Guidance for the diagnosis, prevention and therapy of osteoporosis in Italy

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Summary

Osteoporosis poses a significant public health issue. In recent years, International and National Societies have developed Guidelines for the diagnosis and treatment of this disorder, with an effort of adapting specific tools for risk assessment on the peculiar characteristics of a given population. The *Società Italiana dell'Osteoporosi, del Metabolismo Minerale e delle Malattie dello Scheletro* (SIOMMMS) has recently revised the previously published Guidelines on the diagnosis, risk-assessment, prevention and management of idiopathic postmenopausal osteoporosis, also focusing on male and secondary osteoporosis. These recommendations are based on systematic reviews of the best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on leading experts' experience and opinion, and on good clinical practice. Nonetheless, the practical management of osteoporosis is greatly influenced by economic reimbursement policies, particularly for secondary forms of osteoporosis. The refinement of risk assessment, the long-term treatment of osteoporosis and the prevention and management of disease-associated bone loss constitute open issues.

KEY WORDS: guidelines; risk factors; fractures; DEXA; secondary osteoporosis; male osteoporosis.

Background and epidemiology

Osteoporosis is characterized by low bone mass and structural deterioration of bone tissue, with a consequent increase of bone fragility, with consequent fractures not related to a significant trauma. The prevalence of osteoporosis rises markedly with age and in women this rises from 2% at 50 years to more than 25% at 80 years. It is estimated that in Italy 3,5 million of women and 1 million of men suffer from osteoporosis, with more than 90.000/year hip fractures in the population older than 50 years. Risk of fracture is also increased by factors such as lifestyle, drug treatments, family history, and other conditions that cause secondary osteoporosis.
Recommendations are based on systematic reviews of the best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available recommendations are based on the experts' experience and opinion of what constitutes good practice.
Recommendations are published under the denomination of "Guidance" or "Guidelines", both a national and continental levels, both from institutional boards or groups of independent experts, both dedicated to the osteoporosis in general or to preselected forms of osteoporosis (1-25). The recommendations are intended for all physicians who provide care to patients at risk for or with overt osteoporosis.
This article summarizes the most recent recommendations from the *Società Italiana dell'Osteoporosi, del Metabolismo Minerale e delle Malattie dello Scheletro* (SIOMMMS), focusing on grade A recommendations ("good evidence to recommend the action"), as based on lines of evidence 1-3 (available from http://www.siommms.it), mainly obtained by data from large randomized controlled trials (RCTs) on postmenopausal osteoporosis.

Risk factors

The pathogenesis of osteoporosis is multifactorial. Thus, fracture risk depends upon several independent risk factors. Reduced bone mineral density (BMD), previous fragility fracture, age and a positive family history have best evidence in predicting osteoporotic fractures, as shown in Table 1. Although BMD is used to define the diagnostic threshold, the threshold for pharmacological intervention and the absolute risk of fragility fracture are the result of the independent influences of the various risk factors. In adult osteoporosis, different factors may directly influence BMD (gender, calcium intake, physical activity, age of menopause), or propensity to fall (physical disability, environmental cues, alcohol consumption, drugs such as benzodiazepines or diuretics) or both (age, smoking, low body weight, vitamin D deficiency).
Genetics has a strong influence in determining BMD and bone microarchitecture. Although several polymorphisms (estrogen receptor, vitamin D receptor, COLIA1) have been linked to low BMD and increased risk of low-energy fractures, they account overall for only the 30% of variability of BMD. Thus, they cannot be taken into account for defining risk of fracture.

Diagnosis

The screening and evaluation of postmenopausal or senile osteoporosis must include both a biochemical and an instrumental evaluation, in order to exclude secondary forms of osteoporosis and better define the risk of fracture.

Biochemical tests

First-line diagnostic tests are essential (grade A recommendation)

Table 1 - Risk factors for low BMD and fragility/low-energy fractures: lines of evidence (according to levels of evidence (level 1: evidence from RCTs or metanalyses of RCTs, level 2: evidence from prospective cohort studies or poor quality RCTs; level 3: evidence from case-control studies or retrospective cohort studies).

Risk factors	for BMD	for fractures
BMD	1	1
Age	1	1
Fragility fractures after 40 yrs of age	2	1
Family history of fragility fractures	2	2
Chronic corticosteroid therapy	1	1
Premature menopause (<45 yrs)	1	2
Weight	1	2
Reduced calcium intake	1	1
Reduce physical activity	2	2
Smoking	2	1
Alcohol abuse	2	3
Risk factors for falls	---	1

Table 2 - Recommended first-line biochemical diagnostic tests in osteoporosis.

First-line diagnostic tests
Erythrocyte sedimentation rate (ESR)
Complete blood count
Serum protein electrophoresis
Serum total alkaline phosphatase
Serum creatinine
Serum calcium (corrected for albumin)
Serum phosphate
Urinary (24 hr) calcium

in the initial evaluation of an osteoporotic patient and for the differential diagnosis (Table 2). Taken all together, if normal, they can reasonably exclude with a 90% probability secondary forms of osteoporosis. Focused second-line diagnostic tests are only advisable when a secondary etiology is suspected (Table 3), and cannot be proposed in the initial screening because of the high costs.

Serum or urinary markers of bone formation (bone alkaline phosphatase, osteocalcin, propetides of type 1 collagen) and bone resorption (hydroxyproline, pyridinium crosslinks, crosslinked telopeptides of type I collagen, osteoclast enzymes, non-collagenous proteins of bone matrix) can be measured to assess the risk of fracture in postmenopausal women independently of age and BMD (level of evidence: 2). Indeed, several prospective studies have demonstrated that the levels of markers of bone turnover correlate with risk of subsequent fracture in postmenopausal women. At baseline, if high, they indicate an increased bone remodeling often associated to active bone loss. During a specific treatment they can be monitored in order to check adherence and efficacy of the anti-resorptive or bone-formative drug. Nonetheless, at the moment they cannot be included as the first-line tests in the usual evaluation of osteoporosis and/or to better define fracture risk, also because of a wide biological variability (26).

Instrumental evaluation

Bone mineral measurements must provide reliable data to be used for diagnosis, prognosis (risk assessment) and patient monitoring. For these purposes, the main feature of a given technique is the ability to predict fractures. Dual energy X-ray absorptiometry of bone

Table 3 - Second-line biochemical diagnostic tests in osteoporosis.

Second-line diagnostic tests
Ionized calcium
TSH
PTH
25 hydroxyvitamin D
Serum cortisol after 1 mg dexamethasone suppression
Total testosterone (males)
Serum and urine immunofixation electrophoresis
Antitransglutaminase antibodies
Disease-specific tests (ferritinemia, tryptase)

(DEXA) is the most widely used technique to assess BMD, i.e. the amount of bone mass per unit area (g/cm^2, areal density) of the whole skeleton as well as of specific sites, which include those more prone to fractures, and bone mineral content (BMC, g/cm) (27). DEXA is today's established standard for estimating bone mineralization (grade A recommendation). While total BMD does not predict the risk of fracture, areal BMD obtained by DEXA at specific sites (lumbar spine, proximal femur, distal radius, proximal radius, heel) is the best predictor of fracture risk particularly at the corresponding site in postmenopausal women (level 1 of evidence) and strongly correlates with bone strength, as assessed *in vivo* on isolated bones. DEXA is usually performed at the level of lumbar spine and proximal femur, although there are site-specific limitations of DEXA precision in persons older than 65 years since lumbar spine BMD values can be altered by the presence of osteoarthritis, fracture deformities and/or extraskeletal calcifications. T-score parameter compares the BMD value with the young-normal mean BMD, expressing the difference as a standard deviation (SD) score, while Z-score parameter refers to the number of SDs by which the measured BMD differs from the mean BMD expected for age and gender. The definition of postmenopausal osteoporosis by OMS is based upon a T-score < -2.5 as defined by DEXA. For each SD reduction (T-score), approximately corresponding to 10% reduction in BMD, the relative fracture risk increases 1.5-3 times.

Baseline DEXA evaluation can be proposed to women older than 65 years in order to predict fracture risk. In younger individuals, DEXA can be useful in particular conditions and/or in the presence of other risk factors such as age of menopause<45 years, low body weight (<57 Kg), smoking, drugs or other conditions associated with bone loss. In the follow-up DEXA can be used to monitor the response to a specific treatment and/or conditions characterized by rapid bone loss (grade A recommendation). In any case, since postmenopausal women experience a 0.5-2% yearly reduction in BMD and common treatments increase BMD by 1-6%, and taking into account a least significant change of 2-4% depending on the specific measurement site, it is advisable to perform DEXA scans not before 1 year for the spine, 1.5-2 years for proximal femur and over 2 years for appendicular sites. In general, DEXA of lumbar spine is preferred in the follow-up since it is more sensible to variations induced by specific treatments or by active bone loss. In particular settings characterized by rapid bone loss (i.e. glucocorticoids treatment, primary or secondary hyperparathyroidism, malignancies) shorter intervals between lumbar DEXA scans can be proposed. Conversely, appendicular assessment is scarcely useful in the follow-up, since detectable significant variations can be only appreciated in the long-term.

Bone mineral evaluation by DEXA can be enriched but not replaced by bone trophism assessment by means of other techniques such as quantitative computerized tomography (QCT) and bone ultrasonography. QCT and peripheral QCT (pQCT) provide volumetric 3D mineral density (g/cm^3), allowing a separate assessment of cortical and trabecular bone density (28). Nonetheless, DEXA

is most widely preferred because of lower costs and radiation dose, higher accuracy, shorter image acquisition time. Parameters of bone ultrasonography are able to independently predict the risk of vertebral and non vertebral osteoporotic fractures in postmenopausal women and men older than 65 years (29). If combined with the evaluation of other risk factors, they improve and refine the prediction of risk of fracture. The results of bone ultrasonography and DEXA are sometimes discordant, thus indicating that, although these two techniques can predict independently the risk of fracture, ultrasonographic T-score < -2.5 cannot be used to diagnose osteoporosis. In addition, given the high variability among the various ultrasound machines, the results are not easily comparable. In particular settings such as epidemiological surveys or when DEXA is not readily available, bone ultrasonography represent a valid option to screen patients at risk of osteoporosis, offering advantages in terms of low costs, absence of radiations and easy transportation of the device. Good ultrasonographic parameters in the absence of other specific risk factors indicate that the risk of osteoporotic fracture is low. Conversely, low ultrasonographic values combined with the presence of other risk factors can be sufficient to define the intervention threshold. By any means bone ultrasound can be recommended in treatment monitoring (grade B recommendation).

Vertebral morphometry

Vertebral morphometry is generally used to assess vertebral deformities and this may improve fracture risk evaluation (30). Genant's semiquantitative method performed on a standard radiography is the gold standard to detect vertebral fractures (grade A recommendation). Lateral images of the spine (from T4 to L4) obtained by DEXA (vertebral fracture assessment or VFA) can also be used to detect vertebral deformities (grade B recommendation). While measurement of vertebral height on an X-ray image (vertebral morphometry) can fail to detect vertebral fractures at baseline, a 20% reduction in vertebral height during follow up is diagnostic of new fracture (grade A recommendation).

Non-pharmacological interventions

Non-pharmacological recommendations can be adopted both as preventive measures and as treatment adjuncts. Prevention of osteoporosis and fragility fractures acts on modifiable risk factors such as smoking, alcohol abuse, environmental cues predisposing to falls, implementing physical activity and optimizing calcium intake. These habits can be recommended and implemented also in the case of overt osteoporosis, in individuals at high risk of fracture, who require specific pharmacologic treatment which is not recommended for preventing osteoporosis, with the exception of chronic corticosteroid therapy.

Calcium intake

Intake recommendation for calcium or Recommended Dietary Allowances (RDAs) refer to the daily amounts of calcium required for bone health and to maintain a positive calcium balance in healthy people (Table 4). It is estimated that calcium intake is generally much lower of daily calcium requirements, particularly in elders. The implementation of calcium in the diet (mainly contained in dairy products and calcium-rich mineral water) is preferred to calcium supplements which have been associated with a higher risk of nephrolithiasis and vascular calcifications (levels 2 of evidence; grade A recommendation). Calcium supplements are advisable only when dietary calcium is still insufficient and the amount (in general between 500 and 1000 mg) must be tailored on the specific needs/requirements of each individual. Calcium alone has been proven to be slightly effective in reducing fracture risk in elderly people and also in reducing falls when supplemented with vitamin D, especially in people with deficient intake.

Table 4 - Recommended Dietary Allowances (RDAs) of calcium at different ages. ERT = estrogen replacement therapy.

Age	RDA (mg)
1-5 years	800
6-10 years	800-1200
11-24 years	1200-1500
25-50 years	1000
Pregnancy or lactation	1200-1500
Postmenopausal women +ERT/men 50-65 years	1000
Postmenopausal women – ERT/men > 65 years	1500

Vitamin D supplementation

Vitamin D supplementation is effective also in primary prevention in elders (level 1, grade A recommendation). The cumulative dose can be administered daily, weekly, or monthly, avoiding single annual supplementation, which has been associated with adverse effects in recent studies. Oral administration is preferred. Intramuscolar administration is reserved to severe cases of malabsorption. Hydroxylated metabolites of vitamin D such as 25 hydroxyvitamin D or 1a hydroxylated metabolites are reserved to patients with liver or kidney failure and hypoparathyroidism.

Preventive and maintenance regimens are advisable in at risk individuals and in patients where a previous deficiency has been corrected, respectively. In particular cases (severe malabsorption syndromes, poor nutritional status, obesity, chronic therapies with anticonvulsants, glucocorticoids) higher doses can be required.

The cumulative dose of vitamin D is higher in the case of documented vitamin D deficiency. In order to obtain serum 25hydroxytamin D [25(OH) D] levels of 30 ng/ml, which is considered by many experts the proper value needed to guarantee optimal mineral and skeletal homeostasis, the initial dose will mainly depend on baseline 25(OH) D levels and body mass index. Although there is lacking evidence whether rapid vitamin D repletion could offer some advantages, the estimated cumulative dose of vitamin D is generally administered within 1-3 months (Table 5), followed by a maintenance regimen, trying to avoid fluctuations of 25(OH)D levels in the long-term.

Given the wide therapeutic range of vitamin D supplementation, it is generally not necessary to retest vitamin D status [by measuring serum 25(OH) D levels], especially during maintenance. If a deficiency is suspected and/or in particular conditions (see above), testing and retesting can be advisable.

An adequate calcium and vitamin D intake is essential in the case a specific treatment is established. Insufficient calcium intake and/or poor vitamin D status represent the most common condition of non-responders to conventional anti-osteoporotic therapies.

Physical activity

Only weight-bearing exercises have been proven to be effective in improving bone mass both in young adults and postmenopausal women. However, since randomized control trials are lacking for

Table 5 - Estimated dose of vitamin D to be administered to correct vitamin D deficiency/insufficiency and long-term maintenance of optimal 25(OH) D status.

Baseline serum 25OH D	Cumulative dose of vitamin D (IU)	Maintenance regimen (IU)
<10 ng/ml (25 nmol/L)	1.000.000	2000
10-20 ng/ml (25-50 nmol/L)	600.000	1000
20-30 ng/ml (50-75 nmol/L)	300.000	800

younger subjects, these activities cannot be recommended in terms of primary or secondary prevention (level 2 of evidence). Conversely, weight-bearing activities prevent 1% of annual bone loss in postmenopausal women, with the major benefits at the level of the spine with high-impact exercises (level 1 of evidence).
Although it is not demonstrated that walking (at least 30 minutes/day) yields direct effects on bone mass, it represents a good advice in particular for elders since it decreases risk of falling and improve vitamin D status. Other interventions such as customized muscular rehabilitation programs with gait improvement may decrease the risk of falling (level of evidence 1). There is increasing recognition that the use of certain medications contributes to falls. Thus, a reduction in the use of diurectics, antidepressants, neuroleptics and benzodiazepines is advisable. All in all, proper vitamin D supplementation, personalized physical exercises and intervention aimed to reduce environmental obstacles are highly advisable, particularly in elderly people (grade A recommendation).

Pharmacologic treatment

Identification of therapeutic threshold

Treatments for osteoporosis are reserved to individuals with overt osteoporosis, with or without previous fragility fractures, with the aim to prevent the first fragility fracture and/or to avoid subsequent fractures. While non-pharmacological interventions and removal of modifiable risk factors are advisable for everybody, specific treatments are prescribed after risk assessment and cost effectiveness analyses. Data from RCTs provide simple epidemiological parameters such as NNT (number needed to treat) and NNH (number needed to harm), which indicate the average number of patients who need to be treated to prevent one additional fracture or the average number of patients who needed to be treated in order to detect an adverse event, respectively.
In the individual, it is not acceptable the use of the diagnostic threshold (T-score < -2.5) for therapeutic intervention. Besides BMD, the evaluation of several risk factors which contribute independently to fracture risk, is mandatory in order to estimate overall individual risk (often referred to as 10 year fracture risk, 10YFR), as above stated. Indeed, a positive history of fragility fracture or chronic corticosteroid therapy at equivalent prednisone dose >5 mg/day, being associated to a high fracture risk, can drive the decision to start a treatment independently of BMD values. Specific algorithms have been developed for this purposes. FRAX® algorithm is based on data from the 2008 WHO Technical Report (mainly based on Swedish epidemiological data) on the correlation between 10 year fracture risk at multiple sites or femur, and several risk factors, such as age, BMI, femoral neck T-score and others (www.shef.ac.uk/FRAX/) (31-33). While FRAX® algorithm is reliable for the relationship between fracture risk and continuous variables (age, T-score, BMI) and consistent with other predictive tools, problems arise when dichotomous variables of "clinical risk factors" are incorporated in the formula. The weight of family history appears overestimated. In addition, while rheumatoid arthritis is included, other diseases causing secondary osteoporosis (primary hyperparathyroidism, hyperthyroidism, Cushing syndrome, connectivities) have been not taken into account.
In order to better define the threshold for therapeutic intervention, an Italian revision and correction of these limitations have originated a new algorithm, *derived fracture risk assessment* (DeFRA®, http://defra-osteoporosi.it), which introduce graduated dichotomous variables (smoking, corticosteroid dose), previous fragility fractures at different sites, other diseases potentially causing bone loss, adjusting for different Swedish fracture rates, using the same factorial adopted in FRAX® for Italy. DeFRA® is a dynamic tool since it can be modified and re-validated on the basis of new data acquisitions and results from new longitudinal studies or meta-analyses.
Evaluation of fracture risk by means of specific algorithms can help to identify treatment threshold but must be customized on the basis on cost-effectiveness and extraskeletal effects of a chosen compound, individual evaluation (presence of comorbidities), individual perception of the risk of fracture.
In Italy, the different first-line antiosteoporotic drugs (i.e. alendronate, risedronate, ibandronate, raloxifene, strontium ranelate) are currently reimbursed under "Nota 79" criteria, which identifies as eligible for active treatment postmenopausal women with a history of at least one vertebral or hip fragility fracture or a hip BMD/calcaneal ultrasonography < -4 T-score or < -3 T-score plus other risk factors (family history of fragility fractures, rheumatoid arthritis or other connetivities, previous Colles' fracture, premature menopause < 45 years, chronic corticosteroid therapy).
The efficacy in increasing BMD and reducing fracture risk of the classical and new antiresorptives (alendronate, oral clodronate, etidronate, ibandronate, risedronate, zoledronate, denosumab), osteoanabolics (PTH1-34, PTH1-84), antiresorptive/osteoanabolic (strontium ranelate) at the different sites have been reported in Table 6 (34-36).

Table 6 - Effect on BMD and fracture risk (fx) at different sites of available antiosteoporotic treatments: level of evidence.

Drug	BMD	Vertebral fx	Non-vertebral fx	Hip fx
alendronate	1	1	1	1
clodronate 800mg/die/os	1	1	1	
etidronate	1	1		
ibandronate	1	1	1***	
risedronate	1	1	1	1
zoledronate	1	1	1	1
teriparatide	1	1	1	
PTH1-84	1	1		
strontium ranelate	1**	1	1	1***
ERT*	1	1	1	1
raloxifene	1	1		
bazedoxifene	1	1		
denosumab	1	1	1	1

* no longer recommended because of side effects;
** also determined by strontium high-molecular weight per se;
*** as evidenced in post-hoc analyses.

Other drugs that have been tested in the past for the treatment of osteoporosis (i.e. parenteral or intranasal calcitonin, ipriflavone, thiazide diuretics, calcitriol, fluorides, phytoestrogens), cannot be proposed today as an active treatment since the evidence of antifracture efficacy is lacking and/or because they have been poorly studied.

Bisphosphonates (BPs)

BPs currently approved in Europe (and in Italy) for the treatment of osteoporosis are: etidronate, clodronate, alendronate, risedronate, ibandronate and zoledronate.

Etidronate and clodronate increase vertebral BMD and maintain BMD at femoral neck (level of evidence: 1). Clodronate efficacy in reducing clinical fractures has been proven for the oral formulation (800 mg/daily), but correlation between the oral and parenteral form has not been proven, so far. Administered dose of etidronate is suboptimal in terms of correcting mineralization defects. Thus, these two treatments are second-choice alternatives in the treatment of osteoporosis.

Conversely, the efficacy of alendronate and risedronate in reducing vertebral and non-vertebral (and hip) fractures by 40-50% in 3 years is widely proven.

Ibandronate has been shown to reduce vertebral and non-vertebral fractures when administered orally as 150 mg/monthly (or 3 mg I.V./3 months).

Zoledronate (5 mg I.V./year) is able to significantly reduce the risk of vertebral, non-vertebral and hip fractures. When administered 2 weeks after hip fracture, it is able to reduce further clinical fractures, reducing overall mortality rate.

Gastro-intestinal tolerability issues arose with the amino-BPs. However, with the weekly or monthly administration of these drugs properly taken, the incidence of these events has decreased. Regarding the osteonecrosis of the jaw (ONJ), mainly observed with intravenous BPs and due to infective causes, the Italian guidelines remind to the recommendations contained in a joined document by SIOMMMS and ANDI (*Associazione Nazionale Dentisti Italiani*). In general, a good oral hygiene and/or the use antibiotics during surgical procedures decrease the risk of ONJ (37). Also bisphosphonate-induced acute phase response is mainly observed with intravenous BPs at the beginning of the treatment and can be prevented by the administration of anti-inflammatory drugs. Atipical subtrochanteric fractures constitute an open issue and seem to be correlated to the length of the therapy. This has risen concerns whether BPs should be continued indefinitely or should be stopped. In this regard, the guidelines by SIOMMMS suggest that during bisphosphonate therapy fracture risk must be re-evaluated in order to suspend the drug for 12-24 months after 5 years of treatment in individuals at low risk of fractures. On the other hand, therapy should be continued up to 10 years in individuals at high risk of fracture (T-score at the hip < -2.5, or with prevalent vertebral fractures and a T-score at the hip of -2).

Denosumab

The inhibition of the RANKL by denosumab (60 mg subcutaneously/6 months) yields similar anti-resorptive effects of BPs with some important differences, since it does not depend on the rate of bone turnover (with positive effects also at the level of cortical bone), the effect is selective for bone and stops when the drug is discontinued, and the increments in BMD are greater, with an antifracture efficacy of -67% at vertebral sites and -40% at the hip. So far, its use in Italy is limited for reimbursement purposes (postmenopausal women with a previous fragility fracture at the spine or the hip, aged > 70 years, with T-score at the hip < -3). Postmarketing pharmacovigilance by AIFA serves to monitor possible side effects (infections, ONJ, atypical fractures).

Parathyroid hormone

Teriparatide (PTH 1-34) and full-length molecule (PTH 1-84), administered subcutaneously daily, up to 24 months, are anabolic therapies approved for severe postmenopausal osteoporosis. Major increments in vertebral BMD are observed with both treatments (+9.7% and 6.5%, respectively), along with a reduction in the risk of vertebral fractures (for both) and non-vertebral fracture (for teriparatide). These therapies are reserved for patients with more severe forms of osteoporosis (3 severe vertebral fractures or 2 severe vertebral fractures and a hip fracture) or when undergoing to a new vertebral or hip fracture while being treated with other anti-resorptive treatments.

Strontium ranelate (SR)

The antiresorptive-osteoformative SR (SR, 2 g/daily) has been proven to reduce the risk of vertebral and non-vertebral (and hip) fractures, also in the long term (being the only drug with 5 years controlled clinical evaluation). It is currently approved for the treatment of postmenopausal osteoporosis. Although the increase in BMD has been attributed at least in part to the accumulation of strontium in bone, the variations in BMD are correlated to reduction in fracture risk. Strontium ranelate is contraindicated in case of current of previous venous thromboembolic events (VTE), temporary or permanent immobilization and the need for continued treatment must be re-evaluated in patients > 80 years who are at increased risk for VTEs. Rare serious skin reactions (DRESS syndrome, Drug Rush with Eosinophilia and Systemic Symptoms) may occur within the first weeks of treatment and requires treatment discontinuation.

Estrogen replacement therapy (ERT)

ERT reduces the risk of osteoporotic fractures at any site, as demonstrated by the Women Health Initiative (WHI) study, along with a reduction in the risk of colon-rectal cancer. The counterpart is an increase in the rate of breast cancer, cardiovascular events, VTEs, mainly due to the association of the progestin in non- hysterectomized women. For this reason, ERTs cannot be recommended as a treatment of osteoporosis and/or to prevent osteoporotic fractures. However, in the first years after menopause, a short-term treatment with ERT can be proposed to women suffering from climacteric symptoms (38).

Selective estrogen-receptor modulators (SERMs)

Raloxifene prevents postmenopausal bone loss, determining an increase of 2-3% in BMD of osteoporotic women. Raloxifene (60 mg/daily) has been able to reduce vertebral fracture risk both in women with preexisting vertebral fractures (30% reduction) or without previous fractures (60% reduction), along with a significant decrease in the risk of invasive breast cancer. A reduction in non-vertebral fractures has not been demonstrated. A common side effect is an increase in vasomotor and climacteric symptoms. A history of VTEs is contraindication to therapy.

Bazedoxifene has been shown to reduce risk for vertebral fractures by 42% and 32% at 3 and 5 years, respectively. In a post-hoc analysis, a reduction in non-vertebral fractures at 3 and 5 years has been demonstrated in patients with high risk of fracture. Basedoxifene displays a greater antiestrogen effect at the level of the uterus.

Vertebroplasty and kyphoplasty

Vertebroplasty and kyphoplasty (the intravertebral high-pressure injection of methyl methacrylate and the re-expansion of vertebral body with the injection of methyl methacrylate at low pressure, respectively) have been proposed to treat painful vertebral fractures. The evidence of long-term benefits of these procedures is lacking. These procedures cannot be recommended to asymptomatic patients. In any case, a proper specific antiosteoporotic treatment must be advised after these procedures in order to reduce fracture risk in adjacent vertebrae.

Peculiar types of osteoporosis

Male osteoporosis

It is estimated that 20% of hip fractures occurs in men and the prevalence of vertebral fractures is half the prevalence estimated for women. In addition, fragility fractures in males yield greater morbidity and mortality. Although osteoporosis in men is now recognized as a major health issue, it is frequently misdiagnosed. Most (two thirds) male osteoporosis is considered to have a secondary cause such as hypogonadism, alcohol abuse, multiple myeloma, exogenous or endogenous glucocorticoids excess, malabsorption, primary hyperparathyroidism. Thus, these pathologic conditions have to be always excluded in the diagnostic workup. In the case of a fragility, low-energy fracture in men, DEXA scan is a first-line procedure to define fracture risk (level of evidence: 1) DEXA is also recommended in men of any age with a major risk factor (fragility fractures, positive family history for fragility fractures, corticosteroids or other therapies causing bone loss) or in men > 60 years with a major risk factor or ≥ 2 minor risk factors (level of evidence: 2, grade A recommendation). A T-score value < -2.5 (relative to young adult male) can be adopted in males to define osteoporosis (level of evidence 2, grade B recommendation). The value of baseline bone ultrasound is similar in both sexes (level of evidence: 2). Still, it is not recommended in the follow up.

Vertebral antifracture efficacy of common antiresorptives and teriparatide in male osteoporosis is similar to the one observed in postmenopausal women (level of evidence: 1; grade A recommendation). For this reason, alendronate, risedronate, zoledronate and teriparatide have been approved also for male osteoporosis, although there are no data on the efficacy in the reduction of the risk of non-vertebral fractures. Strontium ranelate, although not included in SIOMMMS Guidelines, has been recently approved by EMA (European Medicines Agency) for treatment of male osteoporosis.

Specific recommendations for secondary osteoporoses

Secondary osteoporosis results from chronic conditions, which contribute to accelerated bone loss (Table 7). Secondary osteoporosis occurs in two thirds of men, more than 50% of premenopausal women and about one fifth of postmenopausal women (39, 40).

Glucocorticoid-induced osteoporosis

A rapid, dose-dependent bone loss (up to 15%) particularly at trabecular sites occurs within the first 6-12 months after initiation of corticosteroid therapy. The risk of fracture is increased just after 3 months of treatment and continues to rise up to 20 fold. Fracture risk during glucocorticoid therapy is significantly greater than the risk estimated by the corresponding BMD values. Fracture risk rapidly decreases when the treatment is stopped. Also the use of intranasal corticosteroids is associated to bone loss and increased fracture risk (41).

The majority of the guidelines agree to set the threshold for therapeutic intervention on prednisone-equivalent dose of 7.5 mg of prednisone equivalents/day, even if doses of 2.5-7 mg/day are also associated with bone loss, and on T-score of -1.5/-1 (18-20). The Italian Guidelines recommend that people aged >50 years, on prednisone-equivalent dose ≥ 5 mg/day should be treated, regardless BMD values.

All patients started on corticosteroids should receive calcium (1000 mg/day) and vitamin D (500 IU/day) (level of evidence: 1; grade A recommendation). ERT or testosterone replacement therapy (TRP) should be considered in the case of postmenopausal women or hypogonadism (level 1 of evidence; grade A recommendation). BPs such as alendronate, risedronate and zoledronate are effective both in the prevention and treatment of glucocorticoid-induced osteoporosis (level of evidence: 1; grade A recommendation). Teriparatide is more effective than alendronate in preventing bone loss and fractures in glucocorticoids-induced osteoporosis. In Italy teriparatide is prescribable in patients with one severe or two moderate vertebral fractures ("Nota 79").

Primary hyperparathyroidism (PHPT)

Bone loss in PHPT occurs mainly at the level of cortical bone. Parathyroidectomy is the only curative treatment for this disease (grade A recommendation). The increased risk of fracture documented during active disease reverts to normal after surgery. Mild forms of PHPT (age>50 years, calcemia within 1 mg/dl above the upper limit of normal range, creatinine clearance>60 ml/min, absence of nephrolithiasis, T-score>-2.5 at any site, no previous fragility fractures) can be followed without surgery, even if studies have shown that they would benefit from surgery (42). In patients with osteoporosis and contraindications for surgery, antiresorptives (alendronate, ERT, raloxifene) have been shown to increase bone mass, although no data are available on fracture risk reduction (level of evidence: 2, grade B recommendation). Cinacalcet reduces calcemia but has no effect on BMD. All patients with PHPT should be advised to maintain a normal calcium intake (grade A recommendation). Vitamin D deficiency, which appears to be associated with a more severe skeletal disease, should be corrected (grade A recommendation) (43).

Transplantation osteoporosis

The long-term or even indefinite therapy with immunosuppressant drugs and corticosteroids after transplantation causes a bone loss which is maximal within the first year and usually persisting in the following years (44). Fractures are common in that 10% of kidney-transplanted patients and 30% of liver-, lung- and/or heart-transplanted patients experience low-energy fractures. Age, sex (female), preexisting disease contribute to fracture risk. It is recommended to obtain a DEXA scan just after transplantation and yearly afterwards (grade A recommendation). A spine X-ray must be obtained yearly in the first 2-3 years after transplantation (grade A recommendation). No data on the antifracture efficacy of BPs after organ transplantation are available. Alendronate, pamidronate, ibandronate and zoledronate have been shown to increase BMD without effect on residual kidney function (grade A recommendation).

Osteoporosis due to cancer treatment

Aromatase inhibitors and GnRH analogs are widely used to induce hypogonadism after surgery for breast cancer and prostate cancer. These drugs cause a significant bone loss, associated with an increased fracture risk (21, 22). AminoBPs and denosumab have proven to be effective in the prevention and treatment of these forms of secondary osteoporosis, although no data are available regarding their effects on fractures. The efficacy of zoledronate (4 mg I.V./6 months) is greater, particularly if administered at the beginning of the anticancer treatment in women. In men receiving GnRH agonists for prostate cancer zoledronate (4 mg/year) is effective in preventing and treat bone loss. In the absence of specific indications, not included in the "Nota 79" criteria neither for BPs or denosumab, the recommendation for initiating a specific treatment is to consider these hypogonadic patients as postmenopausal women/hypogonadic men.

Osteogenesis imperfecta (OI)

OI is a genetic disease due to a defect in type I collagen production with structural alteration in skeletal tissue. Among the 8 different forms, type 1 is the most frequent form. These subjects suffer multiple fragility fractures since young age and they can be misdiagnosed as juvenile osteoporosis of a different genetic origin. OI type 3 is more severe and it is characterized by multiple fractures of the long bones, which result in multiple deformities. The-

Table 7 - Secondary causes of osteoporosis.

Endocrinopathies Hypogonadism Hypercortisolism Hyperparathyroidism Hyperthyroidism Hyperprolactinemia Diabetes mellitus type 1 Acromegaly GH deficiency	**Collagenopathies** Osteogenesis imperfecta Ehlers-Danlos syndrome Marfan syndrome Homocystinuria
Hematologic diseases Multiple myeloma Myelo- and lymphoproliferative disorders Systemic mastocytosis Thalassemia	**Organ transplantation**
Gastrointestinal diseases Chronic liver diseases Celiac disease Inflammatory bowel diseases Gastrectomy Lactose intolerance Intestinal malabsorption Pancreatic insufficiency	**Drugs:** cyclosporine, thyroid hormones in suppressive doses in postmenopause, anticonvulsants, anticancer drugs (aromatase inhibitors, GnRH agonists and antagonists), methotrexate, anticoagulants, loop diuretics
Rheumatic diseases Rheumatoid arthritis Systemic lupus erytematosus Ankylosing spondylitis Psoriatic arthritis Scleroderma	**Alcoholism**
Kidney diseases Hydiopathic hypercalciuria Renal tubular acidosis Chronic kidney disease	**Smoking**
Rheumatic diseases Rheumatoid arthritis Systemic lupus erytematosus Ankylosing spondylitis Psoriatic arthritis Scleroderma	**Drug addiction**
Kidney diseases Hydiopathic hypercalciuria Renal tubular acidosis Chronic kidney disease	**Immobilization**
Other diseases Anorexia Cystic fibrosis Hemochromatosis Chronic obstructive pulmonary disease	**Severe disability**

rapy with BPs has been proven to be effective in increasing BMD, reducing fracture risk and improving overall quality of life. In Italy, neridronate (2 mg/Kg I.V., up to a maximum of 100 mg, every 3 months) is the only approved medication for the treatment of osteogenesis imperfecta (45). Since OI type 1 is very similar to idiopathic juvenile osteoporosis in terms of clinical manifestation, it is reliable to consider these disorder as the same for treatment purposes, as stated in “Nota 79”, besides genetic testing, which is usually not readily available.

Conclusions

Osteoporosis poses a significant public health issue. The recently revised evidence-based recommendations by SIOMMMS focus on the diagnosis, risk fracture assessment, prevention, and management of idiopathic post-menopausal osteoporosis, male osteoporosis and secondary osteoporoses. Still, the practical management of osteoporosis is greatly influenced by economic reimbursement policies. In particular, secondary osteoporoses, with

the exception of glucocorticoids-induced osteoporosis, are not included in the rules of reimbursement and constitute open issues. Besides these considerations, in clinical practice it is always important to tailor diagnostics and therapies to individual patients, taking advantages also of indirect-evidences.

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