Update on bone health: the International Menopause Society White Paper 2021.

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ABSTRACT

Osteoporosis and associated fractures present a major challenge in improving global health outcomes. Key clinical aspects are the definition of osteoporosis and associated fractures, fracture risk prediction, stratification of risk of fracture, intervention thresholds and the most appropriate intervention based on integration of aforementioned. Correct understanding and application of these concepts are essential to stem the increasing tide of fragility fractures associated with an aging population. The role of muscle strength and function, sarcopenia, and the newly emerging concept of osteosarcopenia in maintaining bone health are discussed in detail.

Introduction

The Board of the International Menopause Society (IMS) has decided to focus on bone health for World Menopause Day 2021. Osteoporosis and associated fractures are the most common chronic metabolic bone disease and represent a major global health problem, contributing to 8.9 million fractures worldwide on an annual basis [1]. Worldwide, there are marked variations in the rates of hip fracture and major osteoporotic fractures [2]. Fractures associated with osteoporosis cause not only increased morbidity but also an increased mortality [3]. A special issue of *Climacteric* dealing in great depth with all aspects of bone health will appear later this year. The first part of the present paper deals with demystifying key clinical aspects of osteoporosis, namely definition, fracture risk prediction, stratification of risk, intervention thresholds and the integration of these factors into clinical practice. The second part of the paper deals with the emerging recognition of the role of muscle strength and function in maintaining bone health.

Definition of osteoporosis

In the early 1990s, osteoporosis was defined as a systemic skeletal disease characterized by low bone mass and deterioration in microarchitecture which results in an increase in bone fragility and increased susceptibility to fracture [4]. This definition underpinned the pivotal concepts of fracture and bone mineral density (BMD).

Fragility fractures

Fragility fractures result from mechanical forces that would not ordinarily result in a fracture [5]. The World Health Organization (WHO) has further quantified this as forces equivalent to a fall from a standing height or less.

The presence of a fragility fracture of the spine, hip, forearm or pelvis is generally accepted as being diagnostic of osteoporosis and an indication for treatment, although evidence for other sites is lacking.

The risk of a subsequent osteoporotic fracture is highest immediately after the index fracture and decreases progressively with time [6]. This risk is especially high in the first 2 years post index fracture [7]. The risk of a subsequent fracture is also increased in the presence of multiple fractures.

In the case of asymptomatic morphometric fractures of the spine, the grade of the fracture (mild, moderate or severe) most likely also correlates with risk of subsequent fracture [8]. This can be determined by vertebral

fracture assessment (VFA), a function of most modern dual-energy X-ray absorptiometry (DXA) devices, or by conventional X-rays. Although the International Society of Clinical Densitometry lists several indications for VFA [9] (Table 1), it can be argued that, if available, VFA adds valuable information to the interpretation of any DXA study.

Table 1. Indications for vertebral fracture assessment (International Society of Clinical Densitometry, 2019 [9]).

Lateral spine imaging with standard radiography or densitometric vertebral fracture assessment is indicated:
When *T*-score is < -1.0 standard deviations and one or more of the following is present.
• Women aged ≥ 70 years or men aged ≥ 80 years
• Historical height loss > 4 cm (>1.5 inches)
• Self-reported but undocumented prior vertebral fracture
• Glucocorticoid therapy equivalent to ≥ 5 mg of prednisone or equivalent per day for ≥ 3 months

Based on fracture history, the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) clinical practice guidelines stratify patients at very high risk of fracture as those with a recent fracture (within the past 12 months), those that have fractures while on approved osteoporosis therapy, multiple fractures or fractures while on drugs causing skeletal harm (such as long-term glucocorticoids) [10]. The US Endocrine Society adds a severe fracture to this list [11].

Bone mineral density

Estimations of BMD became a reality with the advent of DXA scanners in the late 1980s. A WHO study group in 1994 defined osteoporosis as a BMD of 2.5 or more standard deviations (SDs) below the mean value of young healthy white women. This setting of a *T*-score threshold of ≤ -2.5 SDs was an epidemiological classification. However, randomized controlled studies to prove anti-fracture efficacy of new drugs used a *T*-score of ≤ -2.5 SDs as an inclusion criterion [12]. As efficacy was proven in these patients, it was widely accepted as an intervention threshold and still remains so in most guidelines. AACE/ACE clinical practice guidelines regard a very low *T*-score of < -3.0 as indicative of a very high risk of fracture.

Fracture risk prediction over time

Whereas most guidelines accept the diagnostic criterion of the presence of a fragility fracture or *T*-score ≤ -2.5 SDs as an indication for treatment, this excludes patients with osteopenia (*T*-score < -1.0 > -2.5 SDs). The majority of fractures actually occur in the osteopenic group, indicative of high specificity but low sensitivity of using *T*-score as a single risk factor.

The need for treatment in this group can be better defined by fracture risk probability over time. This can be achieved by combining DXA-based femur neck BMD with known risk factors such as low body mass index (BMI), a family history of hip fracture, the presence of rheumatoid arthritis, type 1 diabetes, early menopause,

smoking, abuse of alcohol or a sedentary lifestyle. Many models have been designed to integrate these risk factors into a predictive fracture risk over a period of time such as FRAX® [13] and Garvan (www.garvan.org.au). For the purpose of this paper, only the FRAX model will be discussed. The FRAX model is based on fractures recorded in large cohorts including the placebo arms of many modern randomized controlled trials used to establish the efficacy of new bone-specific drugs. The FRAX model is an internet-based tool (www.shef.ac.uk/FRAX) that calculates the 10-year probability of hip fracture or a major osteoporotic fracture (MOF; spine, hip, forearm or a humerus). FRAX has been externally validated in independent cohorts [14] and calibrated to the epidemiology of fracture and death in different countries [15]. Although FRAX can be used without DXA when not available, for the purpose of this paper all references to FRAX predictions are based on FRAX incorporating the femur neck BMD as determined by central DXA. Software additions to DXA now also allow calculation of trabecular bone score (TBS) which reflects bone strength [16]. If available, it is recommended that the FRAX prediction be adjusted by the TBS. It is recognized that FRAX has shortcomings such as not incorporating concurrent spine BMD, risk of falls, type 2 diabetes and quantification of glucocorticoid treatment. Some arithmetric adjustments have been proposed as compensation [17,18].

Intervention thresholds

It is very important to understand that FRAX only predicts future risk of fracture and as such does not tell you when to treat. Intervention thresholds based on FRAX predictions should ideally be calculated for every country to reflect local epidemiology and cost of available medication to determine when it becomes appropriate to treat.

Intervention thresholds based on FRAX predictions can be calculated as fixed values, age-adjusted values or a hybrid model using fixed and age-adjusted values.

The most popular example of fixed values is the USA intervention threshold defined as a risk of MOF over 10 years exceeding 20% or hip fracture risk exceeding 3%. This model is based on 2005 economic factors but is still advised at present [19]. These fixed values have been blindly copied by many countries without taking into account local health economics. AACE/ACE clinical practice guidelines define very high risk as MOF risk and hip fracture risk, calculated by FRAX, as exceeding 30% and 4.5%, respectively over 10 years.

The age-adjusted intervention threshold is set at a risk equivalent to that associated with a prior fracture in a woman of the same age with average BMI. The National Osteoporosis Guideline Group of the UK has developed age-dependent intervention thresholds that have been proven to be cost-effective in the UK when generic alendronate is used [20]. These values are country-specific due to differences in costs and baseline fracture risk and should be individually calculated.

Hybrid models compensate for possible inequalities in treatment, with younger individuals likely to be overtreated and older individuals with no fracture history to be undertreated. In the UK, an age-dependent intervention threshold is used up to the age of 70 years and a fixed threshold is adopted thereafter [21].

The International Osteoporosis Foundation and European Society for Clinical and Economic Aspects of Osteoporosis advise that high risk is defined as a fracture probability exceeding the country-specific threshold for intervention and very high risk as a fracture probability that lies above the upper assessment threshold after a FRAX assessment [22].

Stratification of risk

Recent recommendations further define fracture risk as low, high or very high in order to individualize therapy [9,10,22]. Antiresorptive agents like the bisphosphonates have long been regarded as first-line therapy. Recent studies have shown that anabolic drugs show superior results to antiresorptive drugs as first-line therapy in patients at very high risk of fracture (to be discussed later). In view of much higher costs associated with anabolic drugs, the correct identification of patients at very high risk of fracture becomes a priority [23]. As evident from the previous discussions, there is no clear universally accepted definition of the stratification of fracture risk.

Table 2 summarizes the aforementioned discussion as a clinical guide, but it must still be individualized for every country. It must be emphasized that the fixed intervention thresholds, as illustrated in Table 2, are based on US recommendations. All countries must strive to develop country-specific values.

Strategies in the prevention of fractures

Key to managing bone health is the importance of avoiding fractures, and strategies to prevent fracture must take precedence. These are discussed below. Further information on different interventions may be found in the references and readers should also acquaint themselves with country-specific services. More specific detail will follow in an upcoming issue on Bone health in *Climacteric.*

Lifestyle changes

All postmenopausal women, not only those at risk of fracture, should be educated on a bone-friendly lifestyle. This includes optimization of calcium and vitamin D status, appropriate exercise, cessation of tobacco smoking and the abuse of alcohol, and the avoidance of bone-toxic medication. Attention should be paid to activities aimed at improving balance, to a review of medications which might increase the risk of falls such as sedatives and anxiolytics, and to locally available programs such as fracture liaison services.

Antiresorptive treatment

It is widely advised in most guidelines that antiresorptive therapy should be considered as monotherapy in all patients at any risk of fracture.

Table 2. A guide to stratification of fractures.

Low risk of fracture (all must be present)

- No fragility fractures
- DXA-derived *T*-score < -1 and > -2.5 standard deviations
- FRAX 10-year probability of fracture (adjusted for trabecular bone score):
  - Any major osteoporotic fracture: < 20%
  - Hip fracture: < 3%
  - Or less than the country-specific threshold for intervention

High risk of fracture (any one of the following)

- Presence of fragility fracture
- DXA-derived *T*-score ≤ -2.5 standard deviations
- FRAX 10-year probability of fracture (adjusted for trabecular bone score):
  - Any major osteoporotic fracture: > 20%
  - Hip fracture: > 3%
  - Or exceeding the country-specific threshold for intervention

Very high risk of fracture (any one of the following)

- Recent fracture
- Multiple fractures
- Severe fracture
- Fracture while on treatment
- Fracture while on bone-toxic drug such as corticosteroids
- *T*-score ≤ -3.0 standard deviations
- FRAX 10-year probability of fracture (adjusted for trabecular bone score):
  - Any major osteoporotic fracture: > 30%
  - Hip fracture: > 4.5%
  - Or exceeding the country-specific upper threshold for high risk
  - Other factors such as an extremely high risk for falls.

Bisphosphonates

The most commonly prescribed antiresorptive therapy remains the bisphosphonates. Available bisphosphonates include oral alendronate, risedronate and ibandronate as well intravenous ibandronate and zoledronic acid. The overall benefit/risk ratio of the bisphosphonates remains favorable despite concerns regarding osteonecrosis of the jaw and atypical femur fractures [24]. It is recommended that continuation of therapy be reconsidered after 5 years of oral alendronate therapy or 3 years of intravenous therapy depending on response to therapy and the remaining risk of fracture.

Menopausal hormone therapy

The IMS recommends that menopausal hormone therapy (MHT) be considered in women at risk of fracture before the age of 60 or within 10 years after menopause [25]. This recommendation is based on the risk reduction seen in all fractures in the Women's Health Initiative study and a favorable benefit/risk ratio in the younger woman [26].

The US Endocrine Society basically agrees with this but adds the following other considerations: those at low risk of deep vein thrombosis; those in whom bisphosphonates or denosumab are not appropriate; and those with bothersome vasomotor symptoms [11]. Once initiated for treatment, there is no fixed limitation on duration of use of MHT as long as the indication remains.

Selective estrogen receptor modulators

Selective estrogen receptor modulators such as raloxifene and bazedoxifene are advised in women at risk of vertebral fracture and breast cancer [27].

Denosumab

Denosumab is an alternative to the bisphosphonates. It is a human monoclonal antibody against RANKL and prevents coupling with osteoclasts and its precursors, thus resulting in inhibition of resorption and resultant preservation of bone mass [28]. Bisphosphonates cause an increase in BMD, but this is limited to the first 3 years of treatment. Denosumab, on the other hand, continues to increase BMD beyond the first 3 years. In 10 years of follow-up, the protective effect on the risk of fractures remained over time [29]. Unlike the bisphosphonates, denosumab is not secreted by the kidneys and no limitation is set by poor renal function. Denosumab discontinuation is associated with a rebound loss in BMD, with an increase in vertebral fractures, unless treatment is rapidly transitioned to an alternative antiresorptive drug [30]. This can be best explained by the fact that the blood-borne monoclonal antibodies rapidly decline after 6 months whereas bone-bound bisphosphonates may be metabolically active for much longer. Denosumab is administered as 60 mg subcutaneous injection 6-monthly.

Bone anabolic treatment

Anabolic therapy (stimulation of new bone formation) was previously regarded as second-line therapy and primarily reserved for cases of treatment failure on antiresorptive therapy. This was in part driven by the high costs associated with teriparatide as well as fears of osteosarcoma based on rat models but this never materialized in practice if limited to 24 months of treatment [31]. Two recent trials beckoned a more aggressive approach to anabolic therapy as first-line treatment. In the VERtebral Fracture Treatment Comparisons in Osteoporotic Women (VERO) study, postmenopausal women with severe osteoporosis received the anabolic agent teriparatide (parathyroid hormone analog) or risedronate [32]. After 24 months, teriparatide-treated women had a significantly reduced risk of vertebral and any clinical fracture, with a non-significant trend in reduction of non-vertebral fractures. In the Active-Controlled Fracture Study in Postmenopausal Women with

Osteoporosis at High Risk (ARCH), postmenopausal women with severe osteoporosis received 12 months of romosozumab (a new humanized monoclonal antibody that inhibits sclerostin) followed by 12 months of alendronate and this group was compared to those receiving 24 months of alendronate therapy. The romosozumab-treated women showed a significant reduction in vertebral, hip, non-vertebral and clinical fractures [33]. Another anabolic agent, abaloparatide (parathyroid hormone-related protein analog) has not been investigated head-to-head with any antiresorptive. There is consensus between the recommendations of the International Osteoporosis Foundation/European Society for Clinical and Economic Aspects of Osteoporosis (IOF/ESCEO) [22] and those of the US Endocrine Society [11] that, in postmenopausal women at very high risk of fracture, the use of an anabolic agent followed by the use of an inhibitor of bone resorption should be considered. This entails 12 months of romosozumab or 24 months of either teriparatide or abaloparatide followed by antiresorptive treatment.

Summary

An appropriate strategy to lower osteoporosis-related fractures requires knowledge of the definition of osteoporosis, fracture risk prediction, stratification of risk, intervention thresholds and the most appropriate interventions (Table 3). All societies are encouraged to develop intervention thresholds based on local factors and not to blindly accept fixed values as developed in other countries.

Table 3. Summary of a suggested treatment guideline based on fracture risk.

Low fracture risk
Optimize calcium and vitamin D status
Bone-friendly lifestyle
High fracture risk
Optimize calcium and vitamin D status
Bone-friendly lifestyle
Falls prevention
Start appropriate antiresorptive therapy
Very high fracture risk
Optimize calcium and vitamin D status
Bone-friendly lifestyle
Falls prevention
Consider appropriate anabolic treatment for 12–18 months followed by antiresorptive therapy.

What is the role of muscle in bone health?

Osteoporosis and osteopenia are well defined conditions, as discussed in the first part of this paper with known risks associated with fracture. A recent review of Pubmed found that the first article published with the keyword ‘osteoporosis’ was in 1894; through May 2020 there were a total of 93,335 articles utilizing that

keyword. It was coined by a French pathologist, Jean Lobstein, in the 1820s in the context of osteitis (inflammation of the bone). It was derived from the Greek osteon (bone), to which he added poros (little hole). Thus, osteoporosis means 'porous bone', a condition that Lobstein observed in patients [34].

Sarcopenia is a condition characterized by the loss of skeletal muscle mass and function [35]. The Greek roots for the word are *sarx* for flesh and *penia* for loss and it was coined by Rosenberg in 1989 [36]. The same review of Pubmed with 'sarcopenia' as the keyword revealed the first article in 1993, with a total through May 2020 of 12,068.

Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength, with a risk of adverse outcomes such as physical disabilities, poor quality of life and even death [37]. Muscle accounts for 60% of the body's protein. Muscle mass decreases with age, although younger patients with malnutrition, cachexia or inflammatory diseases are also prone [38]. However, unlike osteoporosis, with a well-accepted definition based on DXA measurements, there is no universally accepted definition of sarcopenia, consensus diagnostic criteria or treatment guidelines. In 2016, in the ICD-10-CM, sarcopenia was finally recognized as a disease entity [39]. In trying to better understand this entity, it may be valuable to look at the findings of various consensus groups:

- Originally, the European Society for Clinical Nutrition and Metabolism Special Interest Groups defined sarcopenia as the presence of low skeletal mass and muscle strength and advised that it could be assessed by walking speed [40].
- The International Working Group on Sarcopenia concurred but added that sarcopenia is associated with muscle mass loss alone or in conjunction with increased fat mass [41].
- The European Working Group on Sarcopenia in Older People (EWGSOP) separated muscle strength and muscle performance (Table 4). Furthermore, they labeled pre-sarcopenia as low muscle mass without impact on muscle strength or performance, sarcopenia as low muscle mass with either low muscle strength or low physical performance, and severe sarcopenia as all three criteria being present [42].

Table 4. Definition and diagnosis of sarcopenia (European Working Group on Sarcopenia in Older People [42]).

Classification	*Muscle mass*	*Muscle strength*	*Muscle performance*
Pre-sarcopenia	Low	Within normal limits	Within normal limits
Sarcopenia	Low	One of these two criteria categorized as low	
Severe sarcopenia	Low	Low	Low

It is worthwhile to note that frailty (an entity beyond the scope of this review) has significant overlap with sarcopenia but is characterized by deficits in multiple organ systems such as psychological, cognitive, and or social functions in addition to physical limitations [43].

In 2019, the EWGSOP revised its consensus [44]. In it, they now recommend that low muscle strength is the primary parameter of sarcopenia and the most reliable measure of muscle function. Thus, the operational

definition of sarcopenia is deemed as 'probable' if there is low muscle strength; it is confirmed by low muscle quality or quantity. If low physical performance is present with the first two criteria, the sarcopenia is considered severe.

Clinical practice tools for assessing sarcopenia

There is no universally recognized methodology for measuring muscle strength, muscle mass or physical performance. An in-depth review is beyond the scope of this article, but some simple but effective tools include:

- Hand grip strength, which is simple and inexpensive to measure. When low, it is a powerful predictor of lower extremity muscle strength. It is done with a hand-held dynamometer and is adjusted for gender and BMI. For women with BMI ≤ 23, 23.1–26, 26.1–29 or > 29 kg/m^2, the cut-off values in kilograms below which grip strength is considered abnormal are ≤ 17, ≤ 17.3, ≤ 18 and ≤ 21 kg, respectively [44].
- Gait speed is probably the simplest measure of physical performance and is usually timed walking over 4–6 m. A gait speed ≤ 0.8 m/s is considered abnormal [44].
- Muscle mass is not as easily measured clinically. Although magnetic resonance imaging and computed tomography are considered the gold standard, they are not readily used clinically. Special software added to DXA is somewhat more widely available. Bioelectrical impedance analysis is more affordable and portable but more studies, especially considering discrepancies based on age, ethnicity and even hydration, are necessary [44]. However, muscle mass does correlate with body size. There is no consensus whether anthropometric measurements can be used as a surrogate for muscle mass. Calf circumference has been shown to predict performance and survival in older patients (cut-off < 31 cm) [44]. Thus, the EWGSOP feels that calf circumference measures may be used as a proxy in older patients in whom other methodologies for measuring muscle mass are unavailable [44].

Osteosarcopenia

Osteosarcopenia is defined as the concomitant presence of osteoporosis or osteopenia combined with sarcopenia [45]. This new syndrome is associated with higher disability and rates of fracture and falls in older people compared with either entity (the bone component or the sarcopenia component) alone [46]. There is increasing evidence of cross-talk between muscle and bone [47]. A review of Pubmed using the keyword 'osteosarcopenia' found its first mention in 2014 and, as of May 2021, only a total of 126 articles.

The clinical significance of a combination of osteoporosis/osteopenia with sarcopenia is well illustrated in a cross-sectional analysis of 253 participants [48]. Of these, 77% were women, with an average age of 78 years, who presented for a 'falls and fractures' risk assessment. *T*-scores were measured by DXA. In addition, components of sarcopenia were measured. Falls in the previous year were self-reported, with 42% having fallen once and 54% having fallen more than once. Those women with osteosarcopenia had a statistically significant increased rate of falls of approximately three-fold and an increased rate of fractures that was approximately four-fold when compared to those women with osteopenia or osteoporosis alone. Another

important aspect was that, despite the links between osteoporosis, fracture and poor clinical outcomes, there were no differences in fracture rates in osteopenic compared to osteoporotic classifications. Other studies have reported discrepancies in fractures and BMD, with osteopenic older adults experiencing fracture rates similar to, and, in some cases, greater than those diagnosed with osteoporosis [49]. Thus, it appears that the use of *T*-scores combining osteopenic and osteoporotic categories into an osteosarcopenic category may be sufficient to capture those at the greatest risk of fracture.

Osteosarcopenia can be expected to increase in clinical importance in age-related and disease-related states as a consequence of immunosenescence coinciding with an increase in sedentary lifestyle, obesity, and fat infiltration of muscle and bone [50].

Summary

Clinicians should acknowledge the increased fracture risk associated with osteosarcopenia. In addition to measuring BMD, they should also consider as useful tools DXA-derived measurement of muscle mass, bioelectrical impedance analysis, the measurement of calf circumference, assessment of muscle strength by grip strength, as well as estimation of functional capacity utilizing gait speed. Clinicians should do a more comprehensive geriatric assessment including medical history, assessment of risk factors for falls and a review of concomitant medications. Treatment may include progressive resistance and balance exercises. Nutritional recommendations, in terms of protein, vitamin D and calcium are necessary. In terms of anti-fracture medication, it must be taken into account that, in the presence of sarcopenia, classification of low risk for fracture may be escalated to high risk of fracture or from high risk of fracture to very high risk of fracture. The diagnosis and treatment of osteosarcopenia should become part of routine health care.

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