Osteoporosis in 10 years time: a glimpse into the future of osteoporosis

Giovanni Adami (ID), Angelo Fassio, Davide Gatti, Ombretta Viapiana, Camilla Benini, Maria I. Danila, Kenneth G. Saag (ID) and Maurizio Rossini (ID)

Abstract: Patients living with osteoporosis are projected to increase dramatically in the next decade. Alongside the forecasted increased societal and economic burden, we will live a crisis of fractures. However, we will have novel pharmacological treatment to face this crisis and, more importantly, new optimized treatment strategies. Fracture liaison services will be probably implemented on a large scale worldwide, helping to prevent additional fractures in high-risk patients. In the next decade, novel advances in the diagnostic tools will be largely available. Moreover, new and more precise fracture risk assessment tools will change our ability to detect patients at high risk of fractures. Finally, big data and artificial intelligence will help us to move forward into the world of precision medicine. In the present review, we will discuss the future epidemiology and costs of osteoporosis, the advances in early and accurate diagnosis of osteoporosis, with a special focus on biomarkers and imaging tools. Then we will examine new and refined fracture risk assessment tools, the role of fracture liaison services, and a future perspective on osteoporosis treatment.

Keywords: bone mineral density, fractures, future perspective, osteoporosis

Introduction

Osteoporosis is a chronic disease characterized by bone fragility and fractures. Osteoporosis represents a relevant global public health problem, which is projected to increase in magnitude in the next 10 years. Fortunately, substantial advances in the diagnosis and treatment of osteoporosis have emerged in the last decade and we have now the knowledge and instruments to tackle the ongoing osteoporosis crisis. In the present review, we will mainly focus on forecasts on the epidemiology of and costs related to osteoporosis in the next decade and we will discuss on the future of osteoporosis diagnosis, fracture risk assessment, and treatment.

Epidemiology and costs of osteoporosis in 10 years from now

Osteoporosis represents a major worldwide clinical, societal, and economical challenge. Osteoporosis prevalence and burden are projected to increase in the following years, mainly in relation to the aging of the population. Scorecard for Osteoporosis in Europe (SCOPE) is an international project aimed to determine the burden of osteoporosis across Europe.[1] The SCOPE panel, which was first established in 2010 and updated in 2021, evaluates the information regarding osteoporosis in 29 countries through structured questionnaires (27 European countries, the United Kingdom, and Switzerland).[2] The SCOPE data provides a comprehensive picture of what is happening nowadays in Europe in terms of osteoporosis burden and can help forecast what will happen in the next decade. The total direct costs related to osteoporosis care (fragility fracture treatment and pharmacological costs) amounted to an astonishing cost of €37.4 billion in 2010, which increased to an even greater amount in 2019 (€56.9 billion, +64%). This observed increase was consistent with 50% increase in costs by 2025 proposed in 2007.[3] In their study, Burge *et al.* used Markov decision models to estimate fracture costs over two decades (2005–2025). What is noteworthy and, at the same time, disheartening, is that despite the cost of osteoporosis care, the pharmacological

Correspondence to:
Giovanni Adami
Rheumatology Unit, University of Verona, Pz Scuro 10, 37134 Verona, Italy.
adami.g@yahoo.com;
giovanni.adami@univr.it

Angelo Fassio
Davide Gatti
Ombretta Viapiana
Camilla Benini
Maurizio Rossini
Rheumatology Unit, University of Verona, Verona, Italy

Maria I. Danila
Kenneth G. Saag
Division of Clinical Immunology and Rheumatology, The University of Alabama at Birmingham, Birmingham, AL, USA

and assessment costs decreased from €2.1 billion in 2010 to €1.6 billion in 2019. Moreover, the costs of Quality Adjusted Life Years (QALYs) lost were not included in the latter estimation of costs. Indeed, the overall costs were even higher when QALYs were included. QALYs lost costs amounted to an overwhelming total of €112.9 billion, resulting in a €169.8 billion of direct and indirect costs related to osteoporosis in 2019. The disparity between costs related to fragility fracture care and pharmacological costs is startling and becomes even more evident when compared with other noncommunicable diseases. Indeed, the pharmacological treatment for cardiovascular diseases represented approximately one quarter of the total expenditures, a proportion that is considerably higher than that for osteoporosis (2.8%).

Osteoporosis is estimated to affect more than 30 million persons in Europe and a similar number of individuals in the United States.[4,5] The vast majority of these are women. However, studies at population level could underestimate the true prevalence of a silent disease such as osteoporosis. Indeed, osteoporosis prevalence strictly depends on screening availability. Screening strategies with standard dual-energy X-ray absorptiometry (DXA) in women aged more than 50 years have been implemented in most western countries but remain underutilized in many other developing countries.[6] Moreover, osteoporosis in men is still largely underdiagnosed, and the diagnosis is commonly made in the presence of a fragility fracture. Concerningly, the proportion of patient living with osteoporosis worldwide is increasing.

Fragility fractures are the consequence of osteoporosis and reducing their incidence represents the primary outcome for all interventions. More than 4 million fractures have been reported each year in Europe in the last 5 years. These numbers are projected to increase substantially in the next 10 years. In fact, the SCOPE analysis has estimated that the overall number of fractures will increase by 20% by 2035. In addition, simulation models have been used to predict the future burden of fragility fracture. A recent study by Cui *et al.* showed that, in China, the annual number of fragility fracture will increase by 135% by 2040, while the proportion of population >50 years will increase by approximately 100%. This increase is partially preventable by adoption of relatively simple and cost-effective strategies, such as increased awareness about the availability of pharmacological options and interventions aimed to improve treatment adherence.[7–10]

In summary, the burden of osteoporosis and fragility fractures is projected to increase at a dramatic pace in the next decade taking in consideration the effect of the aging of the population alone. Of concern, there are individual and environmental factors that can further augment this trend. As an example, obesity and diabetes, which have increased in prevalence worldwide, have been largely associated with higher risk of fracture independently from bone mineral density (BMD).[11–13] Sedentary lifestyle in younger individuals has also been associated with increased risk of osteoporosis later in life.[14] Moreover, environmental air pollution, a well-known issue for present and future generations,[15] has been linked with a substantial increase in the risk of osteoporosis and fractures.[16,17] However, effective interventions exist to help mitigate the challenges posed by increased osteoporosis prevalence. Lifestyle modifications for healthy bones should be advised for all populations, screening strategies should be implemented and harmonized across countries, treatment accessibility should be improved, and treatment adherence should be encouraged.

Advances in early and accurate diagnosis of osteoporosis

Advances in imaging techniques of osteoporosis

For epidemiological purposes, osteoporosis was defined by World Health Organization (WHO) as 'BMD lower than -2.5 SD below the peak bone mass of young healthy adults'.[18] While the WHO definition is widely utilized in daily clinical practice to make a diagnosis of osteoporosis, it should be recognized that it is plagued by several disadvantages. The most important shortcoming of defining osteoporosis merely on BMD levels is that we may miss this diagnosis in all those patients who fracture at *T*-scores above −2.5. Indeed, approximately half of all fragility fractures occurs in patients with osteopenic or even normal *T*-scores.[5] To overcome this fallacy, we commonly incorporate clinical characteristics to BMD for estimating the risk of fracture of an individual. Several clinical risk factors are included in widely available algorithm, such as the Fracture Risk Assessment Tool (FRAX),[19,20] which provides an estimation of the absolute risk over the time of the patient but do not, however, capture all the determinants of fractures. As an

example, the FRAX and other similar algorithms do not account for bone strength or bone microarchitecture. The NIH, in 2001, has further expanded the definition of osteoporosis by adding the 'bone strength' concept, which is largely, but not entirely, dependent on BMD.[21] This is of particular importance in diseases that deteriorate bone quality without affecting bone quantity. As an example, in glucocorticoid-induced osteoporosis (GIOP), the fracture threshold is lower than in postmenopausal osteoporosis, which means that patients fracture at osteopenic or even normal *T*-scores.[22] Diabetes alters the bone microarchitecture and, therefore, is characterized by an increased risk of fracture independently of BMD levels.[11] However, while there are approaches to assess bone microarchitecture or bone flexibility and elasticity,[23–26] measurements of bone strength are not widely available in clinical practice for diagnosing bone fragility long before the BMD criteria of osteoporosis are met.

One of the most promising tools for estimating bone strength is the trabecular bone score (TBS). The TBS is calculated using an analytical tool that processes the gray-level texture of normal DXA scans to estimate trabecular microarchitecture.[26] TBS can be easily implemented in most of the DXA instruments. The Manitoba bone density program was one of the groups that pioneered the role of TBS in fracture prediction.[27] Leslie and colleagues demonstrated that TBS provided an incremental improvement in fracture risk estimate; the authors analyzed data on more than 30,000 women and showed that the TBS was inversely correlated with fracture risk, independently from clinical risk factors and femoral neck BMD. In a meta-analysis of X cohort studies on TBS in 2015, TBS was found to be significant predictor of fracture independently from FRAX.[28] Importantly, this finding was consistent across independent and international cohorts that included racial and ethnic diverse populations. An adjusted version of the FRAX that accounts for TBS is now available for clinical purposes.[29] However, the TBS is proprietary software which is not systematically applied to DXA scans, principally for its costs.

Hip-axis length (HAL), hip-strength analysis (HSA), and finite element analysis (FEA) are other methodologies that, similarly to TBS, can be obtained from DXA analysis. The HAL, which is defined as the length from the great trochanter and the pelvic brim, has been positively correlated with the risk of hip fracture.[30] The longer the HAL the higher the risk of fracture is, independently from other clinical and densitometric risk factors. The mechanism underpinning this increased risk is most likely related to the greater protrusion of the trochanter, which can result in a higher susceptibility of impact in sideways falls. The HSA is an imaging post-processing software that was first developed in 1990 by Beck *et al.*[31] The HSA derives from the analysis of the femoral neck cross-sectional area (CSA) and cross-sectional moments of inertia (CSMI). The HSA estimates the cortical stability in buckling and represents an index of structural rigidity. The ability of HSA in estimating fracture risk has been assessed in few small clinical studies. Addition of HSA to standard BMD measurements can improve the prediction of hip fracture.[32,33] Of note, HSA parameters are not influenced substantially by antiosteoporotic treatments and should be considered a nonmodifiable risk factor for fractures.[32] FEA is another computerized method that estimates the microarchitectural geometry of the hip. In particular, FEA can be used to study the behavior of bone in relation to mechanical loading. FEA has been largely applied in computer tomography but is now available in DXA too, making this technique more accessible. However, despite the enthusiasm around these techniques, the International Society for Clinical Densitometry (ISCD) did not endorse their use in routine clinical practice as recent as 2015[34] based on the scarce data about measurement reproducibility available at that time. In the last years, new imaging processing software have been released and the predictive power of FEA simulations models are getting better; however, large, confirmatory, clinical studies are still lacking.[35]

Radiofrequency echographic multi spectrometry (REMS) is an innovative approach that uses ultrasound to analyze BMD.[36] Raw and unfiltered ultrasound images of lumbar spine and femoral neck are analyzed by a software to provide a DXA-equivalent BMD value. The REMS effectiveness in identifying subjects at risk of fracture has been studied in a recently published longitudinal study.[37] More than 1500 patients underwent a DXA and REMS investigation and were followed up to 5 years. DXA and REMS T-score values were highly correlated, and the fracture prediction ability was similar for both vertebral, hip and non-vertebral, non-hip fractures. Moreover, REMS can provide an estimation of bone strength (fragility index) which is independent from BMD and

has been shown to effectively predict the fracture risk.[38] REMS has recently received the endorsement for clinical use of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO).[39]

High-resolution peripheral quantitative computed tomography (HRpQCT) is an alternative imaging technique that can provide both quantitative and qualitative information regarding the skeleton. HRpQCT parameters, such as cortical thickness or FEA, showed to effectively predict the fracture risk independently from FRAX score and areal BMD measured by DXA alone.[25] Moreover, new advances in the CT technology have reduced the amount of ionizing radiation making this technique attractive for routinely assessing bone quality and bone quantity in patients with osteoporosis. However, HRpQCT is an expensive technology and as such its use might be limited in clinical practice. Table 1 shows the imaging techniques for bone density and structure evaluation.

Advances in biomarkers of osteoporosis

Micro RNA (miRNA) and long-non-coding RNA (lncRNA) are novel markers and targets of great interest in the field of osteoporosis.[40] miRNA and lncRNA can control gene expression and are widely recognized as crucial regulators of cell development and differentiation. miRNA and lncRNA are involved in a variety of cellular pathways.[41] These small RNA molecules are responsible for the differentiation of bone cells by regulating gene expression. miRNA-103a can directly inhibit gene expression that is correlated with osteoblasts differentiation. Interestingly, mechanical unloading is associated with the overexpression of miRNA-103a, which, in turn, results in a strong inhibition of bone formation. Consequently, targeting miRNA-103a with antagomir-103a can rescue the osteoporosis caused by immobilization and mechanical unloading.[42] miRNA and lncRNA are versatile markers of disease and, more interestingly, they represent a novel therapeutic target. However, targeting miRNA and lncRNA is still a futuristic prospect, nowadays only limited to *in vitro* and animal studies. Nonetheless, this field has expanded considerably in the last decade and the promise of having novel agents that target miRNA in the next 10 years is now realistic.

In summary, in the next decade, we may have routine access to novel markers of bone fragility,

such as TBS, FEA, and HR-pQCT, which will help the early diagnosis of osteoporosis. Early diagnosis is crucial to target the right intervention in the right patient population. Indeed, highly sensitive and specific diagnostic tools are key for 'precision medicine' that can enable implementing highly efficacious interventions in those patients who are likely to experience fractures. Novel analytical tools will help refine fracture risk assessment, especially in those patients borderline for pharmacological interventions.

Advances in noninvasive diagnosis of osteoporosis

As mentioned before, the densitometric definition of osteoporosis has several pitfalls, mainly due to uncaptured fragility. Indeed, mechanical testing of bone properties in human might represent a novel approach for osteoporosis definition.[43] As an example, external mechanical loading has been widely used in animal studies but some applications, such as dynamic hydraulic stimulation, might be envisioned for human applications too.[44] In addition, magnetic resonance imaging (MRI) might be considered in the future as it has been shown to effectively differentiate primary mineralization defects (e.g. osteomalacia) from structure defects (e.g. osteoporosis), possibly allowing new, cutting-edge, virtual biopsies.[45]

Novel fracture risk assessment tools

As noted above, algorithms for fracture risk assessment are currently widely used in clinical practice to estimate fracture risk.[19,20,46] Such algorithms are based on fixed multipliers of risk derived from cohort studies. This approach might be limited to the relatively small number of risk factors considered by these algorithms. A novel and promising method might, however, overcome this limitation. Machine learning and deep learning approaches are rapidly revolutionizing and improving our ability to predict health outcomes.[47] Machine learning is a computer-based approach used to generate a predictive algorithm based on training datasets; this approach at first sight might appear similar to what has been done by standard predictive tools since today. However, machine learning approach uses complex datasets derived from electronic medical records that enable consideration of a significant number of risk factors simultaneously. By doing so, machine learning algorithms not only consider more risk factors in the estimation of risk than standard

algorithms but also factors that are usually not thought traditionally to be associated with the outcome. Furthermore, machine learning algorithms continuously learn from data and become more refined with each iteration. This latter aspect represents a major advantage since fracture risk assessment can be tailored to a specific subpopulation and can be informed by treatment modalities. Machine learning approaches have been shown to effectively predict fracture risk and to predict BMD response following antiosteoporotic treatment.[48–51] The major advantages of the machine learning approaches over standard risk algorithms are hundreds of clinical variables are considered, prediction of risk is automatized based on available data and, more importantly, this approach can be easily applied and automatized to hospital that use electronic medical records, reducing the burden on clinicians. Tanphiriyakun *et al.*,[48] for example, developed a computational model from 8981 clinical variables that effectively predicted BMD changes after treatment with antiosteoporotic medications. In other words, this approach can estimate patients' response to treatment based on their characteristics better than physicians. Indeed, it has been estimated that guiding the pharmacological treatment with this model can improve the average treatment response by 9.54%. This and other novel computer-based approaches can guide the therapy choice in osteoporosis and will help personalize the treatment.

Fracture liaison services

Having had a prior fragility fracture is the main risk factor for new fractures and secondary prevention is crucial for fracture incidence reduction at a population level. The risk is exceptionally high in the 2 years following the index fracture; nonetheless, fewer than 20% of patients with a fragility fracture are assessed and treated appropriately for osteoporosis.[52] This treatment gap has been the focus of discussions among bone specialists for the past decade. Identifying, assessing, and treating patients with an acute fragility fracture has therefore become the crucial link in the chain of osteoporosis care. To address this care gap, health centers around the world have developed integrated osteoporosis management teams aimed to recognize and promptly treat osteoporotic fractures. These services, also known as fracture liaison services (FLS), are rapidly proliferating in Europe, but to a lesser degree in the United States given the complex multi-payer healthcare environment.[53] It is now clear that high-intensity FLS (which comprise identification, investigation, and initiation of therapy) have been successful in reducing the incidence of new fractures.[54] Moreover, cost-effectiveness analyses of FLS showed gains in quality-adjusted life years (QALY) for expenses below the willingness to pay thresholds.[55] A recently published meta-analysis showed that the implementation of FLS is associated with lower probability of subsequent fractures with a trend toward mortality reduction.[54] Evidence mostly came from indirect comparisons between hospitals with and without FLS and from the comparison between pre-FLS *versus* post-FLS periods in the same hospital. Majumdar *et al.*[56] in 2018 conducted a pragmatic randomized controlled trial comparing two different FLS strategies. In this trial, 361 patients suffering from an upper extremity fracture were randomized to either a low-intensity FLS (phone call encouraging referral to family physician) or a high-intensity FLS (phone call arranging a visit, laboratory, and BMD tests). The primary outcome of the study was the proportion of patients initiating bisphosphonates within 6 months from the fracture. At 6 months approximately 50% of patients in the high-intensity FLS arm started on bisphosphonates compared with slightly less than 30% in the low-intensity arm. The International Osteoporosis Foundation (IOF) and the American Society for Bone and Mineral Research (ASBMR) strongly encourage the promotion of FLS in hospital facilities; moreover, IOF have initiated the 'capture the fracture' program in 2013, which have provided support and recognition to more than 600 FLS across 49 countries worldwide. The IOF 'capture the fracture' initiative is now available for free peer-review assessment of FLS.

In the future, FLS will be likely to be harmonized across hospitals and will likely leverage automated identification of persons who fracture and their referral to bone specialists for care. Natural language processing algorithm could help recognize fragility fractures from clinical and imaging notes in electronic medical records and clinical decision support algorithms will help define the appropriate investigations for each patient. Moreover, harmonized outcomes reporting across FLS will help define the standard of care for FLS and will help refine and improve this health system intervention. Nevertheless, in many countries worldwide, there is still a lack of awareness for osteoporosis and still FLS are not implemented in the routine clinical practice yet. We should, therefore, acknowledge that it is a long way to the top.

Future perspective on osteoporosis therapies

Pharmacological treatment for osteoporosis began more than 70 years ago with estrogens in postmenopausal osteoporosis; later, in the early 1970s, bisphosphonates were first prescribed for the treatment and prevention of osteoporosis. During the ensuing 40 years, many novel pharmacological agents have been tested and several of these have been approved for the treatment and prevention of osteoporosis to reduce the risk of fracture. Bisphosphonates still represent the most commonly used therapy for osteoporosis worldwide, but therapeutic armamentarium includes another potent antiresorptive drug (denosumab), two bone anabolics (teriparatide and abaloparatide), and a novel agent with a dual anabolic/antiresorptive mechanism of action (romosozumab). However, since the use of bone anabolics and romosozumab are restricted in duration of therapy and since a pharmacologic treatment is likely to be necessary lifelong, a sequential approach is crucial and should be planned in advance. Indeed, it is likely that, in the future, discussions among bone experts will focus more on the sequential approach to treatment, as more scientific knowledge is accumulating rapidly on this topic.

Anabolic agents can build up new bone and possibly reverse the osteoporotic state, but their use is limited to 24 months during lifetime currently and a potent antiresorptive agent is recommended at discontinuation. The PaTH (Parathyroid Hormone and Alendronate) study first investigated the opportunity of bisphosphonate treatment after 1 year of recombinant parathyroid hormone 1–84.[57] Considering only subjects who took parathyroid hormone 1–84 followed by alendronate or placebo, those that received alendronate maintained or increased the BMD at lumbar spine and femur, while women that received placebo lost most of the beneficial effect attained during the first 12 months of treatment. Again, in the ACTIVExtend trial, subjects received 2 years of abaloparatide followed by alendronate,[58] and BMD levels achieved during the anabolic phase of the study were further improved during the alendronate phase. The denosumab and teriparatide transition in postmenopausal osteoporosis (DATA-SWITCH) study explored the effects of sequential and combination therapy with denosumab and teriparatide. In this trial, the combination arm reached the peak in BMD faster than sequential treatment (teriparatide to denosumab) and achieved greater BMD values at cortical skeletal sites. In summary, anabolic agents are associated with a significant reduction of fracture risk, but their use is restricted to 2 years and their discontinuation is associated with a decrease in BMD levels. Therefore, a prompt treatment with antiresorptive after bone anabolic agents is encouraged.

There is increasing evidence that anabolic treatment should be positioned in first line in patients at imminent risk of fracture and in patients at very-high risk of fracture.[59] In such patients, independently from BMD, anabolic treatment is cost-effective in certain regions and should be encouraged.[60] The approach of anabolic treatment positioned as first line in patients at high risk of fracture has been implemented in Italy since 2015 and other countries are now applying similar treatment reimbursement criteria.[61] It is reasonable to think that, in the next decade, anabolic treatment will represent the first line of treatment in all patients with high or very high risk (i.e. fracture probability that lies above the upper assessment threshold after a FRAX assessment)[59] of fracture in most western countries.

Sequential treatment with antiresorptive agents might be required in selected patients. For example, patients, who after a long-term denosumab treatment achieve osteopenic BMD levels, might need a safe exit strategy to avoid the possible rebound effect (i.e. rapid decrease of BMD gain attained during denosumab treatment). Indeed, denosumab discontinuation has been associated with a rapid increase in bone turnover markers and, in some cases, with multiple vertebral fractures.[62–64] Therefore, an exit strategy after denosumab treatment is highly recommended.[65] The rebound effect was shown to be attenuated in patients who were previously treated with bisphosphonates.[66,67] Accordingly, younger patients with high bone turnover seems to be at greater risk of rebound after discontinuation.[68] Nevertheless, case reports and retrospective studies have shown that denosumab discontinuation was associated with multiple vertebral fractures even in patients previously exposed to bisphosphonates.[69,70] In addition, a recent analysis on women that discontinued long-term denosumab therapy showed that the increase in bone turnover markers and Receptor activator of nuclear factor kappa-B ligand (RANKL) serum levels were directly related to the BMD gain during the treatment.[71] This evidence supports the hypothesis of a pool of dormant osteoclast that are reactivated at the time

of denosumab discontinuation, and a potent bisphosphonate seems to be necessary to halt, or at least reduce, the rebound in bone turnover. Moreover, there may be clinically relevant differences in the timing of antiresorptive treatment after denosumab discontinuation. Reid and colleagues demonstrated that the bone loss after discontinuation is only partially prevented at 18 months by zoledronic acid administered 6 months after the last injection of denosumab. The same group of researchers tested the efficacy of a different timing of administration of zoledronic acid in preventing the bone loss following discontinuation. They found that a delayed administration of zoledronic acid was associated with preservation of BMD levels; in contrast, an 'early' administration of zoledronic acid after denosumab discontinuation was associated with BMD loss.[72] Nevertheless, the study was largely underpowered to address the efficacy of different treatment strategies; moreover, the women under study were relatively young (63 ± 6 years), and most of them were treated with romosozumab prior to denosumab and all subjects in study received only 2 years of denosumab treatment. More recently, Anastasilakis *et al.*[73] reported the results of a randomized controlled trial of zoledronic acid for the prevention of the rebound effect after denosumab treatment cessation. In contrast with the results of the study by Reid *et al.*, Anastasilakis *et al.* reported a beneficial effect on BMD of a single infusion of zoledronic acid after denosumab discontinuation. Moreover, albeit not significant, an increase in BMD levels was seen in the zoledronic acid group at 12 months after randomization, a result that is controversial and diverges from other previously published experiences. In conclusion, to date, there are uncertainties regarding the most appropriate exit strategy following denosumab suspension. Large randomized and active-controlled clinical trials are warranted to further explore the topic.

Anabolic agent after an antiresorptive is perhaps the most common situation that clinicians face in their routine practice, especially when patients fracture during an antiresorptive treatment. To date, several studies reported data on the effects of anabolic treatment followed by an antiresorptive drug (bisphosphonate or denosumab).[74–81]

In a recent observational study on long-term bisphosphonate users who switched to either teriparatide or denosumab,[81] annualized BMD increase after switching to teriparatide was 1.3% higher at the lumbar spine, and lower by 2.2% at the total hip and 1.1% at the femoral neck, compared with denosumab. However, pretreatment with different antiresorptive drugs might yield different results. In the study from Ettinger *et al.*,[74] in which patients received treatment with teriparatide after 18–36 months of either alendronate or raloxifene, prior treatment with alendronate was associated with a more than halved BMD gains at lumbar spine than raloxifene at 18 months (4.1% and 10.2%, respectively), while no benefit at all was seen in the alendronate pretreated group at the total hip site. Nevertheless, teriparatide treatment can effectively prevent clinical and radiographic fragility fractures even in patients previously treated with bisphosphonates.[82] The VERtebral Fracture Treatment Comparisons in Osteoporotic Women (VERO) trial demonstrated that pretreatment with risedronate did not affect the efficacy of teriparatide in terms of fracture prevention. Interestingly, the crude incidence rate was the lowest in the risedronate to teriparatide group. Current evidence, mainly from the DATA-SWITCH study, does not support the use of anabolic agents after denosumab. In contrast, teriparatide and abaloparatide use after bisphosphonates seems to be safe and effective in reducing fracture's risk. Nevertheless, combined treatment with bone forming and antiresorptive agents seems to be the best strategy in patients at high risk of fracture.

Wnt pathway has emerged as the central regulator of bone metabolism and its major inhibitors sclerostin and Dickkopf (DKK)-1 have become target of great interest for the treatment of osteoporosis. Wnt is a natural stimulator osteoblasts function, and the inhibition of the inhibitors lead to stimulation of bone formation. Sclerostin inhibitors are now available for the treatment of osteoporosis and other metabolic bone diseases. Romosozumab, a sclerostin inhibitor, represents a new therapeutic option in the armamentarium of the bone specialists. Romosozumab has been shown to increase BMD rapidly and to reduce the risk of fracture to a greater extent than bisphosphonates.[83] Romosozumab use is restricted to a 12-month course and, upon its interruption, the effects on BMD are rapidly lost. Hence, an antiresorptive therapy is recommended after romosozumab discontinuation. It is interesting to note that romosozumab effect is not hampered by prior treatment with bisphosphonates or bone anabolics and seems to effectively reduce the rebound effect upon denosumab discontinuation.

Table 1. Novel imaging techniques for osteoporosis diagnosis and fracture risk[34,39].

Technique	Data acquisition	Advantages	Disadvantages	Radiation exposure (μSv)
DXA	Dual energy X-rays	Reference	Only BMD assessment	1–15
TBS	Post-processing DXA images	Strength analysis, estimate fracture risk independently from BMD	Availability, cost of software	1–15
FEA DXA	Post-processing DXA images	Strength analysis	Availability	1–15
HAL	Post-processing DXA images	Easily obtainable from DXA images	Not modifiable by therapy, not endorsed by international society for fracture risk assessment	1–15
HSA	Post-processing DXA images	Easily obtainable from DXA images	Not modifiable by therapy, not endorsed by international society for fracture risk assessment	1–15
REMS	Ultrasound	No radiation exposure, similar sensitivity and specificity to DXA, transportable instrument	Operator dependent	None
HRpQCT	CT scan	Qualitative and quantitative assessment, strength estimation, estimate fracture risk independently from BMD	Costs, availability, radiation exposure	50–100

BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; FEA, finite element analysis; HAL, hip-axis length; HSA, hip-strength analysis; HRpQCT, high-resolution peripheral quantitative computed tomography; REMS, radiofrequency echographic multi spectrometry; TBS, trabecular bone score.

Other sclerostin inhibitors are now on the pipeline and will likely be available within the next decade. Blosozumab is among the new sclerostin inhibitor in development, which phase III study results are expected within the next few years.[84] DKK-1 inhibitors are in development as well.[85] Although the initial enthusiasm around DKK-1 inhibitors, there has been raising safety potential concern due to the ubiquitous presence of DKK-1 in nonskeletal tissues. An animal study published in 2016 demonstrated that targeting both DKK-1 and sclerostin at the same time resulted in a synergistic effect on bone formation.[86] However, studies on humans are still missing. Nevertheless, the potentiality of dual inhibition (DKK-1 and sclerostin) is staggering. Dual inhibition was shown to enhance cortical bridging improving fracture repair to an extent that was not considered possible before. Indeed, DKK-1 serum levels are increased in response to sclerostin inhibition, possibly explaining the closure of the anabolic window after 12 months of romosozumab. A similar feedback response has been demonstrated with teriparatide, in which the increase of DKK-1 can explain the waning of teriparatide effect on bone formation after 18–24 months.[87] As mentioned earlier, new molecules targeting miRNA are in study with promising preclinical results but no data on human beings are available to date. As an example, Wang *et al.* demonstrated that miR-214 can directly decrease bone formation and mineralization in animal models. In addition, the authors restored osteoblast activity in miR-214 transgenic, ovariectomized, and hindlimb-unloaded mice with antagomir-214.[88] Remarkably, this anabolic approach

appeared to be not influenced by the coupling effect between osteoblasts and osteoclasts.

Pharmacological treatments are the mainstream of fracture prevention. Notwithstanding that, anti-osteoporotic medications can only reduce the risk of fracture with abolishing it; in addition, compliance to therapies is scarce. Therefore, complementary approaches are needed. Local osteo-enhancement procedure (LOEP) is an emerging surgical procedure that has been shown to effectively reduce the risk of re-fracture.[89] In synthesis, LOEP involves the implantation of an osteoconductive, calcium-based, material in the skeleton. The implant is rapidly incorporated and gives biomechanical benefit.[90] To date, LOEPs have been performed at femurs and vertebrae but, virtually, such procedures can be performed at any site.[89,91] In 2020, a long-term prospective cohort study on LOEP was published.[92] The authors treated 12 postmenopausal osteoporotic women with femoral LOEP and found that treated femoral neck BMD rapidly increased by 68% as soon as 3 months of follow-up. Interestingly, the FEA-estimated femoral strength increased by 41% in less than 6 months. The implant resorption and replacement with bone was nearly complete by 24 weeks. In January 2022, the completion of enrollment of the CONFIRM Europe Safety Study (CONFIRM) study has been announced. The study enrolled 60 subjects treated with LOEP and will provide additional evidence on the efficacy and safety of such procedure.

Conclusion
In summary, while osteoporosis is projected to cause millions of deaths worldwide in the upcoming future, we can face this anticipated crisis with novel diagnostic, prognostic, and therapeutic strategies. In the next decade, we will have broader access to novel and more precise methods of fracture risk prediction. Patients at high risk of fracture will be more commonly referred to the bone specialist for treatment thanks to the diffusion of FLS. Osteoporosis treatment will evolve, we will have more confidence with combined and sequential strategies, and we will have access to novel and innovative pharmacological therapies.

Author contributions
Giovanni Adami: Conceptualization; Project administration; Validation; Visualization; Writing – original draft; Writing – review & editing.

Angelo Fassio: Writing – review & editing.

Davide Gatti: Writing – review & editing.

Ombretta Viapiana: Writing – review & editing.

Camilla Benini: Writing – review & editing.

Maria I. Danila: Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Kenneth G. Saag: Writing – review & editing.

Maurizio Rossini: Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Conflict of interest statement

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Competing interests
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Compliance with ethical standard
The study was conducted according to the protocol 1876 approved by our local Ethics Committee, in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical

standards. Informed consent was waived because encrypted retrospective information was used.

Patient and public involvement statement
This research was done without patient involvement. Patients were not invited to comment on the review content. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

ORCID iDs
Giovanni Adami https://orcid.org/0000-0002-8915-0755

Kenneth G. Saag https://orcid.org/0000-0001-6189-8078

Maurizio Rossini https://orcid.org/0000-0001-9692-2293

Transparency declaration
The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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