early risk assessment and identification of those in need of treatment is the key to reducing the costs to national health care system throughout Europe.

4. ROLE OF ESTROGEN ON BONE BIOLOGY

Although the complete bone remodeling process and its control remain unknown, sufficient information exists to reach the conclusion that estrogens play an important role in skeletal homeostasis (18,19). The loss of ovarian sex steroid secretion produces a net loss of bone tissue. In women with sex steroid deficiency, the administration of these hormones reverses many of the effects of loss of ovarian function. Bone cells have estrogen receptors (20,21). Inhibiting bone resorption is the most important action estrogens carry out on bone tissue. This action indirectly regulates the production of cytokines and osteoblast growth factors. Since there are estrogen receptors in osteoclasts, it is logical to think that there is also a direct action. Bone resorption inhibition by estrogens is a probable result of the induction of apoptosis in osteoclasts (22), their action most likely being caused by the increase in TGF-β (23).

Estrogens have been shown to increase osteoblast proliferation and the different gene expressions that codify enzymes, bone matrix proteins, transcription factors, hormone receptors, growth factors and cytokines. Nevertheless, the results have varied depending on the culture models (24). Estrogens have also exhibited the capacity to inhibit TRAP expression or certain pathways of the RANK-JNK signal (25).

At present, it is thought that estrogens act through different pathways. There is, on the one hand, an anti-apoptotic effect of estradiol on osteoblasts and osteocytes due to a rapid non-genomic action (26). On the other hand, it is possible to synthesize a ligand, called ESTREN that would act exclusively through this pathway. Theoretically, it could have the same effect on bone as the estrogens, but without their genomic consequences. This model has given a name to a new class of pharmacological agents called ANGELS (Activators of NonGenotropoic Estrogen-Like Signaling) (27)

It is possible to conclude that the steroid hormones participate in a complex system of actions on bone with a clear influence on bone regulation. They form part of the RANK/RANKL/OSTEOPROTEGERIN mechanism, whose predominant action is that of bone resorption through genomic and nongenomic actions.

5. RISK FACTORS FOR THE DEVELOPMENT OF OSTEOPOROSIS

Whilst aging and menopause are the most important risk factors for the development of osteoporosis, there are many other risk factors that contribute to the disease. These factors include concurrent and previous medical disorders, inheritable genetic factors as identified by family history, drugs, lifestyle factors, immobilization, and specific conditions such as juvenile or pregnancy-related osteoporosis.

5.1. Diseases

The presence or past history of a number of diseases is associated with an increased incidence of osteoporosis. The diseases include endocrine, connective tissue and reticulo-endothelial disorders, metastatic carcinoma and multiple myeloma, respiratory and liver diseases, anorexia nervosa, mastocytosis and thalassaemia (28).

5.1.1. Endocrine disorders

Loss of ovarian function is a major risk factor for women and is covered elsewhere, but hypogonadism *per se* is associated with bone loss in both genders, primarily through increased bone resorption. Other endocrine disorders, too, are risk factors for bone loss. Prolactinoma will often result in hypogonadism. Hyperparathyroidism and hyperthyroidism both result in increased bone turnover, whilst hypercortisolism, as in Cushing's syndrome, may both increase bone resorption and reduce bone formation. Diabetes mellitus type I is also associated with an increased risk for osteoporosis.

5.1.2. Connective tissue disorders

These diseases may adversely affect bone and collagen metabolism and include rheumatoid arthritis, osteogenesis imperfecta, Marfan's syndrome and Ehlers-Danlos syndrome. Inflammatory disorders such as rheumatoid arthritis are associated with increased production of inflammatory cytokines which may have direct skeletal effects, whereas the other conditions are associated with

abnormal collagen which results in high bone turnover through attempts to remove and remodel bone.

5.1.3. Reticulo-endothelial disorders, metastatic carcinoma and multiple myeloma

These include the leukaemias and lymphomas, both Hodgkins, as well as non-Hodgkins. They are associated with an increased production of various cytokines which not only act on bone cells, but also cause bone loss through direct invasion of the skeleton.

5.1.4. Respiratory and liver disorders

A number of these disorders are associated with an increased incidence of osteoporosis. They include cystic fibrosis, where vitamin D deficiency is often a prominent feature, chronic obstructive pulmonary disease; diffuse parenchymal lung disease and primary pulmonary hypertension. Primary biliary cirrhosis is the main liver disease associated with osteoporosis.

5.1.5. Other disorders

Anorexia nervosa is frequently associated with osteoporosis, due to malnutrition and to the commonly associated hypogonadism. Mastocytosis is also associated, probably through increased histamine release. Thalassaemia and thalassaemia trait are both linked to an increased incidence of osteoporosis.

5.2. Family history

A family history of osteoporotic fractures may be associated with increased risk (29). Peak bone mass is largely genetically determined, and hence there may be inheritance of a low peak bone mass which will hasten the development of osteoporosis later in life. It must always be remembered that many collagen disorders are also inherited, and a mild collagen defect, often undetectable by standard screening, may be the link with a family history of fractures. Ethnicity is important, people of Afro-Caribbean ethnic origin have greater bone mass, and hence less osteoporosis, than do the other ethnic and racial groups. This is probably the result of a genetically-determined higher peak bone mass. The genetic basis of osteoporosis is extremely complicated and clearly involves both multiple genes, as well as gene-environment interactions. Whilst some genetic abnormalities have been identified, particularly mutations involving vitamin D and sex steroid receptors, many are still to be uncovered. It seems most unlikely that genetic screening for osteoporosis risk will ever become realistic or viable, despite the enormous research funds that have been lavished on this field.

5.3. Drugs

5.3.1. Corticosteroids

Many drugs are associated with bone loss, and thus increase the risk of osteoporosis and fractures (28). By far, the most common and important are the corticosteroids when given orally. They are most usually given for respiratory disorders, around 40% of users, whereas those using them for rheumatologic disorders comprise around 6%. The commonest use is in the 70 - 79 year age group,

a group which will already be at increased osteoporosis risk because of age-related bone loss. The effect of corticosteroids on bone is both duration-dependent and dose-dependent, with doses above 7.5 mg daily being associated with an appreciable increased risk, although there is a huge inter-individual variation in this dose response. Fortunately, the commonest drug and dose is prednisolone 2.5 - 7.5 mg daily, with a duration usually of <6 months (30).

Corticosteroids have an adverse effect on bone through a number of mechanisms. They cause an increase in osteoclastic bone resorption whilst also causing a decrease in osteoblastic bone formation. They impair gastro-intestinal calcium transport. They cause collagen thinning, which affects not only bone and skin but also inter-vertebral discs. This may be important as the inter-vertebral discs may act as shock-absorbers, and their loss in height will increase vertebral fracture occurrence (31). The effects of corticosteroids on collagen may explain why corticosteroid users have an increased fracture risk compared with non-users at any given level of bone mineral density.

5.3.2. Other drugs

Anticonvulsants are associated with an increased fracture risk, mainly through their adverse effects on vitamin D metabolism leading to osteomalacia. Excess medication with thyroxine leads to bone loss, as does the “medical menopause” induced by GnRH agonists. The deleterious effects of aromatase inhibitors are discussed elsewhere. Various cytotoxic agents can be toxic to bone cells and result in impaired bone formation, whilst heparin increases bone resorption. Rosiglitazone, a thiazolidinedione, increases osteoporosis risk, as do the antidepressant selective serotonin and noradrenaline reuptake inhibitors such as venlafaxine, and the proton pump inhibitors (28).

5.4. Lifestyle factors

A diet inadequate in calcium may result in underachievement of peak bone mass. Nevertheless, the minimum calcium requirement is still not clearly established and may well vary hugely between individuals. Caffeinated and carbonated drinks have been associated with bone loss in some, but not all, studies (32). Low body mass index is a well-established risk factor for fractures (33) whereas overweight or obesity may be somewhat protective. Lack of physical activity may have a slightly negative effect on bone density, although differences between active and non-active people are small. Of more importance is immobilisation which can lead to fairly rapid loss of bone through in increase in resorption together with a decrease in bone formation resulting from the lack of physical stress to the skeleton. Weightlessness, as experienced in space travel, has a similar effect, and this may become a practical problem that will need to be addressed by future generations. Paradoxically, excessive exercise may also result in bone loss due to hypothalamic-induced secondary hypogonadism. Cigarette smoking has a detrimental effect on virtually all tissues, and may be associated with an increased fracture risk. Alcohol may also have a toxic effect on bone cells when consumed at high levels, but interestingly those who abstain totally from alcohol have an increased osteoporosis risk compared to moderate drinkers (34).

5.5. Other causes

There are two osteoporotic conditions worthy of mention. Juvenile osteoporosis is a rare disorder whose cause is unknown (35). It usually reverses at puberty and this may help distinguish it from the other cause of childhood osteoporosis, osteogenesis imperfecta. Pregnancy-related osteoporosis is another uncommon condition that usually presents fractures towards the end of, or soon after, a pregnancy (36). Most cases seem to be associated with a low bone turnover and may be a failure of osteoblasts to adapt or respond to the changes in calcium regulating hormones that occur during pregnancy. Such patients tend to recover with time, and do not seem to recur with subsequent pregnancies. Rarely, there may be evidence of increased bone resorption, perhaps resulting from an imbalance between calcium regulating hormones in pregnancy, and these cases seem to suffer recurrence in subsequent pregnancies.

Risk factors for osteoporosis should be identifiable from a patient's history and assessment. They can be used as part of the screening to identify those at increased risk so as to introduce preventive treatment. They can also be used to identify causes of secondary osteoporosis in patients who present atypical features such as severe osteoporosis, young age or rapid bone loss.

6. ESTROGEN LEVELS, BREAST CANCER TREATMENT AND BONE HEALTH

The majority of breast cancers tend to be estrogen- and/or progesterone-receptor–positive, and grow in response to hormonal signals. Adjuvant endocrine therapy, which deprives breast cancer cells of these signals, is the mainstay of treatment for early stage, hormone-responsive breast cancer (37). Recent years have seen the establishment of aromatase inhibitors (AIs; which effectively block the biosynthesis of estradiol in peripheral tissues) as the treatment of choice for postmenopausal women with early stage breast cancer, (37) a development which has improved disease outcomes compared with tamoxifen (the previous standard of care). Adjuvant endocrine therapies, however, can indirectly interfere with skeletal homeostasis and substantially increase the rates of BMD loss, either through their effects on gonadal steroid hormone production (e.g., ovarian suppression using goserelin, or chemotherapy-induced amenorrhea) or by inhibiting peripheral estrogen synthesis (e.g., AI therapy) (38). Indeed, AIs suppress circulating estrogen levels beyond those observed after natural menopause, and rates of AI-associated bone loss (AIBL) exceed the rate of BMD loss after menopause by more than 2-fold (39). Not surprisingly, increased rates of fracture have been reported in clinical trials comparing AIs with placebo or tamoxifen in women with early breast cancer (40).

6.1. Assessing the need for bone-directed therapy in women with breast cancer

In recent years, an expanded understanding of fracture risk factors in addition to BMD has resulted in an easy-to-use online tool for assessing fracture risk in postmenopausal women with or without BMD data, adapted for different countries. FRAX, however, is not designed to assess fracture risk in women with breast cancer, and might underestimate the effect of adjuvant endocrine therapy for

breast cancer—a long-term intervention with the potential to influence bone microarchitecture, and therefore fracture risk, even after BMD recovers. As a result, the authors and others have developed algorithms to specifically address the need for bone-directed therapy in postmenopausal women with breast cancer (40,41).

6.2. Clinical decision-making for the prevention and treatment of AIBL

An algorithm including multiple risk factors for bone loss and fracture has been suggested to improve management of patients initiating AI therapy for early breast cancer (Figure 1) (40). Moderate exercise (resistance and weight-bearing exercise) and calcium and vitamin D supplements are recommended for all patients beginning AI therapy. For postmenopausal women receiving AI therapy, at least 800 (and up to 2,000) IU vitamin D every day is recommended (40). Patients initiating AI therapy with a T-score ≥ –2.0 and no other fracture risk factors should have their BMD and risk status reassessed after 1 to 2 years of AI therapy. A decrease in BMD of 10% or more within 1 year (or 4% to 5% over the same time in patients who were osteopenic at baseline) should trigger investigation for secondary causes of bone loss (e.g., vitamin D deficiency) and possible initiation of antiresorptive therapy (40). Proactive treatment with an antiresorptive agent is recommended for all patients initiating or receiving AI therapy with any 2 of the following risk factors: T-score < –1.5, age > 65 years, low body mass index (BMI < 20 kg/m^2), family history of hip fracture, personal history of fragility fracture after age 50, oral corticosteroid use of > 6 months, and current or history of smoking. All patients initiating or receiving AI therapy with a T-score < –2.0 should also receive antiresorptive therapy. Indeed, established osteoporosis is not a contraindication for AI therapy provided that antiresorptive therapy is promptly initiated (40).

Assessment of compliance and periodic (annual or biennial) monitoring of BMD is essential in all patients receiving oral antiresorptive therapy. Convenient, noninvasive, and objective assessment of compliance with therapy may be achieved through measurement of bone resorption marker levels. Poor compliance or unsatisfactory BMD improvements after 1 to 2 years should trigger a switch to an intravenous (IV) bisphosphonate. If the antiresorptive agent is administered by healthcare providers, BMD monitoring during therapy should be performed on an individualized basis.

Although no antiresorptive agents are specifically approved for the treatment of AIBL, large randomized clinical trials suggest that IV and oral bisphosphonates, and denosumab, can effectively prevent AIBL (40). These antiresorptive agents were well tolerated in clinical trials and many of them are already widely used in the osteoporosis setting. Therefore, selection of the appropriate antiresorptive should be based on the weight of clinical evidence and on individual requirements.

In summary, depletion of residual estrogen in women receiving adjuvant therapies for breast cancer can negatively influence bone health. Indeed, AIBL is a well-recognized concern during long-term adjuvant therapy for breast cancer. Patient management algorithms including a broad range

of fracture risk factors are available to guide clinical decisions for the prevention and treatment of AIBL, as are a variety of antiresorptive agents with promising activity in this setting. A decrease in BMD because of premature menopause or cancer treatment-induced amenorrhea poses an even larger problem.

7. FRACTURE RISK FACTORS

There is general agreement on the usefulness of bone density measurement to assess the risk of fracture (42). Now it is also possible to use algorithms that can calculate the risk of fracture at 10 years based on the main osteoporosis risk factors. This methodology, developed by Kanis et al, WHO experts, has been patented under the name of FRAX™ and can be accessed at a free Internet site (www.shef.ac.uk / FRAX) (43).

7.1. FRAX™

FRAX is a fracture risk assessment tool that combines clinical risk factors with or without BMD and is useful in the following areas:
A) Health sector: primary care for detecting high-risk groups and optimizing the available diagnostic and treatment resources
B) Clinical practice: as an aid in making treatment decisions.
FRAX, which is not a diagnostic tool, calculates the 10 year probability for any of the 4 osteoporotic fractures (Major Osteoporotic Fractures). These include the following locations of fractures: hip, vertebrae, wrist, and proximal humerus.

FRAX recognizes certain risk factors, but not others (Table 1). The program uses risk factors calculated globally, but also employs country-specific fracture and mortality rates. For countries that do not yet have country-specific FRAX data, the recommendation is to use FRAX with epidemiological data from the country that is most similar.
Recent studies using FRAX have shown a reasonable agreement between the expected and observed rates of fractures e.g., the evaluation of the Framingham cohorts (44).

Among the limitations that have been pointed out (45) there are some risk factors for fractures that are not included in the model: vitamin D deficiency, falls, physical activity, markers of remodelling, previous treatment for osteoporosis, drugs such as anticonvulsants, aromatase inhibitors, and androgen deprivation, among others. The FRAX calculator, when answering "yes" to Secondary Osteoporosis, does not change the risk of fracture when entering the value of BMD. The FRAX calculation model does not allow combinations of secondary risk factors, e.g., a patient with hyperthyroidism and diabetes mellitus type I has the same risk as if she had only one of these diseases. Nor does it consider a low lumbar spine BMD (only accepting the femoral neck). Regarding vertebral fractures, it does not consider the number and severity of them, nor the high risk posed by a history of previous vertebral fractures. FRAX does not consider the dose and

duration of exposure to corticosteroids, tobacco and alcohol. Regarding the patient's weight, a low BMI, which is an established and recognized risk factor for fractures, does not contribute to the risk if the BMD is known.
It is recommended not to use FRAX in patients already receiving treatment.

The FRAX system is a useful tool for detecting people at high risk for fractures. It can also help decide who to treat when the values of absolute fracture risk in the population are added to the system.

The assessment of fracture risk, which changes qualitatively and quantitatively the population suitable for intervention, may be used in primary care by general practitioners and by specialists in the office, with or without BMD as a screening method, either to establish treatment or to use simply as a reference resource.

8. **DIAGNOSIS**

The medical history of a patient is an important tool in the diagnosis and evaluation of osteoporosis in a given patient. Other complementary methods for diagnosing osteoporosis include the following: bone densitometry (DXA, ultrasound), laboratory (biochemical markers and bone turnover markers) and x-rays.

8.1. Bone Mineral Density (BMD) by DXA

Today, physicians treating individual patients for osteopenia/osteoporosis need to evaluate fracture risk before the occurrence of a fracture. The definition of bone strength underlines the role of bone mineral density and bone quality (42). The diagnosis of osteoporosis relies on the quantitative assessment of bone mineral density (BMD), which is a major determinant of bone strength. BMD, measured with dual x-ray absorptiometry (DXA), is expressed in absolute terms as g/cm^2, and it is an areal density. The BMD value of a patient can also be related to a reference value for young normal adults of the same sex by using the T-score. The T-score is reported as the number of standard deviations that a patient's bone mineral density value is above or below the reference value for a healthy, young adult. Various techniques are used to assess BMD, but the most widely used and accepted in clinical practice is DXA, usually performed at the proximal femur and lumbar spine (central DXA) (46). A BMD test with DXA scan is considered the best tool for an early evaluation of fracture risk. A real BMD may explain about two-thirds of the variance of bone strength, as showed in experimental setting on isolated bones (vertebral body or proximal femur) (47). BMD measurement is associated approximately with a 1.5- to 2-fold increase in fracture risk for each standard deviation (expressed as T-score) decrease in BMD (48). Thus, a low BMD is a potent predictor of increased fracture risk. Results of BMD measurements by DXA are used to define four categories of diagnostic thresholds (Table 2) (49).

According to the International Society of Clinical Densitometry (ISCD) Position Development Conference (50), indications for BMD testing in women are listed in Table 3.

As for BMD testing in monitoring anti-osteoporotic treatment, whether the long-term anti-fracture efficacy of various drugs is dependent on the extent to which the therapies increase BMD remains controversial. At present, some analyses of different drugs indicate that larger changes in BMD and other surrogate measures of fracture risk are associated with greater antifracture efficacy, and that most of the antifracture effectiveness is explained by the changes in BMD values, especially in reducing non-vertebral fracture with alendronate (51). Other studies, however, suggest that changes in BMD measurements are not directly related to the degree of reduction in fracture risk and that drug-associated increases in BMD account for only a minor proportion of the observed anti-fracture efficacy, as in a decreasing risk for vertebral fracture for raloxifene and for non-vertebral fracture for risedronate (52,53). In other words, the greater the increase in BMD, does not always translate to a proportionately greater decrease in fracture risk. Generally, osteopenia (BMD T-score between -1.0 and -2.5, termed also “low bone mass” or “low bone density”) is not considered a disease condition (42), but it is well known that the majority of fractures occur in this category (46-48). Thus, osteopenia should be considered a condition that increases fracture risk. For this reason, it may be treated when associated with clinical risk factors and with an increase of fracture risk, as indicated in the FRAX tool (49).

In conclusion, BMD results from hip and spine DXA examinations can be interpreted using the World Health Organization T-score definition of osteoporosis. Moreover, these results have a proven ability to predict fracture risk, proven effectiveness at targeting antifracture therapies and, to some extent, the ability to monitor response to treatment. Intervals between BMD testing should be determined according to each patient’s clinical status, typically one year after initiation or change of therapy is appropriate, with longer intervals once a therapeutic effect is established (51).

8.2. Bone Mineral Density (BMD) by Quantitative Ultrasound

The only validated skeletal site for the clinical use of Quantitative Ultrasound (QUS) in osteoporosis management is the heel (52). Heel QUS, in conjunction with clinical risk factors, can be used to identify a population at very low fracture probability in which no further diagnostic evaluation may be necessary (screening procedure). Validated heel QUS devices predict fragility fracture in postmenopausal women (hip, vertebral, and global fracture risk), independent of central DXA BMD. Discordant results between heel QUS and central DXA are not infrequent and are not necessarily an indication of methodological error (52).

DXA measurements at the spine and femur are preferred for making therapeutic decisions and should be used if possible. However, if central DXA cannot be done, pharmacologic treatment can

be initiated if the fracture probability, as assessed by heel QUS using device specific thresholds and in conjunction with clinical risk factors, is sufficiently high (52).

Data suggest that measurements of broadband ultrasound attenuation (BUA) or speed of sound (SoS) at the heel are associated with a 1.5- to 2-fold increase in risk for each standard deviation decrease in BMD (54).

Comparative studies indicate that these gradients of risk are very similar to those for peripheral assessment of BMD at appendicular sites by DXA to predict osteoporotic fractures (49). The International Society of Clinical Densitometry does not recommend the use of ultrasound in monitoring the skeletal effects of treatments for osteoporosis (52).

8.3. X-ray

Radiography is useful for suspected osteoporosis, and imperative for the possibility of fracture at any location. The detection of low bone mass by radiography is unreliable because it is influenced by several factors, such as X-ray exposure, quality of the film, amount of soft tissue, etc. It is estimated that more than 10-40% loss of bone is needed, depending on the sensitivity of the equipment used, to be detected in a lateral spine X-ray.

X-rays of thoracic and lumbar spine in anteroposterior and lateral positions are recommended for their usefulness in diagnosing vertebral collapse, spondylosis, aortic atheroma or other diseases

*8.4. **Biochemical markers***

The general and specific laboratory testing related to mineral metabolism should be requested according to the background and needs of the patient under study. It is an important aid for the differential diagnosis between various systemic diseases that can affect the bone. The specific parameters of bone metabolism include the following determinations: calcium, phosphate, magnesium, creatinine, tubular reabsorption of phosphate, and urinary levels of calcium and magnesium. The measurements of PTH and 25-hydroxyvitamin D, as well as the bone turnover markers, may be requested according to the particular patient.

8.4.1. Bone Turnover Markers (BTMs)

Over the past two decades detection of subtle change in bone turnover in patients with metabolic bone disease has been enhanced by the use of biochemical markers of bone remodelling (BTMs). Biochemical monitoring of bone depends on measurement of BTMs in serum and/or urine. They are sensitive, easy to perform and relatively inexpensive. BTMs are classified as markers of bone resorption or formation. Resorption and formation are a 'coupled' process, and therefore any marker can be used to determine the overall rate of bone turnover. Markers of resorption are

products of collagen degradation and markers of formation are products of collagen formation (Table 4).

BTMs are not currently used in the diagnosis of osteoporosis but can be useful in assessing response to treatment. They are the marker of choice in the first 1-2 years following the commencement of treatment with anti-resorptive agents as DEXA does not reflect early response treatment. BTMs may be increasingly important in identifying the person at increased risk of fracture in whom bone density alone is not specific (55). Combining BTMs and BMD is likely to aid fracture risk assessment in these cases. BTMs could have a possible future role in tailoring treatment to the needs of the patient.

Would patients with increased remodelling do better on anti-resorptive treatment, should a patient with suppressed bone remodelling do better on an anabolic agent i.e., PTH/ strontium ranelate/? Undoubtedly, further clinical trials are needed to support this approach. However evidence currently does not seem to support the case (56*).* Some studies suggest that those with raised BTM at baseline do far better on anti-resorptive therapies (57)*.*

Since the use of BTMs is not currently recommended by osteoporosis guidelines for routine clinical use, they are largely relegated to specialist practices (table 5). Additionally, interpreting results in individual patients is complicated, reflecting the complexities of bone metabolism. There are also difficulties with inter-laboratory variation in results (58)*.* This is because there is considerable variation in assays as a result of controllable and uncontrollable sources (table 6).

8.5. Threshold for diagnosis

Osteoporosis is currently diagnosed upon the measurement of bone density by DEXA. WHO has defined the diagnosis of osteoporosis as a T score ≥2.5. Patients with a low bone density have an increased risk of fracture. This, however, fails to identify the features which can put an individual at risk for fracture, since bone fragility depends on morphology, architecture and remodelling.

N.B. Studies show that half of patients with incident hip fracture have a base line BMD above the diagnostic threshold of osteoporosis. Clearly there is a need for better identification of patients at risk for fracture (59,60).

The Ofely study indicates that the rate of bone loss in younger, healthy post-menopausal women is significantly associated with fracture risk, independent of other predictors, i.e., history of fracture and BMD (60). The Epidos study, however, showed no significant relationship between serum BTMs and risk of hip fracture in a 2 year follow up of older women (61).

There is a significant positive association between increased urinary and serum C telopeptides of type I collagen CTX or urinary deoxypyridinoline (DPD) and fracture. Values above the normal premenopausal range were consistently associated with a two-fold higher risk of hip/vertebral/other fracture over a follow up period of 1.8 – 5 years. In patients with low BMD, the

presence of raised BTMs suggests an increased risk for fracture compared to normal BMD or low BTMs (62-63)

There is evidence that BTMs predict bone loss independently of BMD. Those with raised BTM lose bone faster than those with normal/low BTM (62-64). Markers of resorption seem to predict future bone loss more than do markers of formation, something more evident in older women (65).

It is possible that using BTM together with other risk factors for osteoporosis may define fracture risk and be a useful tool as a 'threshold to diagnosis'. In women with low bone mass, BTMs are independent predictors of risk. Vertebral fracture is related directly with BTM and negatively with BMD. Relative fracture risk (defined by low BMD or raised BTM) is similar, and the risk is accentuated if both are present.

Should raised BTM and low BMD strongly influence the clinical decision in favour of commencing treatment in order to prevent fracture? A recent publication by Chopin et al (66) concluded that "the measurement of BTM, together with the assessment of other risk factors including a low BMD, will improve the prediction of risk fracture, but there is a lack of practical guidelines."

"The International Osteoporosis Foundation IOF and International Federation of Clinical Chemistry and Laboratory Medicine IFCC (2011) Working Group on Bone Marker Standards (WG-BMS) have evaluated the clinical potential use of BTMs in the prediction of fracture risk and for monitoring treatment (67). Research evidence suggests that BTMs may provide information on fracture risk independently from BMD, so that fracture risk prediction might be enhanced by their inclusion in assessment algorithms. The potential use of BTMs to predict the response to treatments for osteoporosis in the individual patient is also of great interest. Treatment induced changes in specific markers account for a substantial proportion of fracture risk reduction. However, there is still a need for stronger evidence on which to base practice in both situations. IOF/ICC recommends one bone formation marker (serum procollagen type I N propeptide, s-PINP) and one bone resorption marker (serum C-terminal cross-linking telopeptide of type I collagen, s-CTX) to be used as reference markers and measured by standardised assays in observational and intervention studies in order to enlarge the international experience of the application of markers to clinical medicine and to help resolve uncertainties over their clinical use" (67).

9. **OSTEOPOROSIS AND FRACTURE PREVENTION**

General measures have demonstrated their efficacy in the prevention of osteoporosis and fractures. These include healthy diet habits and lifestyle, including the following; milk and other nutrients such as protein, vitamins and minerals, physical activity, sun exposure, smoking cessation, fall prevention and the use of hip protectors. One must keep in mind that osteoporosis is a progressive disease. Therefore one can both intervene, as well as try prevention.

9.1. Dairy products

The benefits of a diet with adequate calcium content have been well established. Dairy products are considered the most important dietary sources of calcium.
From age 50, the diet should provide about 1,200 mg calcium/day. This is provided mainly by dairy products, and preferably those fortified with calcium should be chosen because they contain between 40 and 100% more calcium than non-fortified products (68). In the case of intolerance to dairy products, lactose-free milk or calcium supplements can be used.

9.2. Other nutrients

It is important to ensure a good protein intake (1 g protein/kg/day) and other nutrients (vitamins and minerals). It is advisable to consume adequate amounts of foods rich in protein such as lean red meat, poultry, fish and eggs (69).

9.3. Physical Activity

Exercise, particularly strength training and weight-bearing, provides an important stimulus to maintaining and improving musculoskeletal health. Exercise has been shown to reduce the risk of osteoporosis and 25% of falls (70).
The main components recommended in a program of exercise for bone health are as follows: impact exercise such as jogging (if there is no risk of fragility fractures), brisk walking, stair climbing, strength training with weights and coordination and balance stimulation such as the practice of tango, salsa and other dances (71).

9.4. Sun Exposure

Vitamin D, which is necessary not just for bone health, is found in few foods. Its main source is the skin by exposure to ultraviolet radiation. During spring or summer, 15 to 20 minutes of exposure may be needed, with longer periods necessary during autumn and winter. Patients should exercise caution during the hours when sun exposure may be most harmful, especially in summer.
In many cases it is necessary to supplement with vitamin D, especially in people over 60 years, or those with minimal exposure to the sun. The optimal serum 25-hydroxyvitamin D level should be greater than 30 ng/ml (72).

9.5. Smoking cessation

Avoiding cigarette smoking is important since smoking has recognized detrimental effects on bone. That notwithstanding, a few years after smoking cessation, the risks are reduced (73).

9.6. Preventing Falls

Preventing the risk of falling should be a goal in any treatment to prevent osteoporotic fractures. It should be noted that the tendency to fall increases with age.
Non-vertebral fractures are usually associated with falls from preventable causes, which include the following: A) medications such as sedatives, antihypertensives, and hypoglycaemic drugs; B) visual disturbances; C) obstacles in the road or at home such as irregularities in the floor, rugs, loose

wires, lack of holding bars in bathrooms and handrails on stairways, poor lighting, etc., ; and D) pets (74).

9.7. Hip protectors

Hip protectors to reduce hip fracture risk consist of devices that are placed externally on the hip area by attachment to or insertion into the underwear. In case of a fall they absorb the impact and reduce the risk of proximal femur fractures. They consist of plastic coated pads that are placed in pockets of specially designed underwear. They should be used all day, especially for those elderly people at high risk of falls and hip fractures. These guards have demonstrated effectiveness in reducing fracture risk (75).

9.8. Calcium and vitamin D supplementation

Evidence supports the supplementation of calcium and vitamin D in the preventive treatment of osteoporosis in women aged 50 years or greater (76). Their efficacy was also suggested in the Women's Health Initiative (WHI) study when compared to placebo or to no treatment (77). Jackson et al. reported in the New England Journal of Medicine (78) a 29% reduction in hip fractures after 8 years in women compliant with the intake of supplemental calcium and vitamin D. Unfortunately, the average intake of calcium in the south of Europe is 989 + 433 mg/day and 89.6% of women receive an intake of less than 1,500 mg / day (79). Moreover, the blood levels of vitamin D decrease with age (80), with 63.2% of treated and 76.4% of non-treated women experiencing vitamin D deficiency. In addition, the effectiveness of anti-osteoporotic drugs in clinical trials has always been evaluated by adding calcium and, in most cases, vitamin D. In summary, it is necessary to ensure a sufficient supply of calcium and vitamin D for both the prevention, as well as the treatment, of osteoporosis.

10. **OSTEOPOROSIS TREATMENT**

Treatment of osteoporosis should be aimed primarily at reducing the incidence of fractures. Therefore, it is important to note that the risk factors strongly associated with an increased risk for fracture incidence are these: the patient's age, personal history of fracture (vertebral or non-vertebral), low BMD, low BMI, alcohol consumption, cigarette smoking, use of glucocorticoids and history of hip fracture in a first degree relative (43).

Regarding the results of the BMD, there is no evidence of an absolute value of Z score or BMD T-score indicating the need for treatment in every individual situation since the data guiding drug treatment decisions are derived mainly from population studies. The information provided by the BMD should be taken into account together with that related to other risk factors as well as the effectiveness, safety, risks, side effects and costs of the treatment provided.

In order to decide on a specific treatment for osteoporosis, the risks and benefits for the patient should be determined first. Data derived from large clinical trials are useful for consulting facts or general situations, but they are not, by themselves, a reason or indication for treatment (81).

Patients who should be advised to start treatment for osteoporosis are listed in table 7 (82).
The decision to start treatment and the selection of the type of treatment should be based on the need to reduce fracture risk. These decisions should take into account the characteristics of each specific case: age, sex, renal function, drug allergies, co-morbidities, previous treatments, contraindications, costs, and so on. It is also recommended to take into account the generally low adherence to osteoporosis therapy, and to take the appropriate measures (83).

According to their mechanism of action, the drugs indicated in the treatment of osteoporosis are classified as follows: a) anti-resorptive (bisphosphonates, SERMs, HRT, tibolone, calcitonin, denosumab); b) dual mechanism (strontium); and c) bone-forming or anabolic (PTH).

10.1. Antiresorptives

10.1.1. HRT and Tibolone

HRT is the treatment of choice for the management of menopausal symptoms and urogenital atrophy. In addition, HRT in standard doses decreases significantly the risk of both vertebral and non-vertebral fractures. In the WHI trial, estrogen-progestin treatment reduced the incidence of vertebral fractures by 35% and of hip fractures by 33% in 16,608 women followed-up for a mean of 5.2 years (84). A similar effect was observed in the estrogen-only arm of the WHI trial in 10,739 hysterectomised women during a follow-up of 6.8 years (85). It is important to note that this effect was observed in women not at high risk for osteoporosis, in contrast with all other major trials evaluating drugs for osteoporosis, so the results are more applicable to the general postmenopausal population. Furthermore, women aged 50-70 years receiving HRT in the Million Women Study, had a 38% reduction in the incidence of all fractures during a two-year follow-up, which was apparent soon after the initiation of treatment (86).

The current standard of practice is to prescribe the lowest effective dose of estrogen. Fracture data are not available for lower doses of HRT. There are numerous clinical studies, however, indicating that low-dose, as well as ultra-low dose HRT increases BMD both in the lumbar spine and the hip and decreases serum bone markers (87).
Bearing in mind that HRT is a multi-target therapeutic approach, risk-benefit calculations should take into account the expected improvement of quality of life and the possible cardiovascular benefit in young recently menopausal women. These benefits should be weighed against a possible increase in breast cancer risk. In most cases regarding young postmenopausal women with low to medium breast cancer risk, HRT is considered beneficial. The fracture protection is lost soon after HRT discontinuation, so an alternative treatment should be considered after HRT discontinuation, if fracture risk is high (86).

Tibolone is a synthetic steroid displaying estrogenic, progestogenic and androgenic activity, depending on the target tissue. Its primary indication is the treatment of menopausal symptoms. Low – dose tibolone (1.25mg p.o. daily) reduced vertebral fractures by 45% and non-vertebral fractures by 26% in older postmenopausal women at risk of fracture during a follow-up of 34 months (88). The trial was prematurely stopped because of an increase in the risk of stroke in women receiving tibolone, an effect which was attributed to the old age of the population, since RCTs conducted in younger women have not demonstrated an increase in stroke risk (89).

10.1.2. Bisphosphonates

Currently available, oral bisphosphonates are administered on a weekly (alendronate / risedronate) or a monthly basis (risedronate / ibandronate). Intravenous bisphosphonates are administered every 3 months (ibandronate) or once a year (zoledronic acid). Depending on the drug type and the population studied, bisphosphonates reduce the risk of vertebral and non-vertebral fractures by 40-77% and 25-40 % respectively in women with established osteoporosis. Bisphosphonates are the most widely used drugs for the treatment of osteoporosis, mainly due the good safety profile and the low cost, especially with generic alendronate and risedronate. Their most common side effects are upper gastrointestinal irritation with the oral agents and an acute phase reaction comprising of fever and myalgia with the intravenous agents. Bisphosphonates use has been associated with a significant increase (RR 1.5) of serious atrial fibrillation with bisphosphonates therapy in some trials but not in others (90). According to one analysis of a large databank, the risk of esophageal cancer increases to about 2 per 1000 with five years use of oral bisphosphonates (91), yet another analysis of the same data bank did not observe such an increased risk. (Bis 91).

). Osteonecrosis of the jaw is a very rare event associated mainly with the use of intravenous bisphosphonates in cancer patients (92). Atypical hip fractures occurring in the subtrochanteric region of the femur in patients receiving prolonged bisphosphonate treatment is another extremely rare event that could be associated with bone turnover over-suppression (92,93).

Although the benefit of bisphosphonates is clearly established for older women over the age of 65-70, much controversy exists as to the efficacy of long – term bisphosphonate therapy in younger postmenopausal women, in whom fracture risk is lower and adherence to treatment is poorer. Neither alendronate nor risedronate, which are the cheapest drugs available, have been proven cost – effective in young postmenopausal women with low bone mass and no additional risk factors for osteoporosis (94,95). Therefore, if medical intervention is considered in the young postmenopausal woman for the sole purpose of fracture prevention, careful risk assessment should be performed based on clinical risk factors, with BMD assessment only as an aid to the risk calculation.

10.1.3. Calcitonin

Calcitonin is a natural hormone synthesized by the thyroid C cells and its physiological function is inhibiting bone resorption. Salmon calcitonin is 40-50 times more potent than human calcitonin. It

is approved for the treatment of osteoporosis, and is available as a nasal spray and for subcutaneous injections.

The PROOF study is the only one that has showed salmon calcitonin, by nasal dose of 200 IU daily, to significantly reduce vertebral fractures in severe osteoporosis by 33% in cases with prior history of vertebral fracture, and by 50% in women 70-75 years old after 5 years of treatment (96). There was no significant reduction in fractures at doses of 100 or 400 IU/day. This drug should not be considered as a first-line treatment in postmenopausal osteoporosis. It can be considered in certain situations for the treatment of osteoporosis in men and premenopausal women, as well as osteoporosis secondary to treatment with glucocorticoids.

Calcitonin has an effective analgesic effect, especially in cases of pain associated with acute vertebral fracture. It should not, however, be considered as a first-line analgesic in these cases for financial reasons (97).

10.1.4. SERMs

The SERMs are a structurally different group of compounds that, depending on the target tissue, can exert estrogen receptor agonist actions, e.g., on bone, or antagonist effects, e.g., on breast. These characteristics make them attractive candidates for the prevention and/or treatment of postmenopausal osteoporosis. Since SERMs greatly differ in their clinical profiles, a careful evaluation of each SERM is of considerable importance to clearly define their safety and potential efficacy. Clinical development of some SERMs was discontinued due to their inferiority to current therapy, or to adverse events in the genitourinary tract including uterovaginal prolapse, urinary incontinence, enlarged uterus, increased endometrial thickness, and abdominal pain. The first SERM, tamoxifen, has been used to treat breast cancer for over 35 years (98). Tamoxifen was shown to exert estrogen agonist activity on bone, increasing bone mineral density (BMD) (99). As a result of safety issues including pulmonary embolism, VTEs and a 3-fold increase in endometrial cancer, tamoxifen is not indicated for the treatment of postmenopausal osteoporosis

The second generation SERM, raloxifene, has been marketed and widely used for postmenopausal osteoporosis prevention worldwide, since it was shown to reduce bone turnover and increase BMD, conferring a 30–50% risk reduction of vertebral, but not nonvertebral, fracture (100-102). Raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer, with a significantly lower risk of endometrial hyperplasia, thromboembolic events, and cataracts (102).

A third generation SERM, bazedoxifene (bazedoxifene acetate) is an indole-based ER ligand with unique structural characteristics with respect to raloxifene and tamoxifen. Vast preclinical data support bazedoxifene as an antiresorptive therapy for the prevention and treatment of postmenopausal osteoporosis. Bazedoxifene reduces bone turnover and maintains or increases vertebral as well as total hip, femoral neck, and trochanter BMD (all $p<0.001$) and in comparison to placebo (103). In a 3-year international, double blind, randomized, placebo- and active-controlled

trial of 7,492 women, bazedoxifene reduced by 42% the risk for new vertebral fractures (HR, 0.58; CI, 0.38–0.89) when compared with placebo (104). In a post hoc analysis of 1,772 women at higher risk for fracture, bazedoxifene reduced the risk of nonvertebral fracture by 50% versus placebo (P=0.02). In addition, the risk of nonvertebral fracture risk was 44% lower than with raloxifene in the same group (P=0.05). In a 2-year extension of this study, Bazedoxifene showed sustained efficacy in preventing new vertebral fractures in postmenopausal women with osteoporosis and in preventing non-vertebral fractures in higher-risk women (105).

Bazedoxifene, unlike other SERMs, shows beneficial effects on the endometrium and breast, with a dose-related decrease in endometrium thickness and breast tenderness (101). Bazedoxifene showed an overall favourable safety and tolerability profile (106). Nevertheless, bazedoxifene induced a slight but significant increase in VTE, hot flushes and leg cramps, comparable to that of raloxifene (104). Since bazedoxifene shows unique antiestrogenic actions on breast and the endometrium, studies have been conducted to evaluate the efficacy and safety of bazedoxifene combined with conjugate estrogen (BZA/CEE).

The rationale for adding a SERM to estrogen is to counteract the estrogen stimulation on endometrial and breast tissues, maintaining the estrogenic effects on bone. This combination of a SERM with CEE has led to a new class of menopausal therapy called “tissue selective estrogen complex (TSEC)” based on the blended tissue selective activity profiles of the components (107). The BZA/CEE combination significantly decreased bone turnover and significantly increased bone mineral density at the lumbar spine and hip relative to placebo (108), while treating moderate to severe vasomotor symptoms and vaginal symptoms (109,110). These data support the use of a TSEC containing BZA/CEE as a new menopausal therapy with a balanced “estrogenic” response that can maximize the benefits of both bazedoxifene and estrogen while mutually balancing the potential adverse effects.

10.1.5. Denosumab

Recent discoveries in bone biology have included the identification of RANK, a cell receptor found on osteocyte and precursor cells, and the protein stimulating this receptor, RANK Ligand (RANKL), an essential mediator of osteoclast formation, function, and survival. Another important discovery was the identification of a protein called osteoprotegerin (OPG) which is a decoy receptor for RANKL to neutralize its effects and defend against bone loss. When RANKL is bound and neutralized by OPG, osteoclasts cannot form, function or survive (111). Unopposed RANKL (i.e. an elevated RANKL /OPG ratio) within the skeleton promotes bone loss, while restoring a balanced RANKL /OPG ratio or inhibiting RANKL decreases osteoclast activation and bone resorption (112).

Denosumab, a fully human monoclonal antibody inhibiting RANKL, induces a profound but completely reversible inhibition of bone resorption (113). Denosumab administration every 6 months for 4 years is associated with significant BMD increases in lumbar spine to 9.0% and in total hip to 3.9% over baseline. In postmenopausal osteopenic women, denosumab administration for 2 years induced a significant 6.5 % increase in BMD, even in young women fewer than 5 years since menopause (114). In a 3-year, randomized, placebo-controlled study, the relative risk of new

vertebral fractures was 0.32 (CI 0.26–0.41) for denosumab vs placebo, representing a 68% reduction (P< 0.001). For nonvertebral fractures, the hazard ratio of denosumab vs placebo was 0.80 (CI: 0.67–0.95, P = 0.01). It was 0.60 (CI: 0.37–0.97) for hip fractures (P = 0.04) (115). There was no significant differences vs placebo in the total incidence of adverse events, deaths, or discontinuation of the study treatment due to adverse events. In conclusion, denosumab administration acts through a physiological mechanism of action restoring the RankL-Rank-OPG system, and thus inhibits bone turnover in postmenopausal women, increasing BMDs at different skeletal sites, and leading to a risk reduction for vertebral, non-vertebral and hip fractures.

10.2. Dual therapy: antiresorptive and bone formation

10.2.1. Strontium ranelate (SR)

SR is a divalent salt of strontium, and it is stable when with ranelic acid, an organic molecule. It may be having bone forming effect of increasing growth and differentiation of osteoblasts and of increasing bone matrix synthesis. Additionally, it has an antiresorptive effect, reducing the differentiation and activity of osteoclasts (116).

A pivotal double-blind, placebo controlled trial showed a 49% reduction in vertebral fractures and a 41% one at three years compared with placebo (117). In another pivotal study investigating non-vertebral fractures (118), it was demonstrated that after 3 years, non-vertebral fractures decreased by 16% in the treated group compared to placebo. In a high-risk subgroup there was a reduction of 36 % of hip fractures. In Phase II, the annual incidence of venous thromboembolism observed over 5 years was approximately 0.7%, the_relative risk for patients treated with SR was 1.4% comared with placebo (117, 118). The results after 5 years of this study have been published (119), showing a reduction of 15% in non-vertebral fracture risk, with a post hoc analysis of the group of women at increased risk showing a 43% reduction in hip fractures.

The follow up data after 8 and 10 years for the patients taking strontium ranelate in the two pivotal studies has recently been presented (120,121). The results in the reduction of fractures were similar in the later to those for the early years, concluding that strontium ranelate maintained its efficacy against both types of fractures for 8 to 10 years.

In November 2007, the EMEA published a note concerning serious hypersensitivity reactions associated with strontium ranelate, including the DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms), although this was not subsequently confirmed (122). In these cases, the adverse reaction is usually resolved with the cessation of treatment.

10.3. Bone formation agents

10.3.1. PTH (1-34) or Teriparatide

PTH (1-34) or teriparatide comprises the first 34 amino acids of the human PTH molecule obtained by the recombinant DNA technique. Used daily in patients with osteoporosis at doses of 20 mcg,

PTH (1-34) showed a 65% decrease in the risk for vertebral and 53% in that for non-vertebral fractures after a year and a half of treatment (123,124).

Teriparatide is particularly recommended in the treatment of male and female patients with severe osteoporosis and in postmenopausal women over age 65 with BMD proven osteoporosis and prevalent vertebral fractures (125).

Due to its high cost, the use of teriparatide should be limited to treating patients with more than one fragility fracture and BMD with a T-score <-3.5, or for patients with new fractures after two years or more under treatment with bisphosphonates. The duration of treatment should be limited to no more than two years, during which the patients should receive adequate calcium supplementation of approximately 1.5 g/day, and appropriate supplements of vitamin D. Serum calcium should be monitored at 30 days of treatment and calciuria within 90 days. Mild elevations of blood calcium and/or urine can be handled with intake reduction. When PTH administration is discontinued, loss of bone mass is observed beginning in the first year; therefore it is advisable to subsequently use antiresorptive treatment (126).

10.3.2. PTH (1-84)

This is the complete molecule of PTH obtained by recombinant DNA techniques. In a randomized, double-blind placebo controlled study a 58% reduction of vertebral fractures and 3% (not significant) reduction of non-vertebral fractures was observed after 18 months of treatment. Hypercalcemia and hypercalciuria were more frequent than before treatment (127).

11. **FUTURE TREATMENTS**

Currently, most treatments for osteoporosis are aimed at inactivation of the osteoclasts, either by removal of the osteoclasts (e.g. bisphosphonates and hormone replacement therapy, selective estrogen receptor modulators (SERMs)) or by attenuation of the resorptive activity of the osteoclasts (e.g. calcitonin) (128). These anti-resorptive therapies all lead to secondary reductions in bone formation, as a result of the coupling between resorption and formation, and thus their long term effects become limited (129,130). All of these treatments reduce fracture risk and increase BMD, however, none of the treatments are perfect with respect to side effects, gender specificity, ease of use, efficacy, safety, and effects on fracture healing (131-133). A series of interesting targets for osteoporosis treatment are currently under investigation.

Cathepsin K inhibitors, such as odanacatib, have shown a substantial inhibition of bone resorption, leading to robust increases in bone mineral density (134,135). Interestingly, the secondary effect of cathepsin K inhibitors on bone formation is somewhat smaller than that observed with classical anti-resorptives, a phenomenon most likely explained by the continued presence of osteoclasts (134-136). Upon withdrawal of treatment, though, a resolution effect is initiated which causes rapid bone loss, ultimately resulting in a return to the levels observed in the placebo arms (135).

GLP-2 has, in clinical settings, been demonstrated to inhibit bone resorption (137-139). Reductions in bone resorption by exogenous GLP-2 require an intact gastrointestinal tract (137,140,141). The decreased meal-induced inhibition of bone resorption in the jejunostomy patients, who lack a GLP-2 response, supports the view that GLP-2 plays a role in postprandial reduction in bone resorption (140,141)

GLP-2 has in addition been suggested as a bone resorption inhibitor without affecting bone formation (137), marking this mode of inhibition of resorption for further investigation.

Acid secretion by osteoclasts has been an interesting therapeutic target since the discovery that this process is controlled by the a3 subunit of the V-ATPase and ClC-7, both of which are quite specific to osteoclasts (142-144). In aged ovariectomised rats, early low-potency chloride channel inhibitors were able to prevent bone resorption by approximately 50% as monitored by both BMD and the biochemical markers of bone resorption CTX-I or deoxypyridinoline, while augmenting the number of osteoclasts, and showing no inhibition of bone formation markers (145,146). Similar findings were published for an inhibitor of the V-ATPase (147).This is in contrast to other antiresorptive treatments where a secondary decrease in bone formation was observed (130,148). These studies provide proof for the concept that inhibition of acidification is a very promising target for osteoporosis treatment.

In addition to the anti-resorptives mentioned above, a series of anabolic molecules are under development. The calcilytics are molecules causing activation of the calcium sensing receptor, and thereby leading to secretion of PTH, which then in turn should induce an anabolic effect on the skeleton (149). PTHrP is an analogue of PTH which is known to induce bone formation by the osteoblasts leading to increases in BMD; however, like PTH it is also catabolic and causes an induction of bone resorption (150,151).

Finally, a humanized antibody against the Wnt inhibitor sclerostin is also in development. This molecule called AMG-785 causes a large, systemic induction of bone formation, a minor suppression of bone resorption, and hence robust increases in bone mineral density following single dose injection (152).

In summary, numerous promising treatments for osteoporosis are under development, and all are greatly interested in seeing how these molecules with several different and novel modes of action pan out in the future.

12. **RECOMMENDATIONS**

One important clinical objective consists of identifying patients with an elevated risk of having this disease. Osteoporosis is predictable and treatable, but the lack of warning signals before a fracture means that few patients are diagnosed in the early phases of the disease and effectively treated. It is women under 70 years of age that make up this group. Osteoporosis is the most significant risk factor, and the one with the highest predictive value, for fragility fractures (nontraumatic or minimally traumatic). Knowledge of the risk factors for detecting those patients most likely to have

the disease is important for detecting those patients most likely to develop the disease. Nevertheless, correcting the modifiable factors also has considerable therapeutic implications.

When the risk factors and BMD for each woman have been determined, the clinician will be in a position to be able to speak with the patients about their risk level for fractures.

That notwithstanding, it will also be the clinician's obligation to encourage changes in patient lifestyles, predict which health resources to use and carry out a minimal cost/utility analysis for the intervention alternatives for the disease.

The need to treat osteoporosis is justified by the reduction in the risk for fracture by increasing the bone strength with this intervention. There are no fixed rules or established protocols about which drug or model to use. The decision to initiate and the type of treatment should be based on the necessity to reduce the risk for fracture. In each case, and aside from the BMD and other more important risks, the following factors should be taken into account: renal function, drug allergies, comorbidities, previous treatments, contraindications, secondary effects of drugs and cost. This way, establishing the risks and benefits of a drug is possible for each patient. Furthermore, it is important to take into consideration how to improve adherence.

Osteoporosis, being a chronic disease that requires treatment over many years, makes it necessary to use individualized measures and sequential treatments.

Sequential treatment consists of designing a strategy that uses a drug for a sufficiently long time to reap the benefits with minimal risk and maximum adherence. Thus, it will be possible later on to change to another or other drugs that meet the same requirements. It is necessary to keep in mind the undesired effects of the prolonged use of some drugs, the level of risk for fracture desired, and data from clinical studies that support its use, such as efficacy for the age of the patient. The drug treatment should be static, but should change during the life of the patient so as to adapt itself to the clinical and metabolic needs of the patient at any given moment (85).

In theory, treatment in the first few postmenopausal years could start with the use of drugs aimed at the physiopathology of the rapid loss of bone mass produced by the increase in bone resorption as a result of the decrease in estrogens. The most appropriate drugs for these women are HRT, and, for asymptomatic women, SERMs. Another possibility would be to first use HRT for two or three years, followed by SERMs. Afterwards, there is a period where there is an increase in the resorption and a decrease in formation. This coincides with >10 years postmenopause and with a greater risk for hip fracture. This is when drugs such as the bisphosphonates, strontium ranelate and denosumab have clearly shown their effectiveness. Finally, and in women older than 70-75 years of age, there is an important decrease in formation. PTH suold be used in women who continue to fracture while being on antiresorptive theraphy (Figure 2) (83).

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Table 1. RISK FACTORS CONSIDERED IN FRAX

- Country of Residence
- Race: (only for U.S. model: White, Hispanic, African American, Asian)
- Age: accepts ages between 40 and 90 years.
- Gender: male - female
- Weight (kg) and height (cm): used to calculate BMI
- Previous fracture: spontaneously in adult life, or traumatic but would not have occurred in a healthy individual
- Family history: parent with hip fracture
- Corticosteroids: prednisone 5 mg/day for 3 months in the past or present
- Rheumatoid arthritis (diagnosis confirmed)
- Smoking (current)
- Alcohol: 3 drinks per day
- Secondary Osteoporosis
    - Diabetes mellitus type I
    - Osteogenesis imperfecta in adults
    - Long-standing untreated hyperparathyroidism
    - Hypogonadism or premature menopause (<45 years)
    - Chronic malnutrition or intestinal malabsorption
    - Chronic liver disease
- BMD: T-score or g/cm^2 at the femoral neck

Table 2. CATEGORIES OF DIAGNOSTIC THRESHOLDS BASED ON BMD MEASUREMENTS BY DXA

Normal: a value for BMD that is higher than 1 standard deviation below the young adult female reference mean (T-score greater than or equal to −1 SD)
Osteopenia (low bone mass): a value for BMD more than 1 standard deviation below the young female adult mean, but less than 2.5 SD below this value (T-score <−1 and >−2.5 SD)
Osteoporosis: a value for BMD 2.5 SD or more below the young female adult mean (T-score less than or equal to −2.5 SD)
Severe osteoporosis: a value for BMD 2.5 SD or more below the young female adult mean in the presence of 1 or more fragility fractures.

Table 3. **INDICATIONS FOR BMD TESTING (ISCD OFFICIAL POSITION 2007)(51)**

Women aged 65 and older	Adults taking medications associated with low bone mass or bone loss
Postmenopausal women under age 65 with risk factors for fracture	Anyone being considered for pharmacologic therapy
Women during the menopausal transition with clinical risk factors for fracture, such as low body weight, prior fracture, or high-risk medication use	Anyone being treated, to monitor treatment effect
Subjects with a fragility fracture	Anyone not receiving therapy in whom evidence of bone loss would lead to treatment
Adults with a disease or condition associated with low bone mass or bone loss	Women discontinuing estrogen should be considered for bone density testing according to the indications listed above.

Table 4. MARKERS OF FORMATION AND RESORPTION

Formation: ***Matrix Proteins***

- osteocalcin (OC)
- procollagen type I propeptides
    - C-terminal (PICP)
    - N-terminal (PINP)

Enzyme

- bone isoform of alkaline phosphatise (bone ALP)

Resorption: **Collagen degradation products**

- pyridinium cross-links of collagen
    - C- and N-telopeptides (CTX, NTX)
    - deoxypyridinoline (DPD)

Enzyme

- tartrate-resistant acid phosphatise (TRACP), type 5b
- cathepsin K

Related factors

- OPG, RANK-L

Commercially available assays:

(Serum: OC, PICP, PINP, bone ALP NTX, CTX, TRACP5b

Urinary: CTX, NTX, free DPD)

Table 5. USEFULNESS OF MARKERS FOR AN INDIVIDUAL PATIENT (62):

- Bone turnover changes at menopause and with osteoporosis
- Increased BTMs indicate bone loss and increased fracture risk
- BTMs can measure the effects of treatment in resorption and turnover.
- BTMs are useful for treatment monitoring
- BTMs are raised in 25% of women with primary osteoporosis.
- BTMs are not yet proven to enhance choice of treatment.
- Raised BTMs may be related to other causes of osteoporosis.
- Could BTMs be used to improve compliance also?
- Monitoring treatment improves adherence to treatment with raloxifene

Table 6. BONE TURNOVER MARKERS VARIATION

Controllable source

- Circadian
- Day to day
- Diet
- Exercise

Solution

- Morning, fasting samples
- Take the average of more than one measurement

Uncontrollable source

- Growth
- Age and gender
- Fractures
- Diseases and drugs

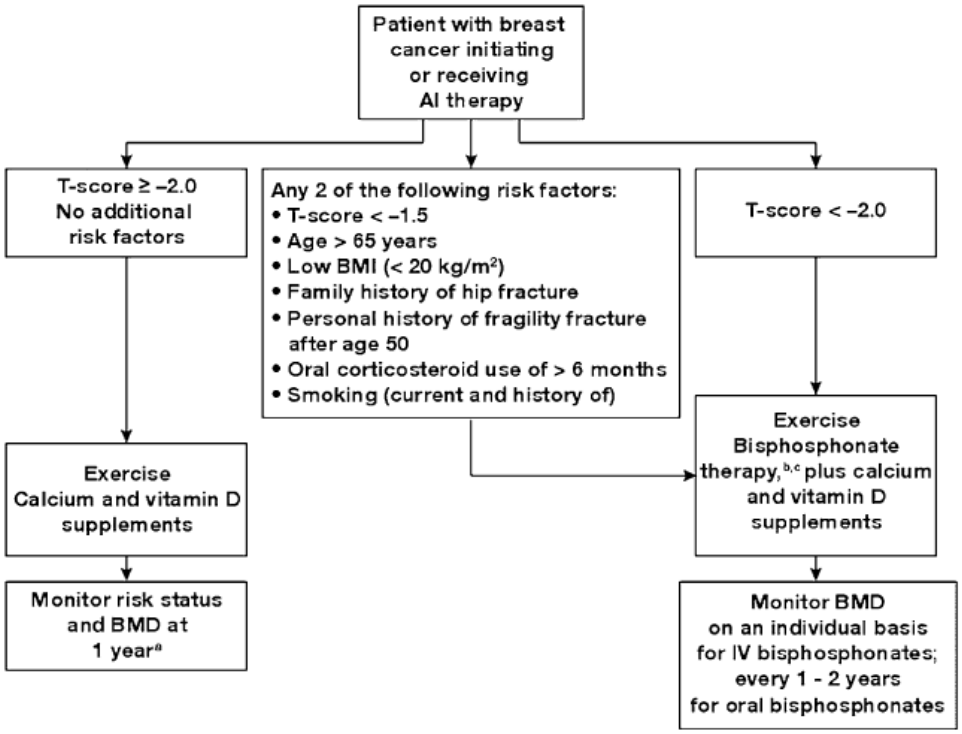
Solution

- Establish an age and gender specific reference range.

TABLE 7. OSTEOPOROSIS TREATMENT RECOMMENDATIONS (82)

1. All women with BMD T-scores of less than or equal to -2.5 at the lumbar spine or femoral neck or hip.
2. All postmenopausal women who have had an osteoporotic vertebrae or hip fracture
3. All women with a T-score between -1.0 and -2.5 and more than two risk factors could also have a calculation of their risk for a major fracture in the next 10 years.

Figure 1. RECOMMENDED ALGORITHM FOR MANAGING BONE HEALTH IN WOMEN RECEIVING AROMATASE INHIBITOR (AI) THERAPY FOR BREAST CANCER



[a]If patients experience an annual decrease in bone mineral density (BMD) of ≥10% or ≥4%–5% in patients who were osteopenic at baseline (using the same dual-energy x-ray absorptiometry machine and lowest T score form 3 sites), secondary causes of bone loss such as vitamin D deficiency should be evaluated and antiresorptive therapy initiated. [b]Denosumab may be a potential treatment option for some patients. [c]Although osteonecrosis of the jaw (ONJ) is an uncommon event, rarely observed in the first years of ZOL treatment in the AIBL setting, regular dental care and attention to oral health is advisable in patients receiving bisphosphonates or denosumab. Abbreviations: AI, aromatase inhibitor; BMD, bone mineral density; BMI, body mass index; ZOL, zoledronic acid.Reprinted from Hadji P, et al.(40)

Figure 2: SEQUENTIAL TREATMENT OF FRAGILITY FRACTURE RISK (83)