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REVIEW ARTICLE

New perspectives on the definition and the management of severe osteoporosis: The patient with two or more fragility fractures

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ABSTRACT. ***Background:*** **Osteoporosis is the most common skeletal disorder in the elderly, being characterized by impaired bone strength and increased risk of fracture. Severe osteoporosis is currently defined by the threshold of bone density value below the –2.5 SDS of T-score, determined by dual-energy X-ray absorptiometry, and the presence of one or more fragility fractures. This definition does not entirely reflect the spectrum of severity of the disease that provides a variable increase in fracture risk.** ***Methods:*** **This manuscript reports a consensus statement on the diagnostic criteria for severe osteoporosis in real-life clinical setting, achieved in an event held by Italian physicians with expertise in osteoporosis and metabolic bone diseases.** ***Results:*** **The group stated that a large number of fractures occur in subjects with T-score above –2.5. In light of recent advances on the structural basis of skeletal fragility, it became clear that bone density represents only one of the contributors to bone strength and number and severity of fragility fractures. The group suggests that the condition of two or more fragility fractures should be considered as severe osteoporosis, independently of bone density.** ***Conclusions:*** **The consensus statement proposes a more specific definition of severe osteoporosis, which should consider not only densitometric measurements, but also the number and severity of fragility fractures. Patients' management and choice of treatment should take into consideration the type and severity of osteoporotic fractures, in addition to bone density.**
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INTRODUCTION

Osteoporosis is currently defined as a skeletal disorder characterized by compromised bone strength and increased risk of fracture (1). Its clinical significance is related to fractures, involving most commonly the forearm, the vertebral bodies and the hip, but fractures at other sites may also be associated with the disease. Osteoporosis is one of the most common disorders in elderly adults and represents a major public health problem, affecting up to 40% of post-menopausal women and 15% of male adults (2).

In 1994, a World Health Organization (WHO) study group published an operational definition of osteoporosis based on bone mineral density (BMD) and expressed as a T-score, which represents the number of SD above or below the mean BMD value for a normal young adult woman (peak bone mass) (3).

The clinicians working in the field of osteoporosis perceive that the current definition of severe or established osteoporosis does not entirely reflect the spectrum of disease severity and diversity presented by patients with multiple fractures. Therefore, a more complete definition of severe osteoporosis would allow physicians to better define the clinical condition of patients with fractures, provide more accurate assessment of disease severity, and perhaps allow more efficient and personalized tailoring of the management of each patient.

A working group of 50 Italian physicians with specific expertise in severe osteoporosis within the largest centers for osteoporosis was convened. This was a multidisciplinary group composed of rheumatologists, endocrinologists, orthopedic surgeons, and internal medicine specialists. The principal goal was to develop strategies for a better identification of patients with the most severe forms of osteoporosis, and to identify the most appropriate management of such patients. Clinical criteria used to define patients with severe osteoporosis were discussed and the group concluded its work by proposing a working definition of severe osteoporosis, and by recommending therapeutic procedures according to the type and severity of fractures.

The following topics related to severe osteoporosis were discussed: 1) improvement of clinical definition, 2) epidemiology and quality of life, and 3) evaluation and management of patients. A literature search for articles relevant to each of the key questions was conducted, using the following databases: Medline, Embase, Cancerlit, HealthStar, Cinhal, Grateful Med, Toxline, and the Cochrane Collaboration. Assessment of quality of evidence was based on randomized controlled trials, expert opinions, and other published studies.

The quality and validity of each statement was scored according to criteria commonly used in developing clinical guidelines (4, 5), adapted to simplify the consensus process, as shown in Table 1. A scoring system considered

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Table 1 - *Criteria used in this study for the evaluation of quality of evidence and strength of recommendations.*

Quality evidence	
1	Randomized clinical trials
2	Other published studies
3	Expert opinion
Strength of recommendation	
A	Good
B	Moderate
C	Poor

each statement accepted when a consensus was reached by at least 50% of the attendees.

DEFINITION OF SEVERE OSTEOPOROSIS AND ITS LIMITATIONS

Severe osteoporosis has been defined by a T-score below –2.5 SD in the presence of one or more fragility fractures (3). The WHO criteria were based on the evidence that emerged from studies indicating that the risk of fragility fractures increases progressively with BMD decline (6-9). However, bone strength is a result of interaction between BMD and other structural and functional factors, such as bone microarchitecture, degree of mineralization, and bone turnover. Such considerations are based on observations documenting risk of bone fractures also in subjects with BMD above the –2.5 SD of T-score that represent the threshold indicated by the WHO (10, 11). Fractures that are typically associated with osteoporosis are localized at wrist, vertebral bodies and hip, but may involve other skeletal sites. It became clear that patients who sustain a vertebral fracture are at particularly high risk of another vertebral fracture within the following year, which has been estimated to be about 3-to-5 fold higher than the risk of subjects without fractures (12, 13). This can be translated to an absolute risk of 10.8% to develop a new clinical fracture within the next 2 yr (14). It has been widely documented that mortality increases significantly and proportionally with the number and the severity of vertebral fractures (15, 16). Moreover, the WHO definition does not take into account risk factors that cannot be corrected with medical treatments. For example, in an 80-yr-old woman at high risk of falling and a T-score at the proximal hip lower than –2.5, the 10-yr fracture risk is very high, but there is no data on antifracture efficacy for any available antiosteoporotic treatment.

The main aim for the pharmacological treatment of established osteoporosis is prevention of "fracture cascade" triggered by the first vertebral fracture. Osteoporosis is a multifactorial and common disorder of the elderly. It is diagnosed and treated by clinicians of different specialties, including rheumatologists, endocrinologist, orthopedists, internal medicine physicians, and geriatricians. They may take care of different types of patients; however, all of them should be aware of the cases of severe osteoporosis.

The lack of integration of clinically relevant parameters into the WHO definition, including number and types of fractures and clinical symptoms, does not allow an appropriate grading of the severity of the condition. Therefore, if the T-score threshold defined by the WHO must be met for the diagnosis of severe osteoporosis, many patients with multiple fragility fractures would be missed. A more clinically meaningful definition of severe osteoporosis would take into consideration the general health condition and the clinical impact of the prevalent fractures. In fact, several clinical studies have documented that both the number and severity of pre-existing vertebral fractures are predictive of the risk of new fragility fractures (either vertebral or non-vertebral) and mortality (12, 17). Accordingly, the definition of osteoporosis that was proposed by the working group (Table 2) includes subjects with a lumbar or femoral BMD T-score lower than –2.5 SD as well as those with a T-score above –2.5 in the presence of a fragility fracture. Severe osteoporosis should refer to patients with a T-score lower than –2.5 and prevalent fragility fracture, as well as to patients with two or more fragility fractures, regardless of BMD values.

SEVERE OSTEOPOROSIS: EPIDEMIOLOGY AND QUALITY OF LIFE

Currently, osteoporosis is largely under-diagnosed and under-treated, thus leading to devastating consequences, negative impact on the quality of life and final increase of social and health costs. The prevalence of osteoporosis is not straightforward since many cases with asymptomatic vertebral fractures are not diagnosed. Hospital discharge codes have been used to assess the prevalence of osteoporosis, but they provided incomplete information because osteoporosis is not reported among the secondary diagnoses at discharge, even if the patients have fragility fractures. Additionally, hospital discharge codes are not specific for vertebral fractures.

Useful information may be obtained from the placebo arms of clinical studies on osteoporosis treatments that have been conducted in the last 10-15 years, even though these data refer to selected populations. Indeed, another related issue is the variability in epidemiology of severe osteoporosis in different geographic regions.

Two large European studies, the European Vertebral Osteoporosis Study (EVOS) and the European Prospective Osteoporosis Study (EPOS) were designed to evaluate the prevalence and incidence of vertebral deformities.

The EVOS was carried out in 19 European countries and documented that the mean prevalence of all deformities is 12% in women (range 6.2-20.7%) and 12.2% in men (range

Table 2 - *Proposed definition for osteoporosis and severe osteoporosis.*

Osteoporosis	BMD T score ≤–2.5 SD or BMD T score ≥–2.5 SD in the presence of a prevalent fragility fracture
Severe osteoporosis	BMD T score ≤–2.5 with a prevalent fragility fracture or ≥2 prevalent fragility fractures independently of BMD values

This definition was endorsed by 83.3% of participants.
BMD: bone mineral density.

7.5-19.8%). In the EVOS study, the prevalence increased with age in both genders. There was also substantial geographical variation in the prevalence of vertebral deformities across countries, with the highest rates in the Scandinavian region (Table 3). The prevalence of vertebral deformities determined by the two Italian centers involved in the study (Milan and Siena) was comparable to that of the other countries surveyed (18). However, not all vertebral deformities are vertebral fractures. Other disorders, including congenital abnormalities, severe osteoarthritis and Scheuermann's disease, may change the vertebral shape and need to be taken into consideration (EVOS).
The EPOS study, which was a continuation of the EVOS study, evaluated the incidence of vertebral fractures in Europe. In the EPOS study, the age-standardized incidence of morphometric fractures in women and men was 10.7/1000 and 5.7/1000 person-years (p-yr), respectively, and it increased with age in both genders. Again, data for Italy did not differ from data for other European countries (women 11/1000, men 9.1/1000) (19). The age-standardized incidence for vertebral fractures evaluated qualitatively by radiology was also comparable, namely 12.1/1000 p-yr for women and 6.8/1000 p-yr in men (19).
The Mediterranean Osteoporosis Study (MEDOS), a case-control study that was conducted in collaboration with the WHO in 14 centers distributed in six European countries within the Mediterranean area, evaluated the epidemiological features of femoral fractures (20, 21). In Italy, the centers of Siena, Parma, and Roma recorded 1437 femoral fractures in a 1-yr period (1162 in women, 275 in men), with an annual incidence of 1.7% (2.5% in women and 0.72% in men). The annual incidence of femoral fractures showed an exponential increase with age, with a doubling time of 5.5 yr in Italy. Incidence rates increased from 1.16% over the age range of 50-54 yr to 16% in subjects over 85 years of age. An Italian survey from 2002 reported 86,719 hip fractures with a 10.0% increase over 4 yr, showing a clear relationship with the incidence of osteoporosis. Additionally, in the Italian population aged >45 yr, hospitalizations following hip fracture and acute myocardial infarction between 1999 and 2002 were comparable, while hip fracture direct costs were higher and grew faster than costs for acute myocardial infarctions (22).
Data from the Incidence and Characterization of Inadequate Clinical Responders in Osteoporosis (ICARO) study show that 25% of patients with at least one vertebral fragility fracture treated with bone resorption inhibitors for up to 2.3 yr may experience an inadequate clinical response to treatment, defined as the appearance of new fragility fractures (vertebral and non-vertebral) within 6 months of therapy (23). Assessing the impact of severe osteoporosis on quality of life is difficult, but available data indicate that quality of life is significantly reduced in patients with fragility fractures (24-26). Multiple and severe vertebral fractures are typically associated with exponential deterioration of quality of life.

Table 3 - *Prevalence of vertebral deformity by gender and region in the European Vertebral Osteoporosis Study (EVOS) study. Modified from (18).*

Region	Male (%)	Female (%)	F:M
Scandinavia	16.2	20.0	1.23
West Europe	11.6	11.4	0.98
East Europe	11.3	11.1	0.98
Mediterranean	13.6	12.2	0.90
Total	12.2	12.0	1.00

F:M: female to male ratio.

PATIENT EVALUATION

It is necessary to highlight the importance of a complete evaluation in patients with osteoporosis (Table 4). Past medical history should focus on known risk factors for fractures including age, family history, smoking/drinking habits, low dietary calcium and vitamin D intake, previous or concomitant serious diseases, sedentary lifestyle, previous treatment with glucocorticoids or other drugs known to affect bone metabolism (immunosuppressants, antidiabetics, and proton pump inhibitors among others), and individual risk of falling. Physical examination should include accurate assessment of the spine and back pain. Height should be measured at every visit to monitor for possible sudden changes that might be indicative of a new vertebral compression fracture (27). It has been reported that even mild sub-clinical spine fractures are associated with worsening of quality of life and increased risk of new fractures (28, 29). Radiological diagnosis by plain radiographs and vertebral morphometry play an important role in the diagnosis of the disease. Vertebral morphometry can be performed by using a digitization of radiographs or by means of dual energy X-ray absorptiometry [DXA, with vertebral fracture assessment (VFA) and spinal deformity index (SDI)]. DXA-based assessment of vertebral deformities on lateral scans of the entire spine, in fact, may also play a role in further characterization of patient's profile.
A surrogate marker of bone strength and risk of osteoporotic fractures is BMD, which should be assessed by DXA or quantitative computerized tomography (QCT).

IMPORTANCE OF INTERACTION BETWEEN PRIMARY CARE PHYSICIANS, ORTHOPEDIC SURGEONS BONE SPECIALISTS, AND RADIOLOGISTS IN THE MANAGEMENT OF SEVERE OSTEOPOROSIS

In emergency departments, one out of 6 elderly patients who undergo chest radiography are found to have vertebral fractures. Only 60% of these fractures are diagnosed due to clinical symptoms, only 25% of patients with fractures receive an appropriate diagnosis and even fewer of them are given any medical treatment for osteoporosis (30). This observation highlights the fact that the radiologist should be more involved in the process of diagnosis of osteoporosis.
Orthopedic surgeons, as well as radiologists and neurosurgeons, play an important role in the management of patients with any type of fracture. They are consulted for treatment of painful vertebral fractures, in the hope that surgical treatment may have a beneficial outcome. Surgical procedures such as vertebroplasty or kyphoplasty

Table 4 - *Statements on clinical evaluation of patient with severe osteoporosis.*

Statement	Quality of evidence	Strength of recommendation
1.Traditional radiography still plays an important role in defining the severity of vertebral fractures	1	A
2. New methodologies (SDI, DXA/VFA) have significant advantages when compared to other clinical signs such as a reduction in stature	1	A
3. During follow-up of patients with multiple fractures on medical therapy it is advisable to monitor biochemical parameters (markers)	2	C
4. During follow-up of patients with multiple fractures on medical therapy it is advisable to monitor BMD	2	B
5. During follow-up of patients with multiple fractures on medical therapy it is advisable to perform radiological monitoring	1	A/B
6. Radiological evaluation is necessary if clinical symptoms suggest a new fracture	1	A
7. Improvement of the QoL and disabilities have an important role in therapeutic strategies	1	A

SDI: spine deformity index; DXA: dual-energy X-ray absorptiometry; VFA: vertebral fracture assessment; BMD: bone mineral density; QoL: quality of life.

may provide an immediate relief of bone pain, but the long-term benefits have never been properly addressed. A rather common clinical perception is that this treatment is associated with an increased risk of new fractures on adjacent vertebral bodies.

Hip fractures are the most common osteoporotic fractures referred to orthopedic practice in Italy. Their incidence substantially increases with age. Although surgical procedures are well standardized and the surgery-related morbidity rather low, hip fractures are associated with a significant decrease in life expectancy and severe reduction of quality of life. Furthermore, osteoporosis increases the risk of non-healing hip fractures by 7.7-fold (31).

Most patients with non-traumatic fractures referred to orthopedic surgeons have severe forms of osteoporosis (Table 5). In these patients, any surgical procedures should be accompanied by an appropriate diagnostic evaluation and treatment. Otherwise, surgical intervention and devices used to fix fractures may have harmful effects on the surrounding bone. Most of the elderly patients with incidental hip fracture are vitamin D deficient and dwelling in places or conditions associated with high risk of falling. Orthopedic surgeons have to increase their awareness and knowledge about pharmacological treatments for osteoporosis. Vitamin D replacement should be given to all patients aged >65 yr, at doses at least 800 IU daily, associated with calcium intake of about 1200-1500 mg daily. Anabolic treatment should be considered as a first line treatment in patients with severe osteoporosis and in those who experience a fracture when on anti-resorptive therapy. These agents are easy to use and cost-effective if given after the surgical treatment of fragility fractures.

Table 5 - *Management of severe osteoporosis in an orthopedic setting.*

Statement	Quality of evidence	Strength of recommendation
1. The definition of osteoporosis can be extended to patients with poor bone quality found during surgical procedure independently of the BMD: - Thinning of the cortical bone - Enlargement of the medullary canal in long bones - Reduced capacity for surgical repair that may be perceived during surgical procedure as low resistance of bone tissue throughout the application of screw/nails and their instability after application; crack of femoral cortical bone during or immediately after prosthesis application; after surgical procedure as failure of surgical osteosynthesis or prosthesis instability	3	A
2. It is useful to evaluate the entity of osteoporosis in patients with low or moderate energy trauma causing fractures in the presence of known risk factors for osteoporosis	3	A
3. Clinical picture that can identify patients with the most severe form of osteoporosis: - Early fragility fractures - Advanced age - Presence of co-morbidities that are known to increase the risk of fracture - Location and characteristics of the fracture	2	B
4. What should be modified in the management of the most severe forms of osteoporosis in an orthopedic setting? - Establishment of a differential diagnostic protocol to define the entity of disease - Consequently, pharmacological treatment together with orthopedic-physical therapy	2	A
5. Necessity of defining a diagnostic algorithm for management of patients presenting to the emergency room with femoral fractures	3	A
6. Vertebroplasty and kyphoplasty - Both surgical indications may be considered - Both techniques have documented positive effects (reduction of pain and fracture stabilization) - Negative aspects have been documented (early increase in the risk of fracture of adjacent vertebra if pharmacological treatment is not associated)	2	A

BMD: bone mineral density.

DISCUSSION

Currently, osteoporosis is defined as a skeletal disorder characterized by compromised bone strength that predisposes to an increased risk of fracture. Bone strength primarily reflects the integration of bone density and bone quality, as defined by the National Institutes of Health Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy (1). The densitometric definition does not clearly identify the amount of bone loss or disruption of bone structure beyond which the bone becomes susceptible to fractures. The concept of the osteoporosis continuum in terms of risk of fracture led to attempts to develop algorithms for assessing the projected (5 or 10 years) fracture risk by both the National Osteoporosis Foundation and the WHO. By using these algorithms, any health care provider is free to identify the most appropriate treatment for each patient. Moreover, the algorithms do take into account risk factors that cannot be corrected with medical treatments such as age and failure risk.

In this consensus statement, the Italian group of experts felt that for practical reasons the structure of the former WHO definition of osteoporosis has to be maintained but updated according to the clinical information gathered in the last 15 years.

The following findings were considered crucially important: a) a large number of fractures occur in persons without osteoporosis as defined by a T-score below –2.5 SD; b) by far, the highest fracture risk is associated with a recent history of a fragility fracture; c) the risk of fracture increases exponentially with the number and severity of prevalent fragility fractures. These conditions may occur even in the presence of BMD values within the osteopenic range, according to the WHO. This reflects alterations in the micro-macro architecture that are not captured by DXA measurements.

Most of the fracture prevention trials on pharmaceutical agents currently used in osteoporosis included patients with previous vertebral fractures even though T-score was above –2.5 SD in some cases. Therefore, it seems legitimate to use number and severity of previous fractures for the definition of the threshold of a pharmacological treatment. Patients with two or more previous fragility fractures should be considered as affected by severe osteoporosis, regardless of BMD values, particularly if the vertebral deformities are moderate or severe. The experts also emphasized the relevance of back pain and its negative impact on quality of life for the definition of severe osteoporosis. Chronic back pain, even when associated with mild vertebral deformities, worsens the condition.

Therefore, an early identification of the patients with spine fracture(s) is critical in order to devise the most appropriate management. Spine X-rays should be recommended whenever a vertebral fracture is suspected, independently of the BMD values. Vertebral morphometry may be systematically implemented during DXA evaluation, particularly among subjects in whom a recent spine X-ray is not available. Mild deformities need to be considered since they are associated with increased risk of new fractures and chronic back pain.

This consensus highlighted the crucial role of orthopedic surgeons. First of all, there should be a general effort in order to guarantee that all patients discharged from an orthopedic unit after a recent fragility fracture do receive immediately an appropriate attention and medical treatment. Vertebroplasty or kyphoplasty are definitely effective in providing a rapid relief in acute bone pain. There are still uncertainties regarding their ability to correct spine deformities. Moreover, it seems that these two techniques increase the risk of new fractures on adjacent vertebral bodies.

In conclusion, this consensus statement by the Italian working group highlighted the most common problems perceived by clinicians involved in the care of patients with severe osteoporosis. The experts' opinions confirmed the limits of the current definition of severe osteoporosis and proposed to implement the WHO definition taking into account the number and severity of previous fractures and the presence of chronic back pain. Future efforts should be oriented to raise awareness on osteoporosis and to develop new prevention algorithms for severe osteoporosis, considering its rather complex treatment. These efforts are supposed to increase the possibility to modify the long-term prognosis of the disease.

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