



Unmet Needs and Challenges in Osteoporosis

15

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Introduction

Osteoporosis is always a hot topic that is discussed on yearly basis at all the international conferences dealing with the topic of bone health, reflecting the importance of the disease. In fact osteoporosis is a major health issue, affecting around 200 million women worldwide. Moreover, although osteoporosis is typically linked to women, it is also diagnosed in men, however, to less extent. While one in three women over age 50 will experience osteoporotic fractures, one in five men aged over 50 will sustain the disease [1, 2]. Worldwide, osteoporosis accounts for a greater disability burden than cancer, with the exception of lung cancer [3]. This is supported by the reports showing that the incidence of osteoporosis is increasing [2]. In contrast, osteoporosis treatment remains a challenge, with 50–70% of the patients discontinuing their osteoporosis medications within the first year of initiation [4]. Therefore, there is an urgent need for improved management of osteoporosis and its consequences.

Over the past decade, several guidelines have been published for the pharmacological management of osteoporosis in postmenopausal women, which highlight the need for earlier, more wide-

spread screening, and treatment are published [5]. However, a US observational study of women experiencing a first hip fracture between 2008 and 2013 showed that only 17% and 23% had evidence of osteoporosis assessment and/or treatment within 6 or 12 months of their fractures, respectively [6]. Furthermore, the Healthcare Effectiveness Data and Information Set (HEDIS), which is a tool used by more than 90% of America's health plans to measure performance on important dimensions of care and service for a number of disease areas [7], assessed the number of women aged 65–85 years who suffered a fracture and who had either a bone mineral density (BMD) test or prescription for a drug to treat osteoporosis in the 6 months after their fracture with the intent to reduce the risk of fractures resulting from osteoporosis in older women. Testing/treatment rate in women who sustained a fracture in the USA reached 49.6% in 2018 [8]. Results from a recently published survey of untreated postmenopausal women with osteoporosis and their physicians reported that patients themselves decided against pharmacological treatment in at least half of the cases of nontreatment. The most frequent reasons for this patient decision were concerns regarding side effects, alternative nonprescription options (including behavioral modification), and questioning medication benefits [6, 9].

Such inconsistency in management, together with underdiagnosis and undertreatment of peo-

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Table 15.1 Unmet needs and challenges in the field of osteoporosis

Optimizing peak bone mass in young adults
Definition of high-risk patients
Inclusion of imminent fracture risk in the FRAX calculation of osteoporosis fracture risk
Optimizing the diagnostic approach of the patients with clinical risk factors for osteoporosis
Inclusion of bone strength as measurable parameter
Closing the treatment gap and the introduction of new drugs with new mechanisms of action
Introduction of critical thinking into share decision making tools
Clear definition of treat-to-target and drug holiday

ple who are at high risk for fracture, represents the unmet need in the diagnosis and management of osteoporosis. It is, therefore, vital to identify and address these factors which may contribute to such challenge. Table 15.1 summarizes the unmet needs and challenges in the field of osteoporosis. This chapter will discuss the unmet needs and challenges of diagnosing and management of osteoporosis and the limitations of currently available tools.

Challenge 1: Fracture Risk Score and Absolute Risk of Fracture

The National Institutes of Health Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy defines osteoporosis as a skeletal disorder characterized by low bone strength and increased risk of fracture [10]. This definition of osteoporosis reflects the changing perspective on this disease, i.e., osteoporosis is no longer considered a disorder of low bone mineral density alone. Epidemiologic studies have been performed to examine the risk factors that are associated with low bone mineral density and fragility fractures [11, 12]. Consequently, assessments of clinical risk factors that are independent of BMD have been identified as important prognosticators for fracture prediction. Namely, in addition to BMD, advancing age, prior history of fragility fracture, chronic glucocorticoid use, low body mass index (BMI), parental history of hip fracture, cigarette smoking, and excess alcohol

intake are the risk factors that have been demonstrated to be most predictive of fracture.

Expression of fracture risk: Absolute risk (AR) is the probability of fracture, usually expressed as a percentage, over a specified period of time. Relative risk (RR) is the ratio of absolute risks of two populations [13]. RR tends to overestimate fracture risk in some populations and underestimate it in others [14]. As an example, a 50-year-old and an 80-year-old woman with a hip T-score of -2.5 each have the same RR for hip fracture compared with an age-matched population with normal BMD [13], while the 10-year probability of hip fracture is much higher in the 80-year-old woman. Both are measures of risk, but estimation of an individual's fracture risk requires knowledge of absolute risk when relative risk estimates are used. Therefore, absolute risk is a measure easily explainable to both the physician [15] and the patient.

Several fracture risk assessment tool have been developed; however, the most popular and commonly used out of them is the developed, in 2008, by the University of Sheffield (FRAX) that estimates the 10-year probability of hip fracture and major osteoporotic fracture (hip, clinical spine, proximal humerus, or forearm) for untreated patients between ages 40 and 90 years using easily obtainable clinical risk factors for fracture and femoral neck BMD (g/cm^2 , using dual-energy X-ray absorptiometry [DXA]), when available [16, 17]. As well as the FRAX tool, other fracture risk calculators are available online which include the Garvan fracture risk calculator (www.garvan.org.au) and QFracture (www.qfracture.org).

There are several important limitations that need to be considered when FRAX is used as a calculation tool. The relationships between risk factors and fracture risk incorporated within the FRAX model have been constructed from the primary data of nine population-based cohorts around the world [18–20]. Databases from most of the countries incorporated into FRAX provided accurate rates of hip fractures because all patients with a hip fracture are admitted to a hospital. However, patients with a wrist or proximal humeral fracture are usually treated as outpa-

tients, leading to an underestimation of the incidence of these types of fractures [21]. Assessing the rate of clinical vertebral fracture is also challenging since it is difficult to distinguish between patients with a clinical vertebral fracture and patients who have back pain with an incidental vertebral compression fracture. Therefore, the reported rates of major osteoporotic fractures at sites other than the hip may not be accurate. Kanis et al. [19] studied the use of clinical risk factors to predict osteoporotic fractures on the basis of baseline and follow-up data from nine population-based cohorts. They found that models for predicting hip fractures were substantially better than those for predicting osteoporotic fractures at other sites, regardless of whether the models included bone mineral density alone, clinical risk factors alone, or a combination of both [22]. For these reasons, the prediction of the risks of three other major osteoporotic fractures (proximal humeral, wrist, and clinical vertebral fractures) may not be as accurate as the prediction of the risk of hip fracture.

There is also a question of the generalizability of data obtained from the population-based cohorts. For example, the US FRAX model was formulated from data from the Rochester cohort, which was recruited from two random population samples in Olmsted County, Minnesota. This community is predominantly White and is better educated than the White population of the USA as a whole [23]. In addition, recent data have shown that the incidence of hip fracture among Olmsted County residents is declining [24]. Therefore, the incidence and mortality data in the US FRAX model may not reflect current incidence and mortality rates.

The use of FRAX sometimes results in 10-year fracture probabilities that lead to treatment recommendations that contradict those of the National Osteoporosis Foundation. For example, a 50-year-old postmenopausal woman with a body mass index of 24.1 kg/m², no clinical risk factors, and a T-score of -2.5 meets the threshold for pharmacological therapy on the basis of the T-score; however, the fracture probabilities calculated with the FRAX tool (8.7% for a major osteoporotic fracture and 2.5% for a hip fracture)

are below the treatment threshold. Conversely, an 80-year-old postmenopausal woman with the same body mass index, a parental history of hip fracture, and a T-score of -1.0 has 10-year risks of 26% and 9.9%, respectively, for a major osteoporotic fracture and for a hip fracture—a level of risk at which treatment should be considered [25]. Yet, there is no strong evidence to support treatment of patients with this level of bone mineral density. In addition, FRAX may not accurately predict fracture risk across all age groups [22]. Furthermore, fracture risk probabilities calculated with FRAX are not valid for patients who have already received pharmacological treatment for osteoporosis such as bisphosphonates.

The magnitude by which FRAX may over- or underestimate fracture risk has been studied using large population databases, and procedures for adjusting FRAX probability have been proposed [26, 27]. As an example, an analysis of the Canadian Manitoba BMD database shows that when there is discordance between lumbar spine and femoral neck BMD, the FRAX estimate for major osteoporotic fracture may be increased or decreased by one-tenth for each rounded T-score difference or offset between lumbar spine and femoral neck (e.g., when the lumbar spine T-score is 1.0 less than the femoral neck T-score, the 10-year probability of major osteoporotic fracture can be increased by one-tenth) [26]. Another analysis using the UK General Practice Research Database showed that for patients exposed to high-dose glucocorticoids (prednisolone >7.5 mg/day or equivalent), the 10-year probability of major osteoporotic fracture may be increased by 15 percent and the 10-year probability of hip increased by 20 percent [27]. The increase in fracture risk associated with type II diabetes mellitus may be captured by entering “yes” for rheumatoid arthritis in the FRAX algorithm [28]. With modifications such as these, the FRAX probability of fracture can be refined [29]. However, these correction factors have not been computed for the majority of countries represented by FRAX, including the USA. Thus, they should be applied to US populations with caution.

Other important risk factors for fractures are not included in this calculation tool. These include

the serum level of 25-hydroxyvitamin D, physical activity, risk of falls, and biochemical bone markers. Therefore, the calculated risk may be less than the actual risk. In addition, FRAX does not take into account bone mineral density at the spine or the substantially higher risk of spine fracture among those with a history of vertebral compression fractures. A cohort study of 6459 women 55 years of age or older with low bone mineral density, of whom 31% (2027) had a radiographically detected vertebral fracture at baseline, demonstrated that a combination of a vertebral fracture on a baseline radiograph, femoral neck bone mineral density, and age predicted incident radiographically evident vertebral fractures significantly better than did use of FRAX and bone mineral density at the femoral neck ($p = 0.0017$) [30]. Nevertheless, FRAX remains an important tool that represents an advance in the care of osteoporosis. The current FRAX model provides an aid to enhance patient assessment by the integration of clinical risk factors alone and/or in combination with bone mineral density. It is anticipated that the limitations described above will be addressed in future FRAX versions.

Challenge 2: Implementation of Health Economics into Clinical Guidelines

The use of health economic thresholds incorporating QALYs (quality-adjusted life year) led to some difficulties with some of the initial guidelines developed [31, 32], as the costs of treatments meant that patients with osteoporosis confirmed by dual-energy X-ray absorptiometry (DXA) would not have access to drugs, since estimated health costs exceeded £20,000/QALY [7]. In response, the National Osteoporosis Guideline Group (NOGG) in the UK developed evidence-based guidelines with alternative treatment thresholds, which were not set using health economic considerations but the clinical fracture risk after a first low-trauma fracture [33]. On the other hand, the National Osteoporosis Foundation osteoporosis treatment recommendations were based on the 10-year fracture prob-

ability model, whereas, in Scotland, “SIGN” (Scottish Intercollegiate Guideline Network) guidelines took an alternative approach, interpreting clinical trial-based evidence to support drug treatment for those who have had a vertebral fracture and hip fracture or with a bone mineral density (BMD) T-score less than -2.5 [34]. The most recent recommendations from NICE [35] are a radical change, with no health economic argument against oral or parenteral therapy down to a 10-year fracture risk of 1%. However, it recently has been suggested that “Unthinking assimilation of the NICE multiple technology appraisal risks a generation of older individuals taking a bisphosphonate regardless of the individual benefit-to-risk ratio” [36]. There are now a number of guidelines on osteoporosis across Europe and North America, with country- and comorbidity-specific recommendations. Each takes a slightly different approach, resulting in inconsistent recommendations (Table 15.1). Consequently, clinicians are faced with an overwhelming amount of guidance on the management of osteoporosis and bone health from international, national, and local governing bodies. No wonder, such global inconsistency would reflect on the patients’ management particularly at the primary care level.

In addition, there is a low reimbursement for DXA investigations in the USA. It is possible that pharmaceutical industries also play a role, as during the first years after introduction of osteoporotic drugs, an increase of bisphosphonate use was observed (in 2007 ~ 15% of postmenopausal women used bisphosphonates) [37]. Currently, there is a growing market share of generics drugs and increased withdrawal of large pharmaceutical industries, which might be related to a decrease in bisphosphonate use. This emphasizes the certain unmet need for new drugs with an even better efficacy/safety profile.

Challenge 3: Treatment Thresholds

After the advent of absolute fracture risk calculators, guidelines for the management of osteoporosis have been published. These have been updated

several times over the past decade. However, there were disparity between different guidelines and the treatment thresholds advised which represent a challenge to osteoporosis specialists trying to manage their patients, according to these guidelines. Best examples are the guidelines released by the US-based National Osteoporosis Foundation (NOF) and the UK-based National Osteoporosis Guidelines Group (NOGG) which differ markedly in their approaches to treatment recommendations.

The National Osteoporosis Foundation recommendations for pharmacological treatment of osteoporosis [38] are based in part on the US adaptations of the World Health Organization 10-year fracture probability model and algorithms for determining treatment thresholds [39]. These recommendations are based on cost-effectiveness in populations of patients and should be used together with other considerations when making treatment decisions for individual patients. According to the National Osteoporosis Foundation recommendations, treatment of osteoporosis should be considered for (1) patients with a history of hip or

vertebral fracture, (2) patients with a T-score of -2.5 or lower at the femoral neck or spine, and (3) patients who have a T-score of between -1.0 and -2.5 at the femoral neck or spine and a 10-year hip fracture risk of $\geq 3\%$ or a 10-year risk of a major osteoporosis-related fracture of $\geq 20\%$ as assessed with the FRAX. The advantages of this new recommendation as compared with the earlier published National Osteoporosis Foundation recommendations include better allocation of limited healthcare resources to patients who are at higher risk for fracture and most likely to benefit from therapy. In addition, these new guidelines take into consideration different ethnicities in the USA and include the male population.

Similar to the National Osteoporosis Foundation, the UK developed by the National Osteoporosis Guidelines Group (NOGG) [39] incorporated FRAX-derived risk calculations. However, the approaches taken to recommendations for intervention by these guidelines differ markedly, as summarized in Fig. 15.1. The NOF intervention thresholds are based upon economic

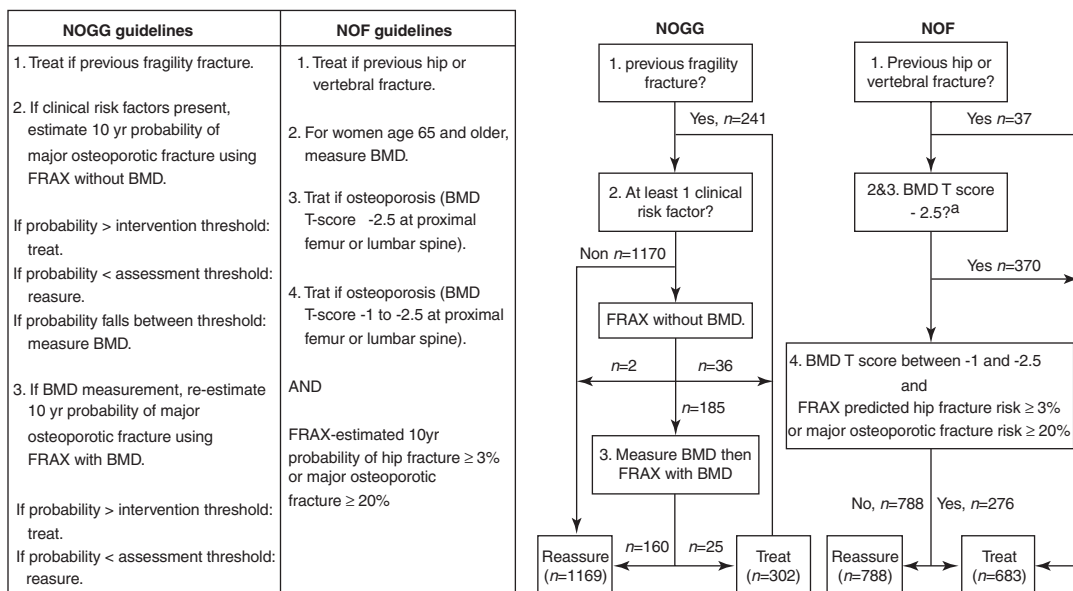


Fig. 15.1 Summaries of the NOGG and NOF guidelines for management of osteoporosis (left), with their application to a cohort of 1471 healthy older women (right). a, Nineteen women in the cohort were younger than 65 yr. at baseline. The NOF guidelines recommend BMD measurement in women younger than 65 yr. if there are con-

cerns based on the risk factor profile. For the purposes of this analysis, we assumed that all these 19 women had a measurement of BMD for this reason. (Unless provided in the caption above, the following copyright applies to the content of this slide: Copyright © 2010 by The Endocrine Society)

cost-effectiveness analyses [40–44], whereas the NOGG guidelines recommend intervention if the probability of fracture exceeds that of a person of the same age who has suffered a previous osteoporotic fracture [45]. Thus, the NOGG intervention and assessment thresholds vary by age and gender, such that reassurance is recommended for older individuals at high risk of fracture, whereas intervention is recommended for younger individuals at lower risk of fracture.

Potentially, the differing approaches between guidelines might lead to different treatment recommendations and fracture outcomes. In the study done by Mark and Grey [46], two illustrative clinical cases were presented to symbolize the difference between the two treatment recommendations. Patient (1) is a female, aged 80 years old, in good health, with BMI of 23.8 kg/m², no personal or parental history of fracture, and a femoral neck BMD T-score of –3. Her estimated 10-year risk of major osteoporotic fracture using FRAX with BMD is 21% and of hip fracture is 9%. Applying the NOGG guidelines leads to a recommendation to reassure, whereas the NOF guidelines recommend treatment. Patient (2) is a female, aged 65 years old, in good health, and also has a BMI of 23.8 kg/m², no personal or parental history of fracture, and a femoral neck BMD T-score of –3. Her estimated 10-year risk of major osteoporotic fracture is 16% and of hip fracture is 5%. Both the NOGG and NOF guidelines recommend treatment. This paved the way for the most recent osteoporosis treatment recommendations published by NOGG in 2017, in which NOGG has released its update in which the intervention thresholds have been based on FRAX probability and so cannot be used with fracture risk derived from QFracture or other calculators [4]. NOGG recommended also that diagnostic assessment should include not only the assessment of BMD where indicated but also the exclusion of diseases that mimic osteoporosis, elucidation of the cause of the osteoporosis, and the management of any associated morbidity. In addition, recommendations for the routine investigation of patients with osteoporosis have been advised and are summarized in Tables 15.2 and 15.3.

Challenge 4: DXA

Appropriate and accurate use of densitometric techniques is of great importance: bone mineral measurements provide not only diagnostic criteria but also prognostic information on fracture risk probability, and they are also used to monitor treated or untreated patient [47]. For this reason, several guidelines have been developed in the last years with a number of recommendations that include indications for BMD testing, which skeletal site to measure and how to interpret and report BMD results, and proper timing for follow-up [48–51]. These guidelines, typically issued by relevant medical societies or specialized working groups, play an important role in clinical practice: they provide valuable suggestions based on the highest level of evidence, which is usually achieved through a critical evaluation of systematically searched primary studies [52, 53].

The distribution of bone density across a population is dependent on race, age, and gender. For example, African-Americans have lower rates of fracture compared to US Caucasians and Asians, and this parallels the population distribution differences among races [54]. In one study, the age-adjusted mean for femoral neck BMD was 0.686 g/cm² in US Caucasians and 0.841 g/cm² in African Americans [55]. Because of such racial and ethnic differences, the significance of T-scores must be considered based on the fracture risk of ethnic and racially matched persons. A similar rationale can be applied to men who have larger skeletal structures compared to women. To control for racial differences, DXA calculates T-scores using normative databases based on NHANES III data that include non-Hispanic White, Black, Hispanic, and Asian individuals [56]. A pediatric normative base is also available. However, while bone size is directly related to strength, DXA does not account for bone size in assessing fracture risk. Attempts to correct bone size for height and weight have been reported [57]. Some DXA manufacturers allow for weight correction in the calculation of Z-scores to adjust for an expected decrease in fracture risk as weight increases. Height correc-

Table 15.2 Comparative analysis of the most popular osteoporosis guidelines, their targeted subjects, as well as thresholds of treatment

Guideline (year)	country	Targeted people	Drugs included	Thresholds of treatment	Comments	Reference
NOF (2014)	The USA	Men and women over 50 years	FDA-approved medications: alendronate, ibandronate, risedronate, zoledronate, calcitonin, raloxifene, bazedoxifene, teriparatide, denosumab	Treatment should be considered for: Hip or vertebral fracture T-score ≤ -2.5 at hip or spine on DXA T-score between -1.0 and -2.5 with a 10-year risk $\geq 20\%$ for major fracture or $\geq 3\%$ for hip fracture	Just recommends the use of an FDA-approved medication Does not give an order for first-line or second-line agents	37
NOGG (2009 and updated 2017)	The UK	Men and women over 50 years	Alendronate, risedronate, zoledronate, HRT, raloxifene, strontium, denosumab and teriparatide	10-year fracture risk used Men and women aged 70+ years With a fracture or On long-term prednisolone over 7.5 mg daily should be considered for bone protection	FRAX used without BMD to determine fracture risk (high, low, or medium), then refine into high or low risk Calculate risk to age 70+ years; thereafter fixed risk of 20% for major and 5% for hip fracture used Oral bisphosphonate first line No alteration to threshold for use of alternative agents High cost of teriparatide restricts use for those at very high risk of vertebral fractures Incorporates guidance on investigation and management of osteoporosis including vitamin D and falls	38
ESCEO and IOF (2008 updated 2013),	Europe	Postmenopausal women	Alendronate, ibandronate, risedronate, zoledronate, HRT PTH therapies, raloxifene, calcitonin, denosumab, strontium ranelate	10-year fracture risk using FRAX Country-specific thresholds for treatment If prior fracture, consider treatment without further risk assessment	Does not specify order of use of medications Note that cost alone would suggest alendronate as first line DXA depends on country, e.g., very good access in Belgium but very difficult in others such as Bulgaria Offers advice on investigation, vitamin D, management, and fall prevention	39

(continued)

Table 15.2 (continued)

Guideline (year)	country	Targeted people	Drugs included	Thresholds of treatment	Comments	Reference
AACE/ACE (2016)	The USA	Postmenopausal women	Alendronate, ibandronate, risedronate, zoledronate, raloxifene, teriparatide, denosumab	T-score ≤ -2.5 at femoral neck, total hip or lumbar spine or A history of fragility fracture or FRAX probability of $\geq 20\%$ for a major fracture or hip fracture $\geq 3\%$	FDA-approved medications considered Different choices of first or second line depending on situation No previous fracture then first line would be alendronate, risedronate, zoledronate, or denosumab Second-line ibandronate or raloxifene switch to injectables if problems with oral bisphosphonate or to teriparatide Prior fractures first-line denosumab, zoledronate, or teriparatide alternatives alendronate/risedronate or switch to teriparatide	40
Scientific advisory Council of Osteoporosis Canada	Canada	Men and women over 50	Alendronate, ibandronate, risedronate, zoledronate, raloxifene, teriparatide, denosumab	Based on FRAX or CAROC fracture risk calculation 10-year major osteoporotic fracture risk $\geq 20\%$ Aged over 50 years with a hip, vertebral or multiple fractures are high-risk T-score ≤ -2.5 moderate risk and moderate risk needs combining with additional risk factors and patient preference	Includes information on investigation and management as well as falls risk Vitamin D checked and targeted ≥ 75 nmol/L in those requiring treatment First-line treatment Women: alendronate, risedronate, zoledronate, and denosumab Men: alendronate, risedronate, zoledronate, and testosterone	41
SIGN (2015)	Scotland	Men and women Over 50 years	Alendronate, risedronate, ibandronate, etidronate, zoledronate, denosumab, HRT, tibolone, raloxifene, strontium ranelate, teriparatide	Primary prevention FRAX risk $\geq 10\%$ for major fracture and T-score ≤ -2.5 Secondary prevention at least one fragility fracture and a T-score ≤ -2.5 Hip fracture Vertebral fracture	Once over threshold any treatment may be used but First-line alendronate and risedronate Teriparatide if severe spinal osteoporosis Second-line zoledronate or denosumab Third-line ibandronate, etidronate, HRT, tibolone, raloxifene, and strontium Treatment can be initiated without BMD measurements in	34

<p>NICE TA464 (2017),</p>	<p>England and Wales</p>	<p>Men and women</p>	<p>Alendronate, ibandronate, risedronate, zoledronate</p>	<p>Oral BP IV BP if 10-year fracture risk is $\geq 10\%$ or $\geq 1\%$ and oral bisphosphonates intolerant, contraindicated, or failed</p>	<p>Replaces TA-160 and TA-161 recommendations on bisphosphonates Denosumab guidance awaited Uses FRAX or QFracture to estimate fracture risk Analysis shows that medications are cost-effective down to low levels of risk because of their low cost. However, these are not treatment thresholds and NOGG guidance highlighted as a possible clinical guideline to treatment</p>	<p>35</p>
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Table 15.3 proposed approach to investigations for a case of osteoporosis

Basic bone profile	Advanced bone profile assessment
History and physical examination Blood cell count, sedimentation rate or C-reactive protein. Serum calcium, albumin, creatinine, phosphate, alkaline phosphatase, and liver transaminases Thyroid function tests Bone densitometry (DXA)	Lateral radiographs of lumbar and thoracic spine or DXA-based lateral vertebral imaging Serum protein immunoelectrophoresis and urinary Bence Jones proteins Serum 25-hydroxyvitamin D Plasma parathyroid hormone Serum testosterone, sex hormone-binding globulin, follicle-stimulating hormone, luteinizing hormone Serum prolactin 24-hour urinary-free cortisol/overnight dexamethasone suppression test Endomysial and/or tissue transglutaminase antibodies Isotope bone scan Markers of bone turnover Urinary calcium excretion
Other investigations, for example, bone biopsy and genetic testing for osteogenesis imperfecta, are largely restricted to specialist centers	

tion is especially important in assessing fracture risk in children affected by short stature or growth delay [58].

DXA images are a two-dimensional (vertical and horizontal) condensation of a three-dimensional structure. As such, bone thickness is not measured in this scan. The BMC measured reflects the amount of cortical and trabecular tissue present within a structure that acts to attenuate the X-ray signal; bones with more tissue attenuate the signal to a greater degree resulting in a higher gray value and BMC measure. Bone area is a measure of the size of the region of interest "ROI." For the hip, the ROI width is fixed, and thus variation in bone area reflects differences in external bone size. The ratio of these two variables provides a measure of the mass density but not a measure of morphology or material properties. Further, BMD does not differentiate whether the variation in BMD arises from differences in

cortical mass, trabecular mass, or external bone size [59].

Conventional wisdom is that women uniformly lose endosteal and trabecular bone in a similar pattern. Recent data however suggest that the pattern of bone loss with aging in women is not uniform [60]. Bone shape and size at the menopause transition may in fact have a critical role in determining long-term bone loss with aging. Women with narrower femoral necks experienced modest decreases in BMC compared to those with wider femoral necks (Fig. 15.3). But, women with narrow femoral necks also had larger increases in femoral neck area compared to women with wider femoral necks. BMD is the quotient of the BMC divided by the area. Because the larger increase in the denominator (area) in women with narrow femoral necks is similarly matched by the larger decrease in the numerator (BMC) in women with wide femoral necks, the result is that both groups have similar losses in BMD over time but for very different reasons. The impact of these structural and mass changes on strength is currently under investigation. In addition to the previous discussion regarding how most fragility fractures occur in persons with T-scores > -2.5 , this example illustrates another limitation of DXA scanning to accurately predict bone strength and fracture risk.

Diagnosis of Osteoporosis: More Than Dual-Energy X-Ray Absorptiometry Alone

It could be argued that performing a VFA (vertebral fracture assessment) in all patients for whom a DXA is indicated and performed would be beneficial [61]. With this technique, (asymptomatic) vertebral deformities can be detected. For example, it was recently documented in a cross-sectional study that vertebral fractures were found in 13% of rheumatoid arthritis (RA) patients [62]. Vertebral fractures are clinically relevant: although only one-third of the vertebral deformities are associated with clinical signs and

symptoms of an acute vertebral fracture, they are a good predictor of subsequent vertebral and hip fractures and may have impact on quality of life [63]. Moreover, assessment of vertebral fractures in addition to BMD enhances fracture risk prediction [64]. Thus, the finding of one or more moderate or severe vertebral deformities in patients with osteopenia may make the difference between starting treatment with anti-osteoporotic medication or not.

The European League Against Rheumatism (EULAR)/ European Federation of National Associations of Orthopaedics and Traumatology (EFORT) recommendations advocate that in all patients 50 years and over with a recent fracture in addition to DXA/VFA, fall risk evaluation and screening for secondary causes of osteoporosis need to be performed [65]. In patients with an elevated fall risk, it is clinically relevant to establish whether modifiable risk factors can be identified; the same is true for potentially treatable causes of secondary osteoporosis and other metabolic bone disorders. Obviously, both high fall rate and untreated secondary osteoporosis may limit the effect of both nonmedical and drug treatment. There are hardly any data on the implementation of these four crucial diagnostic steps in daily practice. However, considering the access to DXA which is suboptimal and the poor implementation of the other four steps (VFA incorporation in DXA, fall risk assessment, fracture risk assessment, and active screening for secondary causes of osteoporosis), this emphasizes that there is an urgent need for better diagnostic procedures in patients at risk for fractures [66].

Challenge 5: Measuring Bone Strength

Although the DXA device is an easy-to-use tool for diagnosing osteoporosis, a limitation is that the DXA device measures only one aspect of bone strength, that is, bone density, which can be considered as the amount of hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$) per bone area. Therefore,

the BMD value measured by DXA is influenced by degenerative changes, atherosclerosis (aortic calcifications), and fractured lumbar vertebrae, as these conditions are characterized by calcifications potentially increasing BMD values [67, 68].

Another limitation of DXA is that it creates a two-dimensional image of bone structures, and therefore details cannot be identified. A large proportion of fractures occur in individuals not identified by a low augmented BMD (aBMD) (Fig. 15.2). For these reasons, new and more advanced techniques such as trabecular bone score (TBS), high-resolution peripheral quantitative computed tomography (HR-pQCT), ultrasound, finite element analysis (FEA), and magnetic resonance imaging (MRI) are under development.

TBS is a surrogate marker for bone microarchitecture and has been associated with prevalent and incident fractures [69]. Although TBS changes during treatment, TBS is less sensitive to change than aBMD. Although TBS may have a role in predicting future fracture risk in specific disorders like hyperparathyroidism and diabetes, its precise role in osteoporotic care remains to be elucidated.

HR-pQCT is probably a more promising technique: one of the biggest advantages of HR-pQCT is that it constructs a three-dimensional image of the bone and it has the additional value of measuring the microarchitecture of bone, that is, both cortical and trabecular aspects of bone. Previous studies showed that several HR-pQCT-derived bone parameters, with or without FEA, are associated with previous fractures [70–72]. More recently, it was shown that cortical area and cortical bone mass by HR-pQCT analysis was independently of aBMD associated with fracture risk, suggesting that HR-pQCT may have additional value on fracture risk calculation [73]. Moreover, it was demonstrated that in individuals with identical BMD at distal radius area, differences in bone microarchitecture were observed by HR-pQCT due to differences in morphological and biomechanical differences, especially at the cortical level of bone [74, 75].

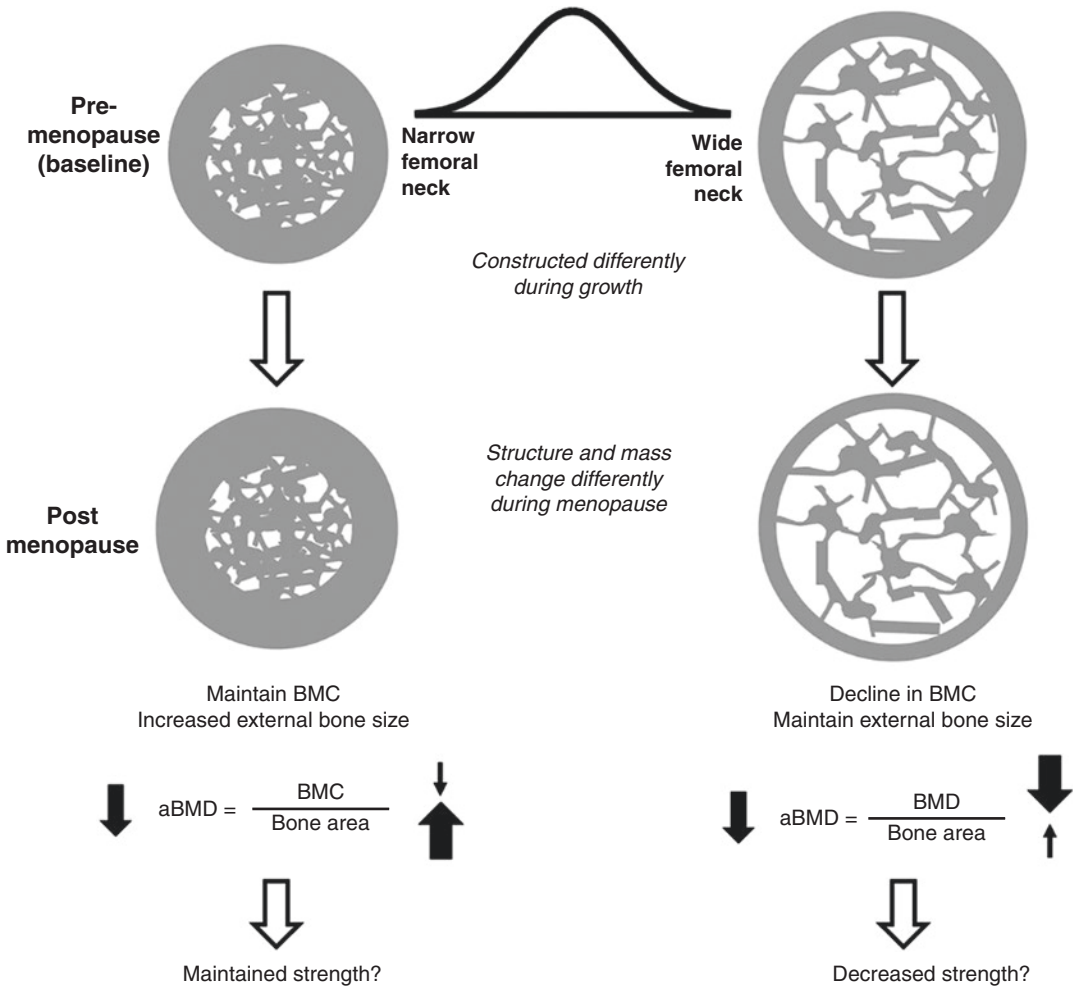


Fig. 15.2 Structural changes in bone with osteoporosis medications. The antiresorptive medications (bisphosphonates and denosumab) and anabolic medications (teriparatide and likely abaloparatide) produce very different structural changes in bone. Although both classes increase trabecular bone, their effects on cortical bone are different. Bisphosphonates and denosumab do not expand periosteal bone but do decrease the endosteal diameter by an increase in endosteal bone volume. Antiresorptives also

reduce cortical porosity. Anabolic agents lead to an increase in periosteal bone with a simultaneous increase in endosteal bone resorption resulting in a bone without a large change in cortical thickness. At the same time, anabolic agents increase cortical porosity. Despite the increase in cortical porosity, the larger bone has increased strength. NC no change. (Adapted from: Choksi et al. [59] (under open access scheme)

Although promising, an important point is that some clinical questions remain: up to now, we do not know what is the most clinically relevant and prognostically optimal region of interest to report in clinical practice. Furthermore, standardization of repetitive measurements of the same region of interest needs to be improved. Therefore, incorporation of this modern diagnostic tool is promis-

ing but remains challenging. In addition, HR-pQCT may have clinical relevance for certain rheumatic diseases like ankylosing spondylitis (AS) characterized by bone formation. In AS patients, suboptimal bone microarchitecture in both axial and peripheral skeleton (distal radius) was demonstrated [76] which is an important finding, as lumbar spine bone density measure-

ment by DXA in AS patients may give an overestimation of BMD due to syndesmophytes or bamboo spine development. Recently, HR-pQCT imaging made it possible to monitor the healing process of fractures by a noninvasive manner, as this technique identified differences in cortices and trabeculae during a follow-up period of 2 years in the fractured and nonfractured site, whereas BMD was similar at both sites [77]. Moreover, a recent collaboration between different bone specialists showed that HR-pQCT imaging is a promising tool to define erosions in RA patients instead of using plane X-rays [78]. Another interesting observation is that HR-pQCT can measure changes in microarchitecture during treatment for a disease. This was illustrated in coeliac disease patients who underwent treatment with gluten-free diet, where it was observed that both BMD as microarchitectural parameters at the trabecular and cortical level improved during intervention [79]. Very recently, data were presented of an observational study in 589 French postmenopausal women with 135 incident fractures, who were followed over 9.4 years. The authors compared the structure fragility score (SFS) combining trabecular and cortical indices by HR-pQCT at the distal radius, with the BMD of the femoral neck and the FRAX® score: the predictive value seems to be comparable for all methods, with no additional value of the SFS on top of the BMD or the FRAX® [80].

Although these studies do not demonstrate that HR-pQCT is superior to DXA for fracture risk assessment, it clearly illustrates that new modern techniques may have additional value and may be promising in the future to have a better fracture risk assessment, especially in certain high-risk patient groups.

These concerns illustrate that the prevention of subsequent fractures after an initial fracture care needs to be improved. An important step forward may be intensification of collaboration between different medical specialists and general practitioners. The recommendations published by EULAR, in collaboration with the European Federation of National Associations of Orthopaedics and Traumatology (EFORT), for

patients with fractures is a good example; in which ten recommendations are advocated for optimal fracture care of patients older than 50 years with a fragility fracture, to prevent subsequent fractures [81].

Challenge 6: Osteoporosis Treatment

The current treatments have one important feature in common; bone resorption and formation remain coupled [82]. This is both from a pharmacological and clinical point of view not optimal and results in unmet needs. First, antiresorptive treatments can only increase bone mineral density (BMD) to a certain extent as the decrease in osteoclast number and release of substances from the bone matrix subsequently impairs the recruitment of osteoblasts and de novo synthesis of new bone by the osteoblasts. Therefore, if the patient initially had very low bone mass, antiresorptive treatments will not be able to improve BMD enough to optimally prevent future fractures. In addition, if the patient also had deteriorated bone architecture, this will be improved, but not restored. Second, teriparatide stimulates osteoblasts and subsequently osteoclasts which limits the effect, and some patients with very low bone mass or suboptimal response to teriparatide are left with very low BMD after treatment. Third, only few studies have examined if the coupling of bone resorption and formation can be overcome by combining the therapies, and the unmet needs thereby may be improved.

Furthermore, while all antiresorptive and anabolic therapies increase spine and hip BMD, with the highest increases in the spine (Fig. 15.3), there is a discrepancy in how these therapeutic agents affect the skeleton (Table 15.4). As newer agents are studied, a trend in more efficacious BMD improvement with each new agent is apparent. Although many osteoporosis treatments have not been directly compared in head-to-head trials, the mechanisms of actions of these newer treatments often predict a superior efficacy in increasing BMD [83].

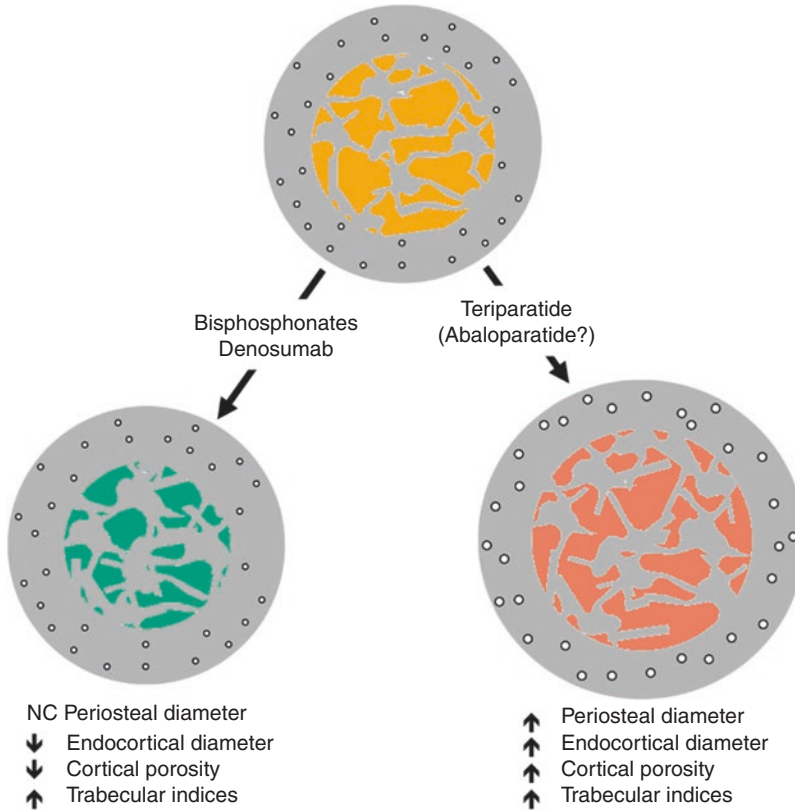


Fig. 15.3 Areal BMD as determined by DXA declines with aging for different reasons. With aging, women with smaller femoral necks tend to increase bone area through an increase in cortical thickness by an increase in periosteal and endosteal bone formation. Since BMD may only decrease slightly but bone area increases more, the result is lower areal BMD as measured by DXA despite likely having little change in

bone strength. In the case of women with larger femoral necks, the endosteal cortex undergoes excessive resorption without periosteal expansion resulting in a thinner cortex. The result is a lower BMC without significant change in bone area. The DXA areal BMD decreases and may result in a bone with less strength. (Quoted from: Choksi et al. [59] (under open access scheme))

All approved osteoporosis medications produce significant increases in spine and hip BMD as measured by DXA. The degree of BMD increase in the spine is likely a consequence of the greater surface area of trabecular-rich vertebral bodies on which the agents act. Twelve months of treatment with bisphosphonates increased BMD by approximately 4% in the spine and 2% in the hip as reported in the landmark FIT, VERT, BONE, and Horizon trials [84, 85, 96, 97]. The efficacy of daily, weekly, and monthly oral and yearly IV bisphosphonate medications are similar [98–102]. Compliance with oral bisphosphonates is a common factor in those patients who fail to respond to treatment

[103–105]. Denosumab has even greater effects likely owing to its enhanced ability to suppress bone resorption [89]. Teriparatide, an anabolic agent, increases spine and hip BMD [59]. Abaloparatide, another recently available anabolic agent, also markedly increases spine and hip BMD [93].

Romozosumab, recently approved for treatment, is a humanized monoclonal antibody that targets sclerostin and has been reported to increase spine BMD approximately 13.5% and hip BMD approximately 6.5% after 12 months of treatment [94, 95].

Numerous published studies have reported the architectural changes in the skeleton with such

Table 15.4 Osteoporosis therapy agents, their doses and grade of recommendation in osteoporotic fractures

Medication	Dosage	Vertebral fracture	Non-vertebral fracture	Hip fracture	BMD (approx. % increase)	
					Spine	Hip
Alendronate	70 mg/week	A	A	A	4 ^a	2–2.5 ^a
Risedronate	35 mg/week	A	A	A		
Zoledronic acid	5 mg IV/annually	A	A	A		
Ibandronate	150 mg/month oral or 3 mg IV every 3 months	A	A ¹	Not adequately evaluated	3.8 ^b	0.5 ^b
Denosumab	60 mg SC every 6-month	A	A	A	5.5 ^c	3 ^c
Raloxifene	60 mg od	A	Not adequately evaluated	Not adequately evaluated	2.9 ^d	No significant change
HRT	Several formulation available	A	A	A	6.76 ^e	4.12 ^e
Teriparatide	20 µg SC every day	A	A	Not adequately evaluated	Teriparatide 9 ^f	Teriparatide 3 ^f
Abaloparatide	80 µg SC once a day					
Calcitriol	0.25 µg twice daily	A	Not adequately evaluated	Not adequately evaluated	No data available	
Romosozumab	210 mg SC qMonth × 12 months	Data only available from phase III trials			13.5 ^h	6.5 ^h
		Reduction by 73%	Reduction by 25%	No data available		

A: grade A recommendations

1: In subsets of patients only (post hoc analysis)

^a12 months of treatment [84–87]

^b12 months of treatment [88]

^c12 months of treatment [89]

^d12 months of treatment [90]

^eAt 24 months of treatment [91]

^f18 months of treatment [92]

^g18 months of treatment [93]

^h12 months of treatment [94, 95]

agents using a variety of techniques that include HR-pQCT and QCT of in situ hip and spine as well as similar techniques of iliac crest bone biopsy samples. What has become clear is that they do not uniformly produce similar results (Table). Bisphosphonates increase cortical thickness primarily by decreasing the endosteal perimeter, partially through the filling in of previously excavated resorption pits at the endosteal surfaces. In addition, bisphosphonates also reduce cortical porosity and increase the amount of trabecular bone. Denosumab has similar effects and

presumably to a higher degree owing to its improved fracture reduction compared to bisphosphonates [59].

Challenge 6: Patient Education

A plunge of around 50% from 2008 to 2012 in postmenopausal women using bisphosphonates was documented in the USA, the so-called crisis in osteoporosis [106, 107], (Fig. 15.4). The reason for the crisis is probably multifactorial: a

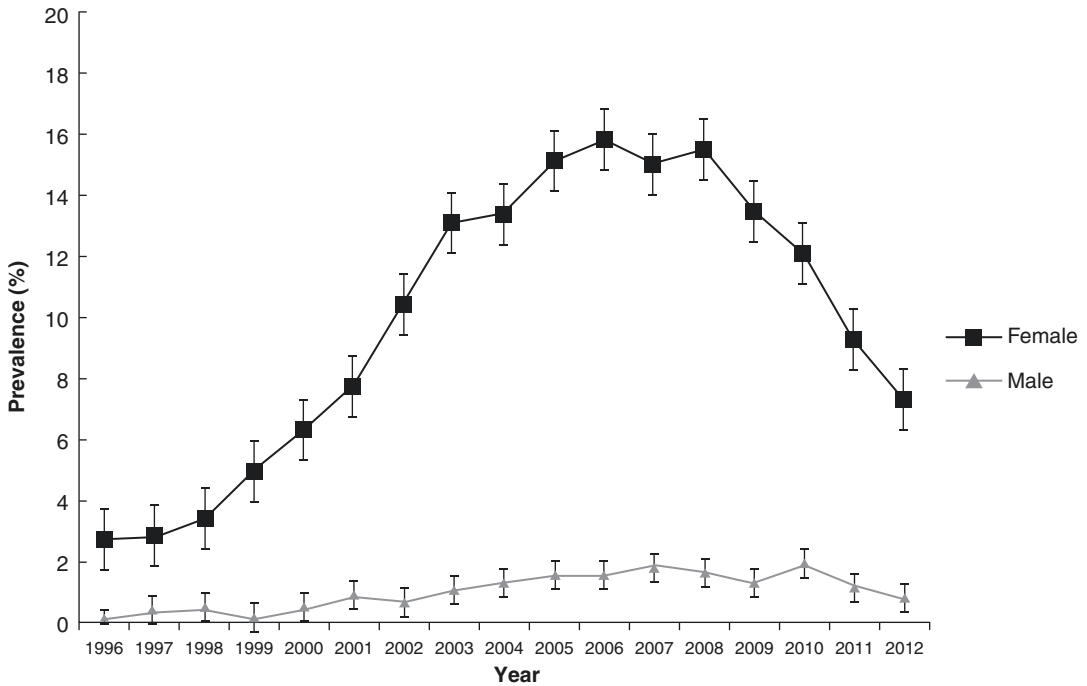


Fig. 15.4 Crisis in osteoporosis treatment: prevalence of bisphosphonate use among females and males aged 55 years and older from 1996 to 2012. Data source:

Medical Expenditure Panel Survey (MEPS). (Jha et al. [37]. To get permission: the author publishing with an STM Signatory Publisher. How can we proceed?)

common public awareness about devastating side effects as atypical femur fractures and osteonecrosis of the jaw is probably the most important. Suboptimal communication by physicians that are not capable of achieving a large fracture reduction by bisphosphonates (30–70% vertebral fracture reduction) versus the very small risk of severe side effects, around 1 in 100,000 bisphosphonate users, may exacerbate this issue. It is important to realize that effective drugs reduce fracture rates, but do not fully prevent the occurrence of fractures. Other explanations are lack of education to and engagement with osteoporosis by physicians, who may regard osteoporosis as a low medical priority, poor coordination of healthcare systems, inadequate access to diagnostic tools such as DXA and VFA, low adherence and compliance to anti-osteoporotic drugs, and the treatment gap [108]. Patient education can be stratified into phases subject to the patients' age.

How to Improve Peak Bone Mass?

In general, it can be stated that peak bone mass can be influenced not only negatively but also positively during young adult age. Therefore, it is important to realize that due to welfare, there is a change in lifestyle not only due to changes in nutrition and diet, but adolescents also seem to have a more sedentary lifestyle. Nowadays, youth has changed activities during leisure to a more sedentary relaxation with game consoles and other video games. This may be a difficult but necessary challenge as several studies showed that sedentary behavior in young children is associated with a lower bone density and ultimately lower peak bone mass [109, 110]. Recently, it could be demonstrated that more hours of watching television per day was associated with a lower BMD [111].

On the other hand, there is a chance to initiate intervention programs to increase peak bone

mass for young adults, as it was observed that physical activity was associated with increased BMD levels [44]. In this study, it was shown that moderate activity, e.g., walking, cycling or exercises, for at least 4 h a week, and participation in recreational sports for at least 4 h a week or participation in hard training or sports competitions several times each week may increase BMD up to 11% and 13%, respectively in girls and boys aged 15–19 years [112]. Moreover, a retrospective cross-sectional study in prepubertal girls that observed global physical activity and not only activities related to sports was associated with a greater peak bone mass [113]. Nevertheless, although physical exercise may have a positive effect on BMD and peak bone mass, there are remaining questions about the optimal intensity and duration of therapy. Promising results were shown in a recent study by Mitchell and colleagues, as this study observed an improvement of bone after physical activity in children genetically predisposed to lower bone density [114]. Another point is how to change behavior from a sedentary type to a lifestyle with more physical exercise in large groups of young adults. Therefore, there is an urgent need for not only limiting the negative modifiable factors (low calcium, low vitamin D, smoking, and alcohol) but also investing in positive modifiable factors (mainly exercise) to aid in achieving optimal peak bone mass values in many individuals.

Proactive Non-pharmacological Measures to Prevent Fractures

Non-pharmacological supplements (including adequate calcium intake and vitamin D levels and exercise) have an important role to play in maintaining a healthy lifestyle, which is crucial for patients at high risk of sustaining a fracture, particularly, on the other hand, a nonhealthy lifestyle may have negative impact on BMD, bone quality as well as risk of falling [115].

Calcium and vitamin D and exercise: there is ample evidence showing a positive effect of healthy lifestyle elements (calcium, vitamin D, exercise) on the bone. In addition, the balance,

though not yet fully proven, between a positive effect of a healthy lifestyle on bone, in combination with the absence of side effects, is attractive. An adequate calcium balance is an important factor in bone strength. Obviously, an extremely low dietary calcium intake, particularly in patients with malabsorption, for example, after bariatric surgery, may induce a strong tendency to serum hypocalcemia and a subsequent elevated bone resorption. This can be counteracted by oral calcium supplementation. On the other hand, earlier data have suggested that calcium supplementation might be associated with increased cardiovascular risk [116]. However, several other studies have not confirmed such assumed relationship between high dietary calcium intake and cardiovascular events [117, 118], leading to a continuing debate about whether calcium supplementation may lead to an elevated myocardial infarction risk. This is even more critical, as a study which included rheumatoid arthritis patients revealed that the risk of a cardiovascular event was elevated after a fragility fracture with a hazard ratio of 1.8 (95% confidence interval: 0.85–1.63) [119]. Another point is that when calcium is prescribed for osteoporotic patients with a low dietary calcium intake, it is difficult to estimate the dietary calcium intake with a simple questionnaire [120], and it is also difficult to assess the percentage of the calcium that has been absorbed in the intestine and which part of that is finally taken up and laid in the bone.

Another important modifiable risk factor is Vitamin D. Lower serum 25-hydroxy(OH) vitamin D levels have been reported to exert a negative impact on bone mineralization, consequently, on bone strength, and may also lead to muscular weakness and an increased risk of falling [121, 122]. Furthermore, low levels of serum 25(OH) vitamin D have been reported in patients who sustained a hip fracture [121]. Other studies have shown an association between low vitamin D levels and an increased risk of all-cause mortality, which could reflect a causal effect but could also result from less exposure to sunshine in elderly individuals with severe underlying diseases and comorbidities [123, 124].

In a large meta-analysis, it was shown that vitamin D supplementation (800 IU/day), in patients who received calcium supplementation, is associated with a 20% reduction in non-vertebral fractures and also with a 20% reduction in falls [125, 126]. In a randomized controlled trial observing different dosages of vitamin D, in >95% of patients, a serum level of 50 nmol/l was found after 6 months of treatment. However, it is not clear to which patients vitamin D supplementation should be prescribed: to all osteoporotic patients or only to those with a vitamin D level deficiency or insufficiency? Strikingly, very high-peak dosages of vitamin D (annually 500,000 IU/year) seem to be associated with increased fall risk and fracture risk [127, 128], while a dosage of 2000 IU per day was associated with a higher fall risk than with a dosage of 800 IU per day [129].

Smoking is another important non-pharmacological factor that has a negative effect on bone strength, mediated by direct negative impact on osteoblasts, upregulation of receptor activator of nuclear factor- κ B ligand (RANKL), alterations in calciotropic hormones and decreased intestinal calcium absorption [130]. In addition, heavy smokers are often physically inactive and have a low body weight, which are also important risk factors for fractures. Thus, there is much evidence that stopping smoking and starting with a healthier lifestyle are crucial in those individuals regarded as heavy smokers; unfortunately it is not easy to stop smoking, particularly for those who are addicted to nicotine.

With regard to alcohol, more than four alcoholic beverages per day show deleterious impact on bone tissue, particularly a negative effect on bone formation [120]. However, even more than two units of alcohol per day increases the risk of osteoporotic and hip fractures, not only because of the negative effect on bone but also because of a negative effect on neuromuscular coordination and fall risk [131].

Other dietary-modifiable factors that influence bone mass and future fracture risk include other nutritional factors like protein intake and

fruit. Previous studies have shown an incremental increase in bone mass with protein intake in young adults, and, recently, different diets have been identified to decrease fracture risk by improving bone strength [132]. Moreover, better milk intake improves bone mineral acquisition in adolescent girls [133]. On the other hand, ketogenic diets may cause a steady rate of bone loss, as measured in the spine, presumed to be because ketones are acidic; and so, keto diets can put people in what's called a "chronic acidotic state." These observations may implicate clinical relevance, although the main question is how much intake of proteins, fruit, or dairy is necessary in general; and the next question is whether these amounts can be applied to the individual patient in standard clinical practice.

Physical exercise, especially weight-bearing activity, has been reported to have beneficial effects on the skeleton in both adolescents [134–136] and the elderly. Many studies have shown that weight-bearing exercise can increase bone mineral density (BMD), particularly at a young age. Many previous studies have demonstrated an osteogenic effect of high impact and weight-bearing exercise on BMD using DXA [137–139]. In humans, the main stresses applied at the level of the calcaneus are ground reaction forces (GRF) as the heel strikes during locomotion [140]. Based on the GRF, swimming (GRF < 1 × body weight), dancing (GRF between 1 and 4 × body weight), and soccer (GRF > 4 × body weight) can be classified as low, moderate, and high impact exercise, respectively [141–143]. The relationship between loading magnitude and bone can be explained by the bone mechanostat theory proposed by Frost [144], who stated that exercise has a combined effect on bone modeling and remodeling, in that bone mass is increased by modeling and the added bone is retained by remodelling. Mechanical loading is also beneficial to bone structure. If a load is imposed, the bone will accommodate and undergo an alteration in mass, external geometry, and internal microarchitecture [108, 145].

Multifaceted Osteoporosis Group Education

In today's healthcare system, patients are expected to play an active role and take responsibility for their own health [146, 147]. In light of this development, disease-specific group education (GE) has become an integral and continuing part of healthcare provision [148] and a recommended way to encourage patients to become active participants in their own care [149–151]. Active participation includes making decisions about medical treatment and learning how to make lifestyle changes. The constant need to make health decisions is evident for patients with the chronic disease such as osteoporosis [152]. These patients face numerous self-care decisions, for example, whether to take medicine and to start doing weight-bearing exercises. Usually patients with osteoporosis consult their physician or general practitioner to discuss and evaluate the treatment within the first year after starting treatment. Afterward, treatment is evaluated every 2–3 years; hence, making decisions on how to manage osteoporosis in daily life relies heavily on the patient.

In the encounter between patients and physicians, decision-making is described as an iterative process including three steps: (1) information exchange, (2) deliberation about options, and (3) deciding on treatment to implement [153–155]. Research on patients with osteoporosis and decision support has shown that decision aids increase patients' knowledge of options for managing osteoporosis and help them clarify their own preferences [156, 157]. A systematic review found that tools, especially those including reminders and education support, may reduce fracture risk by increased use of osteoporosis medicine leading to increase in bone mineral density (BMD) [158]. A study of patients with osteoporosis fractures and their decisions about taking prescribed osteoporosis medication revealed that regardless of whether the decision was easy or difficult to make, patients stated that the decision was not permanent as a number of circumstances could cause them to change it again [152]. Another study explored decision-

making in the context of multifaceted group education for patients with osteoporosis. During group education, patients changed their understanding of lifestyle conducive to bone health, which had an impact on their decision-making. Patients sought clear recommendations on how to manage a life with osteoporosis and were offered information regarding a variety of ways to follow the recommendations. Teachers supported the patients by providing medical information and listening to patients' experiences. Group education led to many healthy decisions on the part of the patients and to advice and directions on how the patients could implement decisions in the future to ensure bone health [159].

In conclusion, osteoporosis is a silent disease with increasing prevalence due to the global aging population. Decreased bone strength and bone quality is the hallmark of osteoporosis which leads to an increased risk of fragility fractures in elderly. This must be considered as a major health concern, as it has previously been established that fragility fracture has been associated with decreased quality of life due to increased disability and more frequent hospital admission, and, most importantly, osteoporotic fractures have been related to an augmented mortality risk. Although multiple national and international osteoporosis governing bodies have developed and updated several guidelines to aid clinical practice, there remain multiple unmet needs in the field of osteoporosis and fracture care. Tackling such challenges would definitely reflect on the patients' management and fracture prevention.

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