The management of the patient with osteoporosis: from evidence to clinical practice

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ABSTRACT

Osteoporosis is the most common bone disease and is an important problem of public health. In fact, it represents the main cause of age-related fractures and disabilities with a consequent increasing sanitary, social and economic impact. Unfortunately, often osteoporosis is not as thoroughly investigated as it would be desirable and it is underestimated in diagnosis and therapy. The aim of this monograph is to sensitize medical internists to a careful evaluation and an efficacious treatment of osteoporosis in order to reduce the risks of this disease, in particular the fractures, with a view to improving the quality of patients' life.

Introduction

Osteoporosis is the most common bone disease[1] and is an important problem of public health. In fact, it represents the main cause of age-related fractures[2] and disabilities with a consequent increasing sanitary, social and economic impact.[3] Osteoporosis is a systemic skeletal disease characterized by a low bone mass and by a microarchitectural deterioration of bone tissue with a consequent increase of fragility and fracture risk.[4]

It can be *primitive*, such as post-menopausal or senile osteoporosis, or *secondary* to multiple factors.[5]

The World Health Organization (WHO) defined *osteoporosis* in postmenopausal women or in men as the presence of bone mass middle peak standard deviation (T-score), which is measured at the femoral neck by dual-energy X-ray absorptiometry (DXA), equal to –2.5 or more, below the average value in young healthy women (T-score ≤–2.5 SD).[1,6] Furthermore the International Society for Clinical Densitometry established that osteoporosis can be diagnosed in postmenopausal women and in men aged 50 and older if T-score of lumbar spine, total hip and femoral neck is equal to –2.5 or less.[7]

Annually worldwide osteoporosis causes nearly 9 million fractures[8,9] the majority of which happens in patients over 65 years old.[10]

Fractures are an important cause of morbidity and mortality; in fact patients with hip and vertebral fractures have a decreased life expectancy.[10] For this reason osteoporosis is an emerging and very interesting public health problem because of its medical, social and economic impact.[3] Therefore the aim of this monograph is to produce a methodological approach and a diagnostic-therapeutic practice to reduce the risk of osteoporosis-related fractures and to improve the quality of patients' life.

Epidemiology: incidence, prevalence and prognosis data

About 200 million people worldwide are affected by osteoporosis[11] with a higher prevalence in women than men; the prevalence of osteoporosis increases progressively with age in post-menopausal period (5% in the fifth decade *versus* 50% in the eighth decade).[12] According to the WHO,[13] osteoporosis affects more

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than 75 million people in the United States, Europe and Japan. Through the ESOPO study (Epidemiological Study On the Prevalence of Osteoporosis) it is estimated that women with osteoporosis in Italy are 4,000,000[14-16] and the projections made by the study data confirms that osteoporosis is considered an emerging problem in our country and throughout Europe due to the progressive and constant aging of the population.

One of the major complications of osteoporosis consists of the fractures, which are responsible for a clear worsening of the quality of life, an increase in mortality and a substantial increase in health spending. It is estimated that osteoporosis causes nearly 9 million fractures annually worldwide,[8,9,13] of these 4.5 million are registered in America and Europe where women, having a lower bone density, have an incidence of hip fractures about double of men.[17]

The most affected sites are femur, vertebrae, wrist and proximal humerus.[9] It is estimated that one-year mortality from a fracture event is 15-30% and in the next 3-6 months after a hip fracture mortality is to be charged for about 30% to direct consequences of the fracture; furthermore 50-60% of patients develop motor disabilities and become completely dependent in basic activities of daily living, and only 30-40% is fully indipendent.[18-23]

Etiology

Osteoporosis is a multifactorial disorder; constitutional, genetic and environmental factors contribute to its pathogenesis. It involves the whole skeleton with qualitative alterations of the bone micro-architecture, especially the reduction in bone mass up to a level below the minimum required for its support function. This is due to fragility and constitutes a considerable risk for the occurrence of fractures caused by minimum trauma or therefore referred to as *spontaneous*. In young people, this process goes with a high turnover; in the elderly, however, the process is less active and it is defined at low turnover. The result is an imbalance between neo-formation and bone resorption in favor of this one. Osteoporosis may be caused by complex interactions between systemic and local regulatory function of bone cells.

Basic pathogenetic mechanisms

Skeletal fragility can result from: i) body's inability to maintain the optimal skeletal size and strength during growth; ii) excessive bone resorption resulting in decreased bone mass and skeleton micro-architectural deterioration; iii) imbalance between formation and resorption during bone remodeling.

In addition, the incidence of fragility fractures, particularly of the hip and wrist, is further determined by the frequency and direction of falls.

The bone remodeling or Bone Multicellular Units (BMUs) described many years ago by Frost and others,[21] can occur either on the surface of trabecular bone as irregular Howship lacunae or in cortical bone as relatively uniform cylindrical Haversian systems which are denominated *primitive Haversian systems*.

The process begins with the activation of hematopoietic precursors to become osteoclasts. Because the bone resorption and remodeling phases are short and the period required for bone osteoblastic replacement is long, any increase in the rate of bone remodeling will result in a loss of bone mass. Moreover, the larger number of unfilled Howship lacunae and Haversian canals will be the further bone weakening. Excessive resorption can also result in complete loss of trabecular structures, so that there is no template for bone formation. Hence an inadequate formation response during remodeling is an essential component of the pathogenesis of osteoporosis.[22]

The role of estrogens

The rapid and continuous bone loss that occurs for several years after menopause indicates an impaired bone formation response. The increased bone formation that normally occurs in response to mechanical loading diminishes in estrogen deficiency, suggesting estrogen is both anti-catabolic and anabolic role.[23] Fracture risk is inversely proportional to estrogen levels in post-menopausal women and as little as one quarter of the estrogen dose stimulating breast and uterus is sufficient to decrease bone resorption and increase bone mass in older women.[24] Osteoporosis in older men is more closely associated with low estrogen levels rather than to low levels of androgens.[25]

Animal model studies and cell cultures showed that estrogens act not only on the BMU cells, but also on other marrow cells.

They act through two types of receptors: i) estrogen receptor α (ERα); ii) estrogen receptor β (ERβ).

ERα receptors appear to be the primary mediator of estrogen's actions on the skeleton.[24]

Osteoblasts express ERβ receptors, but the actions of ERβ agonists on bone are less clear. Some studies suggest that the effects of estrogen signaling through ERα and ERβ are in opposition, while other studies suggest that activation of these 2 receptors has similar effects on bone.[21]

Calcium, vitamin D, and parathyroid hormone

Decreased calcium intake, impaired intestinal absorption of calcium due to aging or disease, as well as

vitamin D deficiency can result in secondary hyperparathyroidism. Vitamin D deficiency and secondary hyperparathyroidism can contribute not only to accelerated bone loss and increasing fragility, but also to neuromuscular impairment that can increase falls risk.[26]

Adequate supplementation of both - calcium and vitamin D - may correct a secondary hyperparathyroidism, reduce bone resorption, increase bone mass, reduce fracture rates, and also decrease the frequency of falls.[26]

Vitamin D effects are mediated by its nuclear receptor. Many studies showed several polymorphisms of the vitamin D receptor gene.

The reduction of vitamin D levels and the increase of circulating parathyroid hormone (PTH) levels in winter is associated with an increase in fractures rate independently from the increase falls rate.[27] In addition, increased PTH levels are associated with increased mortality in frail elderly, independent of bone mass and vitamin D status.

Role of NF-κB, osteoprotegerin and genic stimulation

Many molecules are involved in balance regulation between bone resorption (by osteoclasts) and formation (by osteoblasts). The coupling between resorption and neo-apposition is possible by intercellular cross-talk through various growth factors and cytokines. The principal regulator of osteoclast differentiation is RANKL (*receptor activator of nuclear factor kappa B ligand*), a soluble membrane protein, which is expressed on osteoblasts, activated by T cells and binds to its receptor RANK. This receptor is present on osteoclasts and all the cells of the monocyte line.[28] Osteoclasts formation is limited by osteoprotegerin, a soluble receptor produced by osteoblasts, B lymphocytes and dendritic cells which bind RANKL.[29]

Etiopathogenetic classification

It is possible to distinguish two types of osteoporosis: i) idiopathic; ii) secondary.

Some Authors consider a third type: osteoporosis caused by prolonged immobility.

Idiopathic osteoporosis can be divided into 3 forms: i) senile; ii) post-menopausal; iii) juvenile.

Although none of them responds to a defined mechanism, for the first 2 forms there is an obvious correlation between hormonal activity reduction and reduced bone mass in both sexes.

After menopause, in 25% of women bone resorption is accelerated and there is an increase in serious spontaneous fractures risk. Some Authors attribute the increased incidence of osteoporosis in women to their low bone mass, and to typical post-menopausal reduced hormone calcitonin production that acts as PTH-antagonist. Furthermore, sex hormones, especially estrogen, exert a bone protective effect against the PTH-promoted resorption process. Moreover, in both sexes the intake of calcium-rich foods is reduced and its intestinal absorption with advancing age too, due to calcitriol lower availability and to an increase in sedentary lifestyle that contributes to aggravate the bone resorption process.

Secondary osteoporosis is due to other diseases, more frequently endocrine disorders. It is very frequent in patients with Cushing's disease and in those undergoing prolonged glucocorticoid therapy. These hormones exert a dual action on osteoblasts: reducing the collagen synthesis capacity and increasing its sensitivity to PTH. They also reduce calcium intestinal absorption. Calcium probably interferes with 1-α-hydroxylase activity and causes a slight lowering of serum calcium, followed by PTH hypersecretion. Excessive synthesis of thyroid hormones (thyrotoxicosis) may also determine osteoporosis appearance or preexisting primary form aggravation. Another cause of secondary osteoporosis is diabetes mellitus: insulin stimulates osteoblasts synthesis of collagen and various growth factors; these conditions are reduced in case of deficient synthesis. Secondary osteoporosis is also common in patients with advanced chronic liver diseases in which the intake of calcium is generally reduced because of vitamin D deficient activation in the liver.[2,30] Many risk factors are common to secondary and post-menopausal and senile osteoporosis.

Rarer forms of secondary osteoporosis are: i) *osteoporosis associated with pregnancy and lactation* (PLO): rare condition in which women have vertebral fractures, most often in the third trimester of pregnancy or after giving premature birth.[4,31] In PLO there is a strong genetic component.[31] PLO usually occurs in nulliparous, while symptoms recurrence in next pregnancies is rare. In women without a secondary cause, the course is usually benign with complete clinical picture resolution without relapse and specific therapy; ii) *transient osteoporosis of the hip (TOH)*: is a rare skeletal disease that can occur both in men and in women, but most often occurs during the third trimester of pregnancy. Women have unilateral or bilateral hip pain without obvious associated trauma. While some pregnant women develop hip fractures related to TOH, others have a full resolution of hip pain within six months following childbirth and without the development of fractures. The etiology of this condition is unknown, but it could be related to compression of the pelvic nerve, vascular insufficiency, or changes of the fibrinolytic system with pregnancy.[32]

Risk factors

Osteoporosis and osteoporotic fracture have a multifactorial pathogenesis. You can identify risk factors relating to: i) peak bone mass acquisition; ii) bone mass density in elderly; iii) skeletal structural aspects.

Bone resistance to trauma depends on quantitative factors, such as bone mineral density (BMD) assessed by mineralometric examination, and qualitative factors such as geometry, microstructure, turnover, crystalline and organic composition of the matrix (for which the evaluation has not entered into clinical practice yet). In case of falls, fracture probability depends on the fall characteristics, the protective reactions effectiveness and the trauma possible energy attenuation by soft tissues thickness mediated.

The risk of osteoporotic fracture is determined by a combination of factors that act mainly through a reduction in BMD and factors partially or totally independent of BMD.

Table 1 shows the main risk factors associated with fragility fractures and divided into 4 different categories.[10]

Among the many factors independently associated with osteoporosis and fractures risk, we need to remember advancing age, previous fragility fracture, family history of fragility fractures, steroid therapy and all conditions that increase probability of falls. Moreover, the presence of concomitant diseases accentuates the risk of fracture. In subjects with multiple risk factors the probability of fracture is greater than in subjects with a single risk factor.

BMD assessment is adequate for osteoporosis diagnosis (diagnostic threshold) but the identification of subjects at high risk of fracture - in whom a specific drug treatment (therapeutic threshold) is recommended - requires BMD and independent risk factors combination.[33]

Diagnostic algorithm and diagnosis

Many algorithms such as FRAX® and DEFRA have been developed over the last 10 years. They calculate the risk of major osteoporotic frailty fractures (vertebrae, femur, humerus, wrist) over the next 10 years integrating information derived from BMD measurement with clinical risk factors presence.

FRAX®

FRAX® was developed by WHO to assess fracture risk and is based on individual models that integrate the risks associated with clinical features and femoral neck BMD. The FRAX® tool is a computer algorithm available through a web-based portal (www.shef.ac.uk/FRAX). It gives the 10-year proba-

Table 1. Risk factors associated with fragility fractures.

Risk categories	Risk factors
Non-modifiable risk factors	Previous fractures Parental history of osteoporosis Early menopause (below age of 45)
Modifiable risk factors	BMI <20 kg/m^2 Smoking Low bone mineral density Alcohol intake
Coexisting diseases	Diabetes Inflammatory rheumatic disease Inflammatory bowel disease and malabsorption Institutionalized patients with epilepsy Primary hyperparathyroidism and other endocrine diseases Chronic liver diseases Neurological diseases Moderate to severe chronic kidney disease Asthma
Pharmacological therapy	Antidepressants Antiepileptics Aromatase inhibitors Long-term treatment with acetate medroxyprogesterone GnRH agonists Proton pump inhibitors Oral glucocorticoids Thiazolidinediones

BMI, body mass index. *Modified from Scottish Intercollegiate Guidelines Network, 2015.*[10]

bility of hip fracture or a large osteoporotic fracture.[34,35] In clinical practice this algorithm application could result in initiating a therapy precociously or in assessing BMD.[36,37]

DEFRA

DEFRA is the Italian algorithm for risk fracture prediction (http://www.defra-osteoporosi.it).

This algorithm, calibrated on Italian population, allows calculating the risk percentage of major osteoporotic fracture in a 10-year span. Compared to FRAX®, DEFRA exceeds the limit of dichotomous variables allowing inclusion of more detailed data such as the number and place of fragility fractures, cigarettes number and consumed alcohol, the average steroids dose and other secondary illnesses; it also allows to insert BMD at lumbar and femoral levels as well as some osteosonographic parameters (in FRAX BMD is optional and only femoral).

DEFRA can document severity and potential impact of osteoporosis in an objective manner improving risk perception by patient and other health workers.[33,38]

Diagnosis

Biohumoral diagnosis

A specific blood test is strongly recommended in patients with osteoporosis and has to be considered a useful completion in osteoporosis diagnosis because it: i) may allow a differential diagnosis with other diseases that can cause a clinical picture or bone densitometry similar to osteoporosis; ii) can identify possible causal factors allowing a diagnosis of secondary osteoporosis and then an etiological treatment; iii) can orient in pharmacological choices and judge adherence to therapy.

The normality of first-level biochemical examinations in 90% of cases excludes other diseases or secondary osteoporosis. Sometimes we must proceed with laboratory investigations of second level (Table 2).[33]

The choice of investigations to identify secondary osteoporosis should be based on their prevalence, clinical history and examination, and pharmacological patient's goal. The tests to exclude secondary causes of osteoporosis should be required if BMD value is below the average value BMD of healthy young adults of the same age and sex (Z-score) or if the patient does not get adequate densitometric results despite therapy has been performed in terms of compliance and durability adequately.[33,37,39]

Bone neoformation and resorption markers are bone turnover indices and may also be useful in therapy or even adherence monitoring. However, currently the dosage of bone turnover markers does not appear justified for a clinical evaluation, though blood tests compared to imaging allow time reduction to verify antiresorptive or PTH therapy effectiveness.

Instrumental diagnosis

The diagnosis of osteoporosis is based on quantitative assessment of BMD using dual-energy X-ray absorptiometry (DXA) only. WHO defines osteoporosis in post-menopausal women or in men when axial bone density T-score (measured by DXA) at the femoral neck falls 2.5 standard deviation (SD) or more below the average value BMD of healthy young adults of same sex (T-score ≤2.5 SD).[1,6,10] This policy has no value for premenopausal women or men under 50, if Z-score falls 2 SD or more below the average value BMD of healthy young adults of the same age and sex. It is defined *below the expected range for age*, while if Z-score is above –2 SD it is defined *within the expected range for age*.

Severe osteoporosis is defined by BMD that is 2.5 SD or more below with one or more fragility fractures.[1,6,10,33,38,40]

Table 2. Blood tests of first and second level.

Blood tests of first level	Blood tests of second level
ESR	Transaminases
Complete blood count	TSH, FT4, FT3
Fractionated proteinaemia	Serum parathyroid hormone
Calcemia	Serum 25-OH-vitamin D
Phosphoremia	Cortisoluria/24 h
Total alkaline phosphatase	Free testosterone in men
Creatinine	Urine protein electrophoresis
24 h calciuria	Anti-gliadin or anti-endomysium or anti-transglutaminase antibodies Specific tests for associated diseases Specific markers of bone turnover

ESR, erythrocyte sedimentation rate; TSH, thyroid stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine. *Translated and modified from* SIOMMMS, *2013*.[33]

Dual X-ray absorptiometry

Currently DXA is the technique of choice in bone mass evaluation and monitoring and the best predictor of osteoporotic fractures risk.[41] It is recommended in: i) women over 65 and males over 70 years old; ii) all age people in the presence of previous fragility fractures, radiological finding osteoporosis or major osteoporosis risk factors; iii) post-menopausal women and men over 60 years old in the presence of risk factors.[41]

Quantitative computerized tomography

Quantitative computerized tomography (QCT) allows to measure total and compartmental volumetric BMD (g/cm^3) at vertebral and femoral level and it is able to separate trabecular and cortical BMD. There is sufficient evidence that QCT predicts vertebral not hip risk fractures in post-menopausal women and in men. But it involves a high dose of radiation (about 100 μSv) so DXA is preferred because of accuracy, shorter scan times, more stable calibration, lower radiation dose and lower costs.[41]

Quantitative ultrasound

The quantitative ultrasound (QUS) survey provides two parameters, velocity and attenuation. They are indirect indicators of bone mass and structural integrity. They are measured in phalanges and calcaneus mainly. US parameters are able to predict osteoporotic femoral and vertebral fractures risk in post-menopausal women and in men as well as DXA. They are independent predictors of fracture risk because they are influenced by other bone tissue characteristics. For this reason, QUS cannot be used for diagnosis of osteoporosis according to the WHO criteria (T-score ≤2.5). A major limitation of the method is represented by devices heterogeneity that gives uncorrelated values.[41] It can be useful when it is not possible to assess DXA and can be recommended for epidemiological investigations and first level screening because of relatively low cost, easy portability and absence of radiation.

Vertebral morphometry

Vertebral morphometry is the vertebral bodies measurement in order to verify new vertebral fracture when there is a 4 mm or 15% reduction of one of vertebral body heights and to describe the severity.[42] It is performed on dorsal and lumbosacral spine images and is not able to leave a previous qualitative X-ray analysis to exclude different deformities causes.

Additional diagnostic imaging

Spinal magnetic resonance imaging (MRI) is indicated when fractures involve several vertebrae because it is able to distinguish recent from old fractures. Spinal computed tomography should be performed to complete MRI when there are doubts about bone lesion nature.

Monitoring

The evaluation of bone mass may be able to monitor drug therapy strength and to find subjects at risk.

The annual bone mass loss is 0.5-2% in post-menopausal women and many therapies increase 1-6% per year BMD. The *least significant change* that is the minimum not attributable used imaging detectable change to measurement error can modify from 2 to 4% depending on site and technique. So, a control is generally justified only after 1.5-2 years. They are comparable densitometric exams carried out with the same instrument in undergoing quality controls centers only.[33,37]

Osteoporosis in man

Occurrence of hip fractures in men is approximately 20%. Vertebral fractures incidence is usually concerns the half of women, but vertebral and femoral fractures mortality and morbidity are higher than in women. In men, the most common form of osteoporosis is secondary to hypogonadism, alcoholism, multiple myeloma, hyperparathyroidism, malabsorption, and corticosteroids use mainly.

In men, a bone mass DXA assessment is justified if there is a major risk factor at all ages or lower risk factors after age 60.[33]

Therapy

Osteoporosis treatment should be aimed to reduce fracture risk. It is a multidisciplinary treatment characterized by pharmacological and non-pharmacological measures.

Non-pharmacological therapy

Calcium

The recommended daily calcium intake is 1000-1200 mg[43] and calcium supplementation appears to be justified only if it is really necessary to compensate inadequate dietary sources.[33]

Vitamin D

The recommended intake of vitamin D is 800 IU per day (25,000 IU monthly).[43] Vitamin D sufficiency status can be measured evaluating the serum levels of 25-OH-vitamin D: values >30 ng/mL are considered normal, values >20 ng/mL are considered deficiency;[44] values comprised between 20 and 30 ng/mL configure

failure state. In patients with osteoporosis, supplementation with cholecalciferol was effective in primary and secondary prevention.[33] The dose for the treatment of vitamin D deficiency is cholecalciferol 50,000 IU orally per week for at least 6 weeks, the maintenance is 50,000 IU per month.[45] The administration of active metabolites is justified only in patients with severe kidney disease and serious liver disease.[33]

Diet and other nutrients

A balanced diet is considered necessary to maintain good bone health, allowing a good intake of B, K group vitamins, protein and micronutrients. However, there is no evidence that identifies a particular type of diet useful for primary or secondary osteoporosis prevention.[10]

Physical exercise

Physical activity is able to regulate bone remodeling through the stimulation of mechanoreceptors at bone sites.[46] It is also acknowledged that the gravitational load withdrawal, or physical exercise can reduce bone density.[10] Aerobic (jogging, gymnastics, soccer, basketball) strength and resistance exercise (weight lifting, swimming, cycling) are considered valid to maintain bone health, particularly when combined.[33,47] Furthermore, physical activity has indirect protective effects against osteoporotic fractures: a worse physical condition, evaluated through the *prehensile force*, is associated with a higher fracture risk.[48]

Life habits and other protective measures

Smoking influences bone physiology: the functional recovery and fractures healing improve with smoking cessation.[49,50] Also smokers have a low bone mineral density than non-smokers.[51] Likewise, the alcohol consumption is considered a risk factor for osteoporosis and pathological fractures.[52] Finally, some interventions on the falls risk were effective to reduce fracture risk: improving the sarcopenic condition through a balanced diet and an appropriate exercise, muscle strengthening programs and restoring balance; administration of tests for falls risk assessment and subsequent prophylactic maneuvers, such as rationalization of comorbidities therapy, mechanical protection intervention and domestic barriers removal; improvement of information on bone-health-related factors and fracture prevention.[33]

Pharmacological therapy

The use of specific drugs appears justified when fracture risk at 10 years is particularly high as in patients with a T-score less than –2.5, in patients with a previous osteoporotic fractures or with steroid therapy (at least for doses greater than 5 mg/day of prednisone or equivalent taken chronically). In the latter two cases, the fracture risk is so high that the decision to initiate a drug therapy can be initiated regardless of densitometric values.

Osteoporosis drug treatment may exist through two mechanisms of action: reducing bone turnover (antiresorptive therapy) and/or stimulating bone formation (anabolic therapy). The antiresorptive drugs include bisphosphonates, raloxifene, ormone replacement therapy (HRT) and denosumab. Parathyroid hormone and teriparatide have anabolic action; strontium ranelate has a dual antiresorptive and anabolic activity.

Bisphosphonates

Bisphosphonates are synthetic compounds that can be attached on the bone undergoing remodeling surfaces electively; in these locations, they are able to block osteoclastic activity with a different mechanism of action in function of the presence or absence of an amino group. All bisphosphonates for osteoporosis treatment developed so far reduce in a dose-dependent manner bone turnover with a proportional increase in bone density. They are only absorbed to 0.5-5% from the gastrointestinal tract.[33] They are taken orally mainly;[53] patients must take the tablet in the morning at least 30 min before any medication and food, the tablet should be swallowed with a glass of water. The patient also must not lie down for at least thirty minutes after taking the drug and should not eat or take medication for at least 30 min after taking the pill.[53] These drugs are contraindicated in patients who are unable to stand or remain in sitting position for at least 30 min, hypocalcemia, hypersensitivity to bisphosphonates, and in patients with severe renal impairment (creatinine clearance <35 mL/min).[53] They can cause gastrointestinal problems and important species esophageal ulcers in patients with esophageal transit disorders or when taken improperly. Other adverse effects of bisphosphonates include: atrial fibrillation, osteonecrosis of the jaw and atypical stress fractures such as subtrochanteric fractures.[54]

Alendronate

Alendronate is a nitrogen containing bisphosphonate. It has a high affinity for bone mineral binding and high duration of action. It is widely used in the treatment of postmenopausal osteoporosis.[54,55] The treatment in women can be 70 mg once per week or 10 mg daily, for male osteoporosis 10 mg daily.

It is indicated to prevent postmenopausal osteoporosis at a dose of 5 mg daily, to prevent and treat osteoporosis induced by glucocorticoids at dose of 5 mg daily and in postmenopausal women not receiving hormone replacement therapy.

The optimal duration of treatment appears to be 5 years. In the following five years there is no significant increase in the risk of fractures.[56,57]

Ibandronate

Ibandronate or ibandronic acid is a potent nitrogen containing molecule with intermediate bone binding properties between alendronate and risedronate. It is used to treat postmenopausal osteoporosis at fracture risk; it can be taken orally at 2.5 mg daily or 150 mg once a month, or intravenously at 3 mg every 3 months.

It is indicated orally at 150 mg per month to reduce vertebral fractures risk in postmenopausal women with osteoporosis. Instead, ibandronic acid is indicated intravenously at 3 mg dose once a month in postmenopausal osteoporotic women to prevent vertebral fractures when they are intolerant to oral therapy or when there is difficult adherence to treatment.

Risedronate

Risedronate is a nitrogen containing bisphosphonate. It has potent inhibitory effects on osteoclastic bone resorption, but with a lower affinity for bone mineral binding compared with alendronate. It is indicated to treat postmenopausal osteoporosis, to reduce vertebral and hip fractures risk and to treat osteoporosis in men at high risk of fracture. The recommended doses are: 5 mg once daily, 35 mg once per week or one 75-orally for 2 consecutive days of the month.

It is indicated to prevent osteoporosis induced by glucocorticoid in post-menopausal women at a dose of 5 mg daily.[53] Treatment duration can be continued for up to seven years in postmenopausal osteoporotic women.[58-60]

Zoledronic acid

Zoledronic acid is a nitrogen containing bisphosphonate with a potent inhibitory effect on osteoclastic bone resorption and high binding affinity for bone. It has a long duration of action and is the most potent bisphosphonates currently used to treat osteoporosis. It is indicated to treat osteoporosis in postmenopausal women and in men at high fracture risk and treat osteoporosis induced by chronic steroid therapy. The recommended dose is 5 mg intravenously once a year at an interval of at least 15 min. Zoledronic acid is recommended to prevent vertebral of non-vertebral and hip fractures in postmenopausal women with prior vertebral fractures or DXA-proven osteoporosis. It should be considered in patients who are intolerant to oral therapy or in those where adherence to therapy is difficult.

Treatment with zoledronic acid is indicated up to a maximum of three years in women with postmenopausal osteoporosis; after a period of three years without treatment, the risk of fracture should be reassessed to determine the need of additional therapy.[61]

It has been shown that the drug reduces the incidence of vertebral, non-vertebral and hip fractures in postmenopausal women with osteoporosis; furthermore, it appears to reduce mortality when it is given to patients after their first femoral fracture.[62,63]

Denosumab

Denosumab is a monoclonal antibody indicated for the treatment of osteoporosis. It acts by binding the RANKL, by blocking its interaction with RANK and thus its activation. Denosumab, therefore, has a potent inhibitory effect on osteoclastic bone resorption. The recommended dose is 60 mg every six months as a single subcutaneous injection.[10]

Denosumab is used to prevent vertebral, non-vertebral and hip fractures in post-menopausal women with DXA-proven osteoporosis for whom oral bisphosphonate therapy is contraindicated and in men to treat osteoporosis and bone loss resulting from a decrease in testosterone levels due to surgery or drug therapy in patients with prostate cancer as established by the Italian Drug Agency recommendations (*Agenzia Italiana del Farmaco*, AIFA).

Treatment with denosumab is safe and effective for a maximum period of 5 years for the treatment of post-menopausal osteoporosis.[64,65]

It may give: skin infections, cellulitis predominantly, and hypocalcemia; the risk of hypocalcemia increases with the degree of renal failure. It is contraindicated in women with hypocalcemia and should be used with caution in patients with renal impairment.

Strontium ranelate

Strontium ranelate is a molecule containing two strontium atoms bound to ranelic acid. It appears to have dual anti-resorptive and anabolic activity. The recommended dose is 2 g daily taken orally.[66] It must be taken at bedtime and at least 2 h after the meal.[66]

It should be taken for the treatment of severe postmenopausal osteoporosis and in men at high risk of osteoporotic fracture to reduce the risk of vertebral and femoral fractures when other types of therapy are not possible.[66]

It should not be used in patients with a medical history of ischemic heart disease, peripheral arterial disease, cerebrovascular disease and uncontrolled hypertension.[67]

Parathyroid hormone

There are two molecules of parathyroid hormone family: the intact molecule (1-84), PTH, and the N-terminal fragment (1-34), teriparatide. The intermittent exposure to once daily exogenous PTH results in an increase in bone formation more than resorption re-

sulting in anabolic effect and increased bone mass. The effect of parathyroid hormone is maximum at skeletal sites, which are essentially composed of trabecular bone such as the spine. The European Commission withdrew marketing authorization for parathyroid hormone 1-84 in May 2014.[68]

Teriparatide is a recombinant peptide containing the first 34 amino acids (chain N-terminal) that represent the biologically active human parathyroid hormone sequence. It is indicated to prevent vertebral and non-vertebral fractures treatment in postmenopausal women with severe osteoporosis and in patients at high risk of vertebral fractures.[10] The recommended dose is 20 mcg daily administered as a subcutaneous injection and the duration of treatment is limited to 18 months.

It is contraindicated in patients with hypercalcemia and should be used with caution in patients with moderate renal impairment.

Calcitonin

Different evidence showed an increased cancer risk in long-term treatment, so the authorization to use calcitonin for osteoporosis treatment was withdrawn in the UK and Europe.

Hormone replacement therapy

Hormone replacement therapy is defined as a therapy based on estrogen or estrogen/ progestogen combinations, which aims to replace the physiological reduced production of these hormones during postmenopausal period. HRT constitutes a valuable therapeutic approach in the peri- and post-menopausal treatment against osteoporosis.[69] Although these therapies have been shown to reduce the risk of vertebral, non-vertebral and hip fractures, it is preferred to limit its use in younger postmenopausal women at high risk.[10]

There is good evidence that HRT prevents fractures in post-menopausal women, but the risk of cardiovascular disease and cancer has increased in older women and in long-term therapy.[70]

Tibolone

Tibolone is a selective estrogen enzyme modulator (SERM), has estrogenic progestogen and androgen properties, and improves menopausal symptoms.[10] It may be considered to prevent vertebral and non-vertebral fractures in younger postmenopausal women with menopausal symptoms.

Raloxifene

Raloxifene is also a SERM and inhibits bone resorption. It is indicated to treat and prevent osteoporosis in postmenopausal women at a dose of 60 mg daily. It can be taken at any time, regardless of mealtime[53] and reduces the risk of vertebral fractures.

Raloxifene can be considered as a therapeutic option for the prevention of vertebral fractures in postmenopausal women when other treatments are contraindicated or unsuitable.[10]

It is contraindicated in women of childbearing age with a medical history of venous thromboembolism or unexplained uterine bleeding, kidney and liver failure. It should be used with caution in women with a history of stroke or with risk factors for stroke.

Note 79

AIFA introduced Note 79[33,71] governing the prescription of drugs charged to the National Health System (NHS) for the treatment of osteoporosis.

It clarifies that osteoporosis drug treatment is NHS responsibility only for those patients with high risk high of fracture to justify the inevitable risks associated with long-term treatment.

The note should be applied to all people over 50 years old, regardless of sex, where a treatment of corticosteroid at a prednisone dose of 5 mg daily lasting more than three months is foreseen. It can always be applied if there is a bone mass decrease reading DXA or US.

The management of patient with osteoporosis: rationale and objective

Often osteoporosis is silent until it is not complicated by fractures with consequent disability mostly in older age groups. For this reason, a primary and secondary osteoporosis prevention is very important. The aim of this monograph is to provide a correct methodological approach and a diagnostic-therapeutic process to reduce osteoporosis and fractures risk.

The management of osteoporosis: methodology

In order to provide Evidence-Based recommendations for the management of patient with *osteoporosis* first we verified the existence of guidelines about this disease.

So, we conducted a search using the following guidelines database: i) Scottish Intercollegiate Guidelines Network (SIGN); ii) Institute for Clinical Systematic Improvement (ICSI); iii) National Institute for Health and Clinical Excellence (NICE) (NHS evidence); iv) National Guideline Clearinghouse; v) Canadian Medical Association, CMA infobase; vi) New Zealand Guidelines Group; vii) National System Guidelines; viii) Clinical Practice Guidelines Portal; ix) eGuidelines.

The research was carried out by five authors independently, using the term *osteoporosis* as keyword.

The results obtained separately were compared and discussed together subsequently.

The guidelines thus obtained were evaluated using the AGREE instrument (Appraisal of Guidelines, Research and Evaluation II)[72] by four authors. In our opinion, the guidelines submitted shall, be recommended as the most complete and the most valuable.

AGREE II assesses compliance with 23 requirements, meeting 6 domains as the explanation of the purpose, the clarity, the involvement of all stakeholders, the rigor of development, applicability and editorial independence of the same. Each author assessed the compliance of individual requirements with a score from 1 (disagree completely) to 7 (complete agreement). The scores assigned by each author were added within individual domains and reported with the highest and the lowest possible score within the domain based on the included number of requirements and evaluators.

The management of osteoporosis: results

Through the databases listed above, we identified 12 guidelines.

The overall quality of selected guidelines was assessed by 4 authors using the AGREE II and we obtained different results.

The guideline *Management of osteoporosis and the prevention of fragility fractures*[10] was evaluated adoptable by all assessors except one and it was used as the reference guidelines for the preparation of this monograph. It totalized high percentages in almost all domains.

The guideline *Osteoporosis Clinical guideline for prevention and treatment. Royal College of Physicians 2014*[53] was considered adoptable in 100% of cases, but for three assessors with changes. It achieved high rates in different dimensions although never higher than 90%.

Moreover, the guideline *Diagnosis and treatment of Osteoporosis ICSI 2013*[73] was assessed adoptable by 100% of the evaluators, even if for one with changes. Highest scores were obtained in all domains.

The guideline *Osteoporosis: assessing the risk of fragility fracture. NICE 2012*[9] was considered adoptable by a single evaluator, with changes by two evaluators and not adoptable by an evaluator. In six dimensions, it obtained scores between 65%, representing the lowest score of the domain about rigor of development, and 79%, which is the highest score for editorial independence.

The guideline *Guidelines for preventive activities in general practice. National Guideline Clearinghouse 2012*[74] was considered not adoptable by ¾ of the evaluators, and only one can be adopted with modifications. It scored low rates in all dimensions.

Likewise, the guideline *European guidance for the diagnosis and management of osteoporosis in postmenopausal women 2012*[37] was judged not adoptable by all evaluators except one who considered it adoptable with modifications.

The guideline *Osteoporosis Screening, Diagnosis, and Treatment Guideline. Group Health. 2011*[75] was evaluated adoptable with changes by 75% of the evaluators and not adoptable by 25%. In single domains, the percentages were between 47% for domains 2 and 3, and 75% for domain 4.

The guideline *American Association of Clinical Endocrinologists. Medical Guidelines for Clinical Practice for the diagnosis and treatment of postmenopausal osteoporosis 2010*[3] was considered adoptable by 25% of the evaluators, adoptable with modifications by 50% of the evaluators and not adoptable by 25%. The totalized percentages were quite heterogeneous in six dimensions.

The guideline *NOFSA Guideline for the Diagnosis and Management of Osteoporosis National Osteoporosis Foundation of South Africa 2010*[76] was evaluated adoptable by 100% of the evaluators, although by two evaluators with modifications. In all dimensions, the scores are high.

The guideline *Clinician's Guide to Prevention and Treatment of Osteoporosis 2010*[41] was judged to be adopted with modifications for all evaluators; the highest percentage was obtained in size 1 (92%) and 6 (96%) and the lowest percentage in domain 3 (44%).

The guideline *Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men. The Royal Australian College of General Practitioners 2010*[77] was evaluated adoptable by 25% of the evaluators, adoptable with modifications by 50% and not adoptable by 25%. In all dimensions, the totalized percentages were variable, in fact it was very high in the domain 4 (93%) and very low in the domain 3 (53%).

Finally, the guideline *Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada. Canadian Task Force on Preventive Health Care 2010*[78] was judged not adoptable by all evaluators except one who evaluated it adoptable with modifications. It scored low percentages in all domains.

Clinical approach to patient with osteoporosis

The management of patient with osteoporosis consists in six steps which are: i) to identify subjects at risk through history and physical examination; ii) to make blood and instrumental (DXA) exams; iii) to exclude secondary osteoporosis; iv) to correct modifi-

able risk factors; v) to begin drug therapy based on the calculated risk with algorithms in use and on BMD values obtained through DXA; vi) to monitor answer to treatment. In Figures 1 and 2[10,33,39] diagnostic and therapeutic algorithm are schematized shortly.

Conclusions

Osteoporosis and osteoporotic fractures represent an important and frequent cause of disability mostly in older age groups. An appropriate expertise in the management of this disease by internists is imperative. A correct methodological approach, an adequate diagnostic protocol and an effective pharmacological treatment are important for primary and secondary osteoporosis prevention in order to decrease fractures incidence and improve the patients' quality of life.

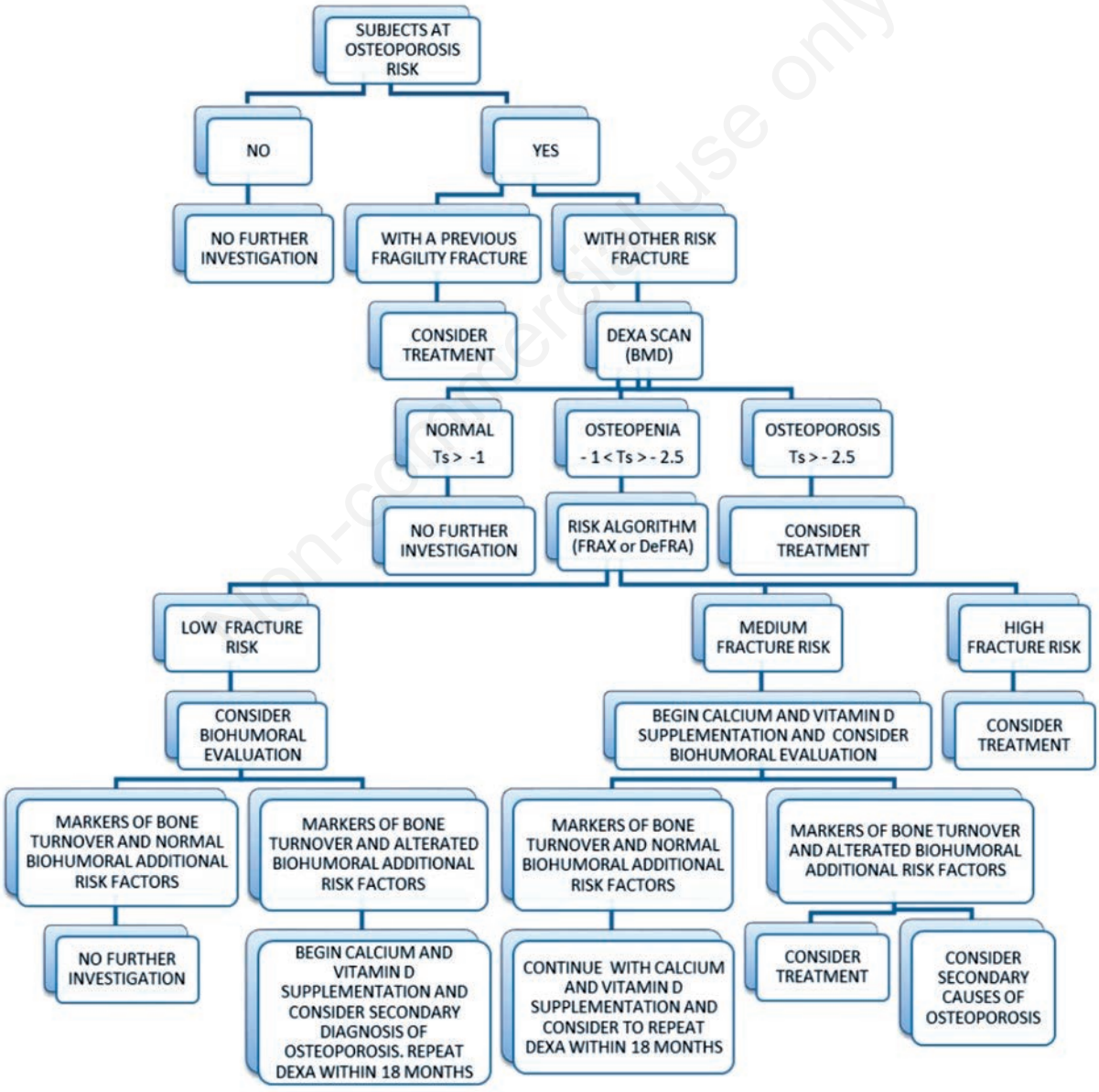

Figure 1. Diagnostic algorithm modified from *SIOMMS*, 2013 and *Kanis et al.*, 1997.[33,39]

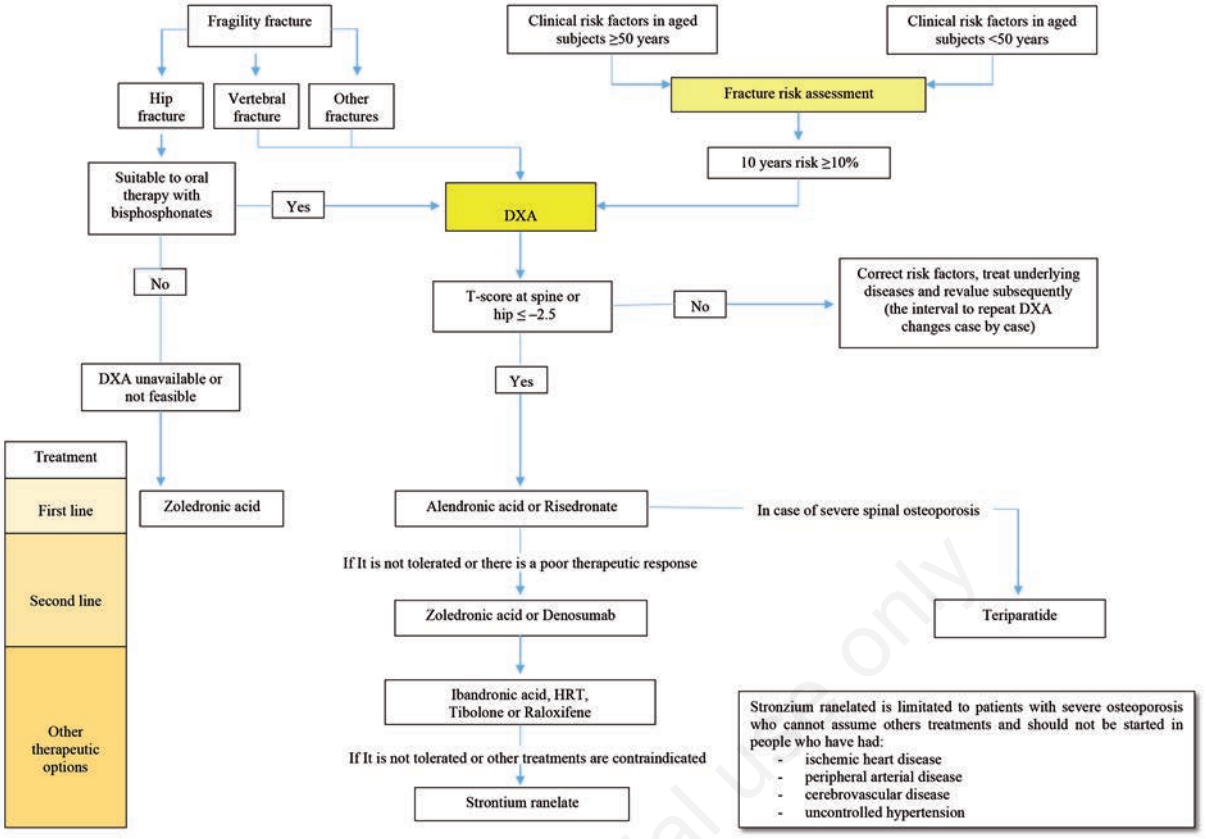

Figure 2. Treatment algorithm modified from *Scottish Intercollegiate Guidelines Network*, 2015.[10]

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