Screening, diagnosis and treatment of osteoporosis: a brief review

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Summary
Osteoporosis is a highly prevalent condition characterized by decreases in bone mass and microarchitectural alterations. Bone fractures, especially of the hip and vertebrae, are the most burdensome complications of osteoporosis, being associated with high risk of disability, institutionalization and mortality. The detection of osteoporosis relies on the quantification of bone mineral density via imaging techniques such as dual-energy X-ray absorptiometry. However, therapeutic decision-making should be based on a comprehensive fracture risk assessment, which may be obtained through validated algorithms. Once the decision of treating has been taken, non-pharmacological strategies should be implemented together with the prescription of anti-osteoporotic agents. Numerous drugs are currently available to treat osteoporosis and the choice of a specific compound should be guided by efficacy and safety considerations. The present review provides a concise synopsis of the current evidence in the management of osteoporosis, from screening to drug prescription. Novel anti-osteoporotic agents are also briefly presented.

KEY WORDS: vitamin D; denosumab; bisphosphonates; teriparatide; strontium ranelate.

Introduction
Osteoporosis is a bone disease characterized by a decrease in bone mass and microarchitectural alterations which results in bone fragility and increased risk of fractures. According to the World Health Organization (WHO), osteoporosis is defined as a bone mineral density (BMD) at the hip and/or the spine at least 2.5 standard deviations below the mean peak bone mass of young healthy adults as determined by dual-energy X-ray absorptiometry (DXA) (1). The prevalence of osteoporosis rises steadily with advancing age and is projected to increase substantially due to the demographic transition occurring worldwide. Osteoporosis is estimated to cause 1.5 million fractures annually in the United States (2). In Italy, approximately 3.5 million persons are osteoporotic, with over 90,000 fractures yearly in those aged 50 years or older (3).

Mortality associated with osteoporotic fractures ranges from 15 to 30%, a rate similar to breast cancer and stroke (3). Furthermore, 50% of women with osteoporotic hip fractures develop disability, with significant impact on the capacity to live independently and, in most cases, institutionalization (3). Several risk factors have been identified for primary osteoporosis (Table 1). Secondary osteoporosis may be the consequence of endocrine and metabolism disorders (e.g., hypogonadism, hypercortisolism, hyperparathyroidism, hyperthyroidism, anorexia), lymphoproliferative disorders, intestinal malabsorption conditions, rheumatoid arthritis, renal failure, collagenopathies, or certain drugs (e.g., corticosteroids, selective serotonin reuptake inhibitors, anticoagulants and antidiabetic medications) (3). Regardless of the etiology, in all cases of osteoporosis an imbalance exists between bone resorption and formation: the rate of bone formation is often normal, whereas resorption by osteoclasts is increased (4). However, the initiating event in the process of osteoclastic activation is not yet completely understood.

Screening and diagnosis of osteoporosis
The presence of osteoporosis should be ascertained in all women aged ≥ 65 years (2). Men ≥ 65 years or women aged ≤ 65 years should be screened for the presence of risk factors such as early menopause (≤ 45 years), anorexia, smoking habit or alcohol abuse, chronic use of certain drugs or diseases associated with an increased risk for osteoporosis. The presence of osteoporosis should be ascertained in all women aged ≥ 65 years (2). Men ≥ 65 years or women aged ≤ 65 years should be screened for the presence of risk factors such as early menopause (≤ 45 years), anorexia, smoking habit or alcohol abuse, chronic use of certain drugs or diseases associated with an increased risk for osteoporosis.

Table 1 - Major risk factors for primary osteoporosis.

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<tr>
<td>Advancing age</td>
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<tr>
<td>Female sex</td>
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<tr>
<td>White or Asian race</td>
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<tr>
<td>Low body weight / body mass index</td>
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<tr>
<td>Family history of osteoporotic fractures</td>
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<tr>
<td>Early menopause</td>
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<tr>
<td>Sedentary lifestyle</td>
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<td>Excessive alcohol (&gt; 2 drinks per day), caffeine, and tobacco use</td>
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<tr>
<td>Low calcium and/or vitamin D intake</td>
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<td>Inadequate sun exposure</td>
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(3). The first-line assessment includes the determination of erythrocyte sedimentation rate, blood cell count, protein electrophoresis, serum calcium, serum phosphorus, serum alkaline phosphatase, serum creatinine, and 24-hour urinary calcium excretion, in order to exclude possible causes of secondary osteoporosis (3). Determination of bone turnover markers is not recommended.

DXA is presently considered the gold standard imaging technique for the diagnosis of osteoporosis because it shows the best predictive value for fracture risk (3). An estimate of fracture risk may be obtained with DXA of radius, ulna, spinal column or proximal femur. In persons aged ≥ 65 years DXA should be performed at the proximal femur because osteoarthritis of the column may bias the results. Moreover, BMD of the hip is a stronger predictor of future fracture risk than spine BMD. As a general rule, the risk of fracture increases 1.5-3 times each standard deviation of BMD below the reference population (3). Normal BMD is indicated by a T score of 1 to -1, whilst a T score ≥ -2.5 is diagnostic for osteoporosis. T score values between -1 and -2.5 identify a condition known as osteopenia which is associated with low to medium fracture risk, but frequent progression to osteoporosis. The correct identification and management of osteopenic subjects is a high-priority public health issue, if one considers that approximately 35 million Americans suffer from osteopenia (5).

The estimation of absolute risk of fractures and, therefore, therapeutic decision-making should not be based solely on BMD determination; rather, it requires a comprehensive evaluation of the patient, taking into account all of the known risk factors for osteoporotic fractures. In this context, sensitive tools have been developed which are routinely used in clinical practice. Besides its role in the identification of osteoporosis, DXA is also useful to monitor the efficacy of specific treatments. Roughly, 0.5-2% of bone mass is lost every year, whilst anti-osteoporosis therapies allow gaining approximately 1-6% yearly. Since the least significant change of DXA is 2-4%, it is recommended to repeat it not earlier than 1-2 years from the beginning of treatment (3).

Therapeutic strategies against osteoporosis

Non-pharmacological treatments

Many strategies are available to prevent osteoporosis and its complications, such as supplementation with calcium (500-1,000 mg daily) and vitamin D, physical activity and multidisciplinary interventions to decrease the risk of falls (5). These premises also represent the basis for every specific pharmacological treatment, since calcium and vitamin D deficiency is the most common cause of non-responsiveness to anti-osteoporotic medications.

Vitamin D supplementation

The major active metabolite of vitamin D, 1α,25-dihydroxycolecalciferol [1,25 (OH)2D3], derives for 80% from the conversion of 7-dehydrocholesterol by UV light and 20% from the diet, in particular blue fish and dairy products. The vitamin D precursor is liposoluble and settles mostly in the adipose tissue. The free quota is converted in the liver into 25-hydroxycolecalciferol [25 (OH) D3], the major circulating vitamin D metabolite, whose levels are the most reliable index of vitamin D status. 25 (OH) D is converted into the active metabolite in the kidney, through a complex homeostatic mechanism involving parathyroid hormone (PTH) and calcium and phosphorus serum levels (6). Vitamin D receptors are ubiquitous and are especially abundant in osteoblasts, chondrocytes, hepatocytes, parathyroid cells, and muscle cells (6). Vitamin D promotes cell proliferation and differentiation by a genomic pathway (7, 8). Vitamin D also acts via a non-genomic mechanism to modulate cell responses to various stimuli (7, 8). The major actions of vitamin D in the context of bone homeostasis include the regulation of calcium metabolism by increasing intestinal absorption and renal reabsorption, and the stimulation of the synthesis of bone proteins such as osteocalcin by osteoblasts (9).

The daily vitamin D allowance ranges from 1,500 IU (healthy adults) to 2,300 IU (elderly with low calcium intake). Since the average Mediterranean diet provides around 300 IU per day, subjects with insufficient sun exposure should receive 1,200-2,000 IU vitamin D daily (10-12).

In Italy, approximately 50% of young healthy individuals show vitamin D insufficiency [i.e., serum 25(OH)D levels 20-30 ng/mL] during the winter season (13). The prevalence of vitamin D deficiency [i.e., serum 25(OH)D levels < 20 ng/mL] increases with advancing aging, affecting virtually all non-supplemented elderly subjects (14). As such, individuals aged 70 years or older should be considered vitamin D insufficient unless they pursue a lifestyle characterized by extensive sun exposure (15). It is therefore recommended to prescribe older adults with vitamin D supplementation (800 per day) as a primary prevention measure (Table 2) (15).

If vitamin D deficiency is detected, a cumulative dose of 300,000-1,000,000 IU over 1-4 weeks is recommended, followed by a maintenance dose of 800-2,000 IU/day (or weekly/monthly equivalent) (15). The dosage should be based on age, degree of sun exposure, and baseline 25(OH)D levels (Table 2). In subjects persistently at risk for deficiency, it is recommended to check vitamin D serum concentration after 3-6 months from the beginning of the supplementation regimen (15). Finally, vitamin D supplementation should be carefully monitored in patients at risk of vitamin D intoxication (granulomatosis) or with primary hyperparathyroidism (15).

Physical activity

Physical activity is highly effective in attenuating the age-related bone mass loss (16, 17). It is therefore recommended to carry out a minimum of activity (for example, 30 minutes of walk daily) for its positive effects on bone mass and the risk of falling (18).

Comprehensive interventions on the risk of falls

Exercises for muscle strengthening and gait training have shown to reduce the risk of falls and related injuries in elder-
the probability of repeated stresses to the gastro-esophageal mucosa (23-28). Acute phase response (APR) is a transient flu-like syndrome, usually lasting 2-3 days, that develops in 30% of patients after the first intravenous administration of amino-bisphosphonates (29). It is associated with a rapid reduction of circulating lymphocytes and increases in serum levels of C-reactive protein. APR can be prevented or managed with paracetamol or non-steroidal anti-inflammatory drugs (30).

Atypical femoral subtrochanteric/diaphyseal fractures have been described in patients under long-term bisphosphate treatment, particularly in those receiving glucocorticoids and/or another anti-resorptive medication (31-35). Atypical femoral fractures develop spontaneously or after a minimal trauma. Additional studies are needed to determine the mechanisms underlying these fractures and the characteristics of patients at risk for them.

Treatment with bisphosphonates has been associated with higher risk of atrial fibrillation in some (36-38) but not all studies (39, 40). In 2011, the Food and Drug Administration (FDA) has concluded that there were not enough reasons to suspect that treatment with bisphosphonates could induce atrial fibrillation. Moreover, a reduced risk of myocardial infarction was recently observed during bisphosphate treatment in patients with rheumatoid arthritis (41).

Osteonecrosis of the jaw (ONJ) is a rare event in patients treated with bisphosphonates and the level of evidence and prediction of risk factors are relatively low (42). From a pathological point of view, ONJ consists in a chronic osteomyelitis caused by germs of the oral flora, in particular actinomycoses (43). However, the pathogenesis of ONJ has not yet been clearly defined. The main risk factors for ONJ include prolonged treatment with oral bisphosphonates, corticosteroid therapy or immunosuppressive agents. Tooth extraction and dental and periodontal diseases are the main predisposing factors (44, 45). Cases of ONJ have been described also in subjects who have never been treated with bisphosphonates (43).

Musculoskeletal pain, usually reversible after discontinuation (46, 47), ocular inflammation (48), urticaria (49), or mucositis (50) have rarely been reported after use of bisphosphonates.

Denosumab
Denosumab is a human monoclonal antibody that blocks the interaction of receptor activator of nuclear factor kB ligand (RANKL) with receptor activator of nuclear factor kB (RANK), whereby inhibiting bone resorption strongly and rapidly (51). In postmenopausal women with low BMD, denosumab administered subcutaneously 60 mg every 6 months increased BMD by 1 to 7% depending on the skeletal site (51). The increases in BMD are higher than those obtained with the more potent bisphosphonates (51). In postmenopausal osteoporotic women, denosumab decreased the risk of vertebral and non-spine fractures by 70% and 20%, respectively (52). Denosumab slowed bone turnover also in older men receiving androgen-deprivation therapy for prostate cancer, increasing BMD by 4 to 7% as well as decreasing the incidence of vertebral fractures by 60% and the incidence of multiple fractures by 70% (53). An association with ONJ has been observed in denosumab registration trials, although the event appears to be extremely rare (6 cases/4450 patients) (54). The pathogenesis of this side effect has not yet been clearly defined, but it seems reasonable to equate denosumab to bisphosphonates in this re-
In osteoporotic women with prevalent vertebral fractures, rhPTH decreases the incidence of new vertebral fractures by 65% and non-vertebral fractures by 53% (72). The best candidates for teriparatide and rhPTH(1-84) treatment are patients with pre-existing osteoporotic fractures, patients with very low BMD and those with unsatisfactory response to anti-resorptive therapy. The effects of the combination therapy with rhPTH(1-84) and alendronate on BMD are controversial, with some authors reporting no synergy (73), while others found an additive effect (74). However, according to guidelines, the combined treatment with recombinant PTH and bisphosphonates should not exceed 24 months (74). The safety profile of teriparatide is overall good. A transient increase in serum calcium levels and calcium renal excretion without clinical manifestation has been reported. Absolute contraindications to teriparatide include primary hyperparathyroidism, Paget's disease of bone, previous radiation therapy of the skeleton and primary or metastatic bone cancer (20).

**Strontium ranelate (SR)**
SR is adsorbed onto the bone surface and increases bone strength by being incorporated in a dose-dependent manner into bone tissue to change the crystal structure without affecting mineralization (75). SR increases bone formation markers, reduces bone resorption markers and increases BMD progressively and dose-dependently (76, 77). In postmenopausal osteoporotic women during long term treatment (4 years), SR decreased the incidence of vertebral fractures by 33% (78). SR also decreases the incidence of non-vertebral fractures by about 15% and even more (31%) in the oldest women (79, 80). The European Medicines Agency (EMA) Committee for Medicinal Product for Human Use (CHMP) recommended SR only be used for the treatment of severe osteoporosis in men and postmenopausal women at high risk of fracture (81).

The most common side effects of SR therapy are nausea and diarrhea which usually develop at the beginning of the treatment and generally disappear after 3 months of therapy. Albeit rarely, SR administration has been associated with severe, potentially lethal, skin reactions, such as drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome and toxic epidermal necrolysis (82-85).

Recently, the EMA warned against a possible association between the use of SR and cardiovascular events, above all myocardial infarction (86). SR is therefore contraindicated in patients with history of cardiovascular disease or uncontrolled hypertension. In addition, it is recommended patients be evaluated for cardiovascular risk before starting treatment with SR and at regular intervals during treatment. The possible association between SR and venous thromboembolism (VTE) makes the drug contraindicated also in patients with current VTE or a history of VTE, as well as in those who are temporarily or permanently immobilized (87). Taking all this into account, SR is not a first-choice option in older osteoporotic patients (88).

**Other “non-hormonal” drugs and novel therapeutic agents**
A number of drugs with beneficial effects on bone metabolism and calcium-phosphorous homeostasis include calcitonin, ipriflavone, and thiazide diuretics. However, none of these agents is currently recommended for osteoporosis treatment because either ineffective or not supported by adequate evidence.
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Research into anti-osteoporotic therapeutics has led to the discovery of new candidate drugs. For instance, odanacanib acts as a selective inhibitor of cathepsin K, an osteclast-derived protease that degrades bone collagen. This property makes odanacanib an alternative anti-resorptive drug (89). Indeed, odanacanib provided incremental BMD gains in osteoporotic women under alendronate treatment (89). Another compound, tert-butyl 4-[3-(1H-indole-2-carboxamido)benzoyl]piperazin-1-yl-carboxylate (OA10), inhibits RANKL-mediated osteclast formation and osteoclastic bone resorption in a dose-dependent manner (90). Similarly, C(25)(H)(32)(N)(4)(O)(4)(S)(2) (NecroX-7) inhibits osteoclast differentiation by suppressing nuclear factor kB activity and c-Fos expression (91). Pharmacological inhibition of selenostatin, a negative regulator of bone formation, may represent another potential approach to the treatment of osteoporosis by promoting bone anabolism (92).

Conclusion

The escalating prevalence of osteoporosis and its burdensome clinical correlates urge health professionals to abandon the old notion of osteoporosis as a mere “natural byproduct” of aging. Rather, the medical community is called to promote an adequate awareness on the subject and put in place large-scale screening and diagnostic procedures in order to identify people with osteoporosis or at risk of developing the condition. This would allow the early correction of risk factors for osteoporosis and the prompt institution of anti-osteoporotic treatments. In this regard, it needs to be considered that therapeutic decision-making should be based not solely on BMD, but on comprehensive fracture risk assessments. A relatively large number of medications is currently available. Each drug (or class of drugs) possesses specific advantages and side effects and should therefore be prescribed or avoided in selected patient populations. New and potentially highly effective agents are currently under development which may offer novel therapeutic tools to counteract what has rightly been called the osteoporosis epidemic.

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