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Review article

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Single-component imaging and ultrasound-based tools for the assessment of fracture risk

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Abstract

Emerging imaging and computational technologies are reshaping how osteoporosis and low bone mass are assessed. Dual-energy X-ray absorptiometry (DXA) is key for the operational definition of osteoporosis, but advances in single-component tools such as finite element analysis, trabecular bone score, DXA-based 3D shape modelling, quantitative ultrasound, radiofrequency echographic multi-spectrometry and artificial-intelligence-driven interpretation of routine radiology offer complementary insights into bone strength, microarchitecture and fracture risk. Some of these approaches provide additional fracture-risk measures beyond areal bone mineral density, whereas others enable opportunistic identification of people with low bone density in populations who would otherwise be missed. Strong pre-clinical and encouraging observational data support the use of these technologies and, although their current use in clinical practice varies with the age of the technology, they all have a potential role in the assessment of fracture risk at a variety of points in the patient journey (from screening to monitoring response to therapy). As their use becomes more widespread, monitoring performance, assessing the equitability of implementation and evaluating the health-service benefits of these tools in clinical practice will be key.

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Key points

- Dual-energy X-ray absorptiometry (DXA) remains the foundation of osteoporosis assessment, but access is limited, and in established fracture liaison services, up to 30% report inadequate access to meet clinical need.
- Areal bone mineral density alone does not fully capture fracture risk, and around 50% of hip fractures occur in individuals whose bone density is not within the osteoporotic range.
- Single-component tools are aimed at complementing conventional densitometry by capturing additional aspects of skeletal fragility, including bone microarchitecture, geometry and mechanical competence.
- The use of bone-quality-derived measures (including trabecular bone score, 3D shape modelling and radiofrequency echographic multi-spectrometry fragility score) is supported by a rapidly growing body of evidence.
- Ultrasound-based methods and opportunistic analysis of routinely acquired imaging could improve access to fracture risk assessment in settings in which access to DXA is limited.
- The key challenge is no longer proof of concept alone but demonstrating robust clinical use, equitable implementation and patient-centred benefit across diverse healthcare settings.

Introduction

Dual-energy X-ray absorptiometry (DXA) has had a vital role in facilitating the operative definition of osteoporosis and enabling the field of bone health and fragility fractures to move forward[1]. However, many individuals at risk of osteoporosis or fragility fracture are not identified, investigated or monitored in a timely manner. Substantial variability in the availability and accessibility of DXA scans, coupled with insufficiently trained operators and ongoing reimbursement and financial constraints, suggests that DXA alone might not be able to close the screening and monitoring gap in osteoporosis[2,3]. Indeed, in established fracture liaison services, up to 30% report inadequate DXA access to meet the necessary clinical need of patients[4]. Additional challenges include machine calibration, operator-dependent errors and inconsistency in reporting, which suggests that alternative technologies could be needed to advance imaging for the assessment of fracture risk.

Osteoporosis is conventionally defined via bone densitometry by a DXA T score of −2.5 or lower, but many hip fractures occur in individuals whose bone mineral density (BMD) does not fall within this osteoporotic range, suggesting that areal bone mineral density (aBMD) alone is insufficient to guide treatment[5]. Thus, a range of approaches have emerged to complement conventional DXA assessment, reflecting that fracture risk is influenced by bone structure, microarchitecture and strength (as parameters of bone quality). Some of these are multicomponent tools, including the Fracture Risk Assessment Tool (FRAX)[6], Garvan[7] and QFracture[8], which combine clinical risk factors with imaging or densitometric information to estimate the probability of fracture over a 5-year or 10-year period. Other tools derive fracture-risk predictive variables from a single modality, referred to as single-component tools, which include image-analysis techniques, ultrasound-based methods and artificial intelligence (AI) approaches that can be used throughout the patient journey (Fig. 1). In this narrative Review, which was conducted under the umbrella of the WHO Collaborating Centre for Epidemiology of Musculoskeletal Health and Aging, Liège, Belgium, we explore emerging single-component tools for fracture-risk assessment, including non-ionizing techniques to assess bone health; ionizing techniques such as CT- and DXA-based approaches that can assess bone microarchitecture and tools using AI for the opportunistic screening of low BMD and vertebral fracture from routine imaging.

Non-ionizing techniques

Ionizing radiation has a central role in the assessment of human anatomy and tissues via medical imaging. However, despite the benefits of this technique, radiation is also associated with potential risks. Non-ionizing technologies, including various ultrasound techniques, avoid these risks and provide an opportunity to assess otherwise under-served populations.

Quantitative ultrasound

Quantitative ultrasound (QUS) is a portable, radiation-free technology that assesses bone properties through the interaction of sound waves with the skeleton. The most established applications involve the calcaneum, where parameters such as broadband ultrasound attenuation, speed of sound and composite stiffness indices reflect material properties of density, elasticity and microarchitecture. The QUS-derived stiffness index is a composite measure calculated from broadband ultrasound attenuation and speed of sound, with calculation methods differing between manufacturers. Evidence (including large-scale meta-analyses) has accumulated over the past two decades to suggest that lower QUS measures (although performed at peripheral sites) are associated with an increased risk of incident vertebral, non-vertebral and hip fractures (axial sites), independently of DXA-derived BMD[9,10]. Risk estimates for QUS typically range between 1.6 and 2.3 per standard deviation decrease, similar to hip BMD[9,11]. These associations remain after FRAX adjustment, suggesting that QUS provides fracture-predictive information beyond that of BMD alone.

Although measurements at the calcaneum form the bulk of clinical studies, comparable associations have been demonstrated at the phalanges, radius and tibia, including through axial-transmission techniques, which estimate cortical thickness and elastic properties at mid-shaft long bone sites[12]. In more than 7,000 elderly women, heel QUS devices were predictive of hip fracture risk, whereas measurements using the phalanx QUS device were not predictive[13]. This study, combined with evidence from chronic disease cohorts provides support for the use of calcaneal QUS to predict incident fractures in people with chronic disease, including all stages of chronic kidney disease with modest but consistent hazard ratios[14], and in a study of chronic type 1 and type 2 diabetes mellitus, QUS often outperformed DXA for identifying individuals at an increased risk of fracture[15]. The usefulness of QUS in these contexts suggests that it could be sensitive to microarchitectural deterioration that is not adequately reflected in DXA-derived BMD.

Pulse-echo ultrasound is a type of QUS that provides a standardized measurement of cortical thickness at the proximal tibia and produces a density index that correlates with femoral neck and total hip BMD. Unlike traditional calcaneal QUS, pulse-echo devices are positioned at a peripheral cortical site, potentially improving the stability of measurements. The most extensive evaluation comes from

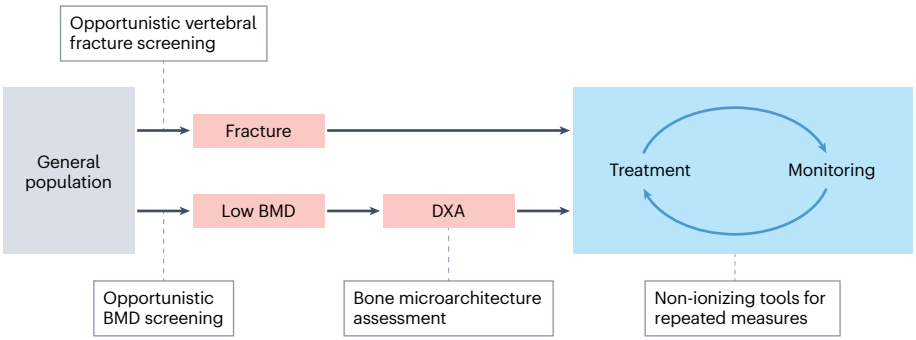


Fig. 1 | Single-component tools in the patient journey. Patients are drawn from the general population using opportunistic screening to identify those individuals with previously undetected fracture (such as vertebral fractures) or previously undetected low bone mineral density (BMD) using opportunistic tools for detection. Dual-energy X-ray absorptiometry (DXA) can be supplemented with bone microarchitectural information derived from tools (such as 3D-Shaper and trabecular bone score) and non-ionizing technologies can be used for repeated measurements of bone density.

a large primary-care cohort of women 50–80 years of age in Finland. The use of pulse-echo ultrasound to generate a multi-site density index in this cohort achieved high sensitivity (93.7%) and specificity (81.6%) for identifying DXA-defined osteoporosis, with negative predictive values approaching 99% (ref. 16). Sensitivity increased with age and reproducibility was acceptable. Crucially, integrating pulse-echo QUS into a triage pathway reduced DXA referrals to approximately one-third of participants, highlighting its role as an efficient first-line assessment tool to 'screen out' those with normal bone density. These findings were supported by data from a US multiethnic cohort, in which the same density index cut-offs yielded 80% sensitivity and specificities approaching 90% across both white and Hispanic women, with excellent reproducibility[17].

Pulse-echo ultrasound has also been examined in relation to fracture history and risk discrimination. Strong associations between multi-site density index and DXA-defined hip osteoporosis have been reported, with odds ratios exceeding 3 per standard deviation decrease[18]. Sensitivity and specificity were approximately 80–82%, and although the strength of association was diminished in individuals with BMI of ≥ 30 kg/m^2 (possibly owing to adiposity-related signal attenuation), the overall discriminatory capacity was good. Combining density index with femoral neck BMD modestly improved fracture classification, and triage pathways incorporating pulse-echo ultrasound reduced the need for DXA to around 27–31%, reinforcing its potential to reduce pressure on DXA departments.

In an Austrian pilot study of 33 older adults (mean age 82 years) with substantial comorbidity, pulse-echo ultrasound maintained a substantial ability to rule out osteoporosis, although specificity differed between men and women[19]. Used alongside FRAX, clinical decisions for 90.9% of patients were made without the need for DXA, highlighting the practical role for QUS in geriatric assessment.

From a health economic point of view, a cost–utility analysis that evaluated postmenopausal women 65–85 years of age in Finland found that pulse-echo ultrasound (whether used alone or followed by DXA) consistently saved costs compared with DXA-only care pathways; the national savings were estimated to be between 3 million and 4.8 million Euros annually when scaled to population-level screening[20]. These strategies remained cost-effective across sensitivity analyses (including patient populations, care setting and effect estimates) and willingness-to-pay thresholds, supporting a role for QUS across healthcare systems.

Thus, QUS (particularly pulse-echo ultrasound) offers an opportunity to 'screen out' patients with normal bone density to reduce pressure on DXA services, and to design multi-modal frameworks for fracture-risk assessment. However, QUS is only a peripheral measure of bone health, which might limit the assessment of axial bone health and fracture risk, and longitudinal monitoring could also be limited.

Radiofrequency echographic multi-spectrometry

Radiofrequency echographic multi-spectrometry (REMS) is a radiation-free, portable ultrasound technology that assesses the axial skeleton (at sites that include the lumbar spine, total hip and femoral neck). Transmitter-emitted ultrasound is directed at the target site, and the resulting back-scattered waveforms undergo B-mode reconstruction and spectral analysis, which are used to predict measures of internal bone microarchitecture[21,22]. The ultrasound signal obtained is compared with signals in a reference library from people with a matching age, biological sex, BMI and anatomical site to derive BMD measures (including T scores and Z scores) and a fragility score (measure of bone microarchitecture and quality)[23]. The BMD equivalent reported by REMS is based on calibration studies that link these ultrasound-derived parameters to contemporaneously acquired DXA measurements, rather than on direct measurement of aBMD. The REMS fragility score, which is reported for the lumbar spine and femoral neck, is derived from the proportion of scan-line spectra that more closely match a fracture-associated ('fragile') spectral model than a normal model, aiming to reflect microarchitecture-related fragility fracture beyond aBMD. The score (ranging from 0 to 100) is then used to generate 5-year fracture risk estimates using models developed in manufacturer datasets that include individuals with and without fractures, and has been validated against incident major osteoporotic and hip fractures, with performance compared with DXA-derived and REMS-derived BMD scores and T scores[23]. The strong correlation between REMS and DXA values was demonstrated in a large, multi-centre European study of post-menopausal women 30–90 years of age (Pearson's regression coefficient, $r = 0.94$ for lumbar spine BMD and $r = 0.93$ for femoral neck BMD)[24]. Furthermore, prospective observational studies support the predictive performance of REMS in the assessment of fracture risk[25,26].

In a large ($n = 1{,}516$) prospective cohort study of women in Italy, REMS T score was associated with 5-year incidence of fragility fractures with the odds ratio for sustaining a fracture, if classed as osteoporotic on REMS, being 2.6 (95%, CI 1.77–3.76) for lumbar-spine measurements and 2.8 (95%, CI 1.80–4.39) for femoral-neck measurements[25]. Overall, REMS showed discriminative performance comparable with DXA in the fracture subgroups considered (vertebra, hip, other sites or all sites). REMS T score at the lumbar spine showed equivalent prediction of vertebral fractures to DXA (area under the curve (AUC) 0.78), whereas lumbar spine AUC was higher with REMS than with DXA, both in the overall analysis (the prediction of a fragility fracture at any site, 0.65 versus 0.61, $P = 0.001$) and in the subgroup termed 'other sites' (0.59

versus 0.54, $P = 0.001$). In another validation study, REMS T score AUC, both at the lumbar spine and at the femoral neck, was comparable with the corresponding DXA values ($P < 0.05$)[25].

A cohort study ($n = 1,989$) investigated the use of REMS-derived fragility score for predicting the 5-year incidence of fractures in both women and men (248 of which suffered an incident fracture)[26]. The findings from this study showed the predictive capacity of REMS-derived fragility score for 5-year incidence of fracture in both women (lumbar spine AUC 0.81 and femoral neck AUC 0.78) and men (lumbar spine AUC 0.78 and femoral neck AUC 0.81)[26]. The lumbar spine REMS-derived fragility score odds ratio for incident fragility fracture was 9.2 (95%, CI 6.47–13.17), whereas the femoral neck REMS-derived fragility score odds ratio for incident hip fracture was 6.4 (95% CI 2.89–14.06). An association was also observed between lumbar spine REMS BMD T score and incident fracture (odds ratio 3.58, 95% CI 2.57–4.99) and for lumbar spine DXA BMD T score (odds ratio 2.50, 95% CI 1.81–3.44)[26].

A cross-sectional study of individuals with type 2 diabetes mellitus compared REMS with DXA in 223 patients and 102 non-diabetic individuals 50–80 years of age. REMS recorded lower BMD values at the spine and total hip than DXA, whereas femoral neck BMD was not different across modalities[27]. REMS also identified a higher proportion of patients as osteoporotic. Both REMS BMD and the REMS fragility score distinguished those with previous major osteoporotic fractures from those without, with clear differences at the lumbar spine compared with those observed using DXA. However, these findings are derived from cross-sectional analyses, and longitudinal studies are required to determine whether REMS could be used to identify bone fragility in people with type 2 diabetes mellitus, in which conventional BMD measurements of bone quantity often fail to detect skeletal deficits, despite a high risk of fracture.

In a Bulgarian study ($n = 100$), REMS T score and the REMS fragility score were combined to stratify participants into defined 5-year major osteoporotic fracture risk categories. The mean REMS fragility score across the cohort was 36.9 ± 17.4 (out of 100), with between-category differences in age, height, BMD, T score, Z score, age of menopause, FRAX for major osteoporotic fracture and FRAX for hip fractures between the risk class groups[28].

In a cross-sectional study of kidney transplant recipients ($n = 30$), all patients (who were receiving long-term glucocorticoid therapy) were categorized as 'high risk' (fracture risk classes R5-6 on the REMS fracture risk matrix). Although this study was small, the preliminary findings are in keeping with the knowledge that these patients are often at a higher risk of fractures, for example, owing to glucocorticoids and immunosuppressive therapy[29].

The performance of REMS has been examined in geographic regions beyond Europe (such as Brazil, Mexico, Japan, Colombia and Indonesia)[30–33] where results comparable with those achieved in the studies performed in Europe were obtained, demonstrating that this tool has broad applicability.

The radiation-free assessment of BMD enables REMS to be used in individuals for whom exposure to radiation from DXA would preclude assessment (including patients who are pregnant and children)[23]. This tool is also portable, which enables the assessment of underserved groups who cannot travel to DXA facilities (including those in domiciliary care or those who are unable to leave an in-patient ward)[3]. Beyond patient-level access, REMS might also offer advantages at the health-system level, particularly for healthcare facilities that cannot afford DXA infrastructure or lack a sufficiently trained workforce to operate and maintain densitometry services, making it a potentially valuable option in resource-constrained settings and low-income and middle-income countries. Consistent with these access-related advantages, health-economic modelling has suggested that REMS-based diagnostic pathways could be cost-effective compared with conventional DXA-based strategies in Italy and the USA[34,35].

One study suggested that 91% of the variance in REMS BMD of the femoral neck could be explained by the demographic factors of age, biological sex and BMI, and BMD did not change at the hip before and after total hip replacement, with the prosthesis in situ[36,37]. However, subsequent publications have questioned aspects of the technical acquisition and statistical methodology underlying this study. These findings remain the subject of ongoing debate, and further validation of these results is needed[36,38–41].

Overall, prospective 5-year data[25,26] indicate that REMS T scores, either at the lumbar spine or proximal femur, could be a feasible adjunct to DXA, or an alternative for fracture risk prediction in certain settings (for example, when DXA is unavailable). Furthermore, the REMS fragility score potentially adds clinically relevant information on bone quality beyond that provided by measures of BMD (and bone 'quantity') alone.

Image analysis for bone microarchitecture

BMD is an important measure of bone health, providing a measure of bone 'quantity'. However, BMD does not necessarily provide information on bone quality or the distribution of bone across the cortical or trabecular compartments. This topic is addressed by tools that assess bone microarchitecture.

Trabecular bone score

Trabecular bone score (TBS) is a DXA-derived, textural analysis of greyscale variation that provides an indirect measure of trabecular microarchitecture at the lumbar spine and was developed by correlating the 2D image features of 3D cadaveric human bones. Early studies (mainly in postmenopausal women) show that the TBS is lower in those patients with a history of vertebral or major osteoporotic fractures[42–45]. Odds ratios for vertebral fracture were between 1.3 and 2.0 per standard deviation decrease in TBS.

Results of a large (29,000 women) population-based study conducted in Manitoba, Canada, supported these findings. In the study, TBS predicted major osteoporotic fractures independently of lumbar spine BMD, with hazard ratios between 1.20 and 1.40 per standard deviation. A further prospective study (also conducted in Manitoba) of more than 3,600 older men showed good discriminative performance of TBS for major osteoporotic fracture (AUC 0.59, $P < 0.001$), hip fracture (AUC 0.67, $P < 0.001$) and clinical vertebral fracture (AUC 0.57, $P = 0.032$)[46] with good performance also observed in the Osteoporotic Fractures in Men (MrOS) study[47]. Data from 1,805 men in Japan (8,140 person-years of follow-up) also showed that TBS improved classification of elderly men with major osteoporotic fracture[48]. A meta-analysis of over 17,000 participants confirmed that lower TBS was consistently associated with higher fracture risk with a gradient of risk (hazard ratio per 1 standard deviation change in risk variable in the direction of increased risk) of 1.44 (95% CI 1.35–1.53)[49]. These studies established that TBS predicts fracture risk across biological sexes and across different studies.

The incorporation of TBS into FRAX has been evaluated in studies with sample size ranging from 2,500 to 50,000 people[50–53]. Although TBS adjustment resulted in a small increase in AUC overall, it shifted 5–15% of individuals across treatment thresholds, demonstrating that

TBS can have a meaningful impact on clinical decision making. The percentage was smaller in the Manitoba BMD cohort with 1.1–3.0% of patients moving across treatment thresholds[54], which could be because of the specific characteristics of the cohorts (including age, other demographic variables or BMD distribution) or that the measuring of additional skeletal sites did not materially improve fracture-risk prediction[55]. Reclassification was most evident in younger postmenopausal women, in people with osteopenia and in those with lower BMI[50–53]. These results indicate that TBS is most useful when BMD alone provides limited discrimination.

Updates to the TBS algorithm also improved performance, including the provision of soft-tissue correction derived directly from DXA images, which addressed previous limitations in individuals with higher BMI and often greater thickness of adipose tissue[56]. A prospective study of 1,362 postmenopausal women showed better fracture discrimination with the updated algorithm, with odds ratios increasing from 1.43 to 1.54 per standard deviation[57]. A second study of 1,632 women demonstrated similar improvement across all possible, adjacent vertebral combinations (from L1 to L4)[58].

Two registry-based studies of 4,838 and 5,536 women treated with bisphosphonates found that TBS predicted major osteoporotic fractures (hazard ratios around 1.30 per standard deviation) and hip fractures (around 1.49 per standard deviation), even after adjusting for femoral neck BMD[59]. As BMD often stabilizes during therapy, the persistence of these associations suggests that TBS captures aspects of bone quality that are missed by DXA BMD alone. However, as lumbar spine and femoral neck aBMD are only moderately correlated and because TBS can increase during anti-resorptive therapy (such as denosumab) despite limited effects on trabecular microarchitecture, fracture associations that persist after adjustment for femoral neck aBMD alone should be interpreted cautiously[55].

Numerous studies have assessed TBS in specific patient populations and disease contexts. In type 2 diabetes, bone mineral density can be relatively unaffected, but a high fracture risk exists. In studies of type 2 diabetes with sample sizes up to 29,000 adults, TBS predicts vertebral fractures independently of BMD[27,60–64] with decision-tree analyses selecting TBS before BMD in the classification hierarchy for vertebral fractures[63].

In rheumatoid arthritis, studies with sample sizes of 100–300 people show that TBS predicted vertebral fractures with odds ratios between 1.6 and 2.9 per standard deviation[65–67]. Analyses of patients with axial spondyloarthritis produced larger effects, with odds ratios above 5.0 (ref. 68), consistent with the severe trabecular deterioration masked by structural changes that artefactually elevate BMD. Studies in systemic lupus erythematosus, systemic sclerosis and polymyalgia rheumatica also indicate that TBS identifies trabecular impairment, even with normal BMD[69–71].

Endocrine conditions provide further examples that emphasize the importance of bone microarchitecture in addition to BMD for the assessment of fracture risk. In primary hyperparathyroidism, cohorts of 100–250 individuals demonstrated lower TBS in those with vertebral fractures, despite only modest reductions in BMD[72–74].

In chronic kidney disease, studies of adults (sample size of up to 1,426 people) show that TBS predicted major osteoporotic and hip fractures independently of BMD (at the femoral neck or lumbar spine) and FRAX (with femoral neck BMD)[75–77]. In a larger study of 8,289 participants, weaker associations in advanced chronic kidney disease were reported but maintained predictive value in those with preserved renal function[78]. Some haemodialysis cohorts show no independent association after adjustment[79]. However, in a longitudinal study, TBS was identified as a predictor of clinical vertebral fractures in patients with chronic kidney disease, supporting the use of TBS in this population[80].

Studies of thalassaemia, sickle-cell disease, HIV and liver cirrhosis (sample sizes ranging between 60 and 200 participants) found that TBS predicted vertebral or non-vertebral fractures independently of BMD[81–85]. The largest effects were seen in haemoglobinopathies, with odds ratios above 11.0 (ref. 85), reflecting substantial trabecular bone loss in these conditions.

These studies demonstrate that TBS has an important role in the assessment of trabecular bone health and its validity has been demonstrated across a variety of large population-based studies and disease contexts. It can be meaningfully used in combination with DXA to provide a measure of bone quality.

Finite element analysis

Finite element analysis (FEA) originates from mechanical and aerospace engineering, in which it was developed to estimate how complex structures respond to external loads. The method operates by dividing an object into multiple small, interconnected elements, each governed by equations describing the material behaviour under stress. By solving these equations across the entire mesh of the object, FEA provides an estimate of how a structure will deform or fail when forces are applied. When adapted to bone, the same principles enable investigators to model how skeletal tissue might behave under physiological or injurious loading (associated with fracture), using imaging data to inform material properties and geometry.

The application of FEA to bone research began with the analysis of 2D hip DXA data from 12 people (10 women and 2 men). The approach was then validated in vitro using composite femur replicas, in which failure load and stiffness were measured[86].

The use of DXA-based FEA, which is probably the most scalable method owing to the use of DXA as a screening tool for low BMD, has been explored in a variety of populations. These populations include community-dwelling older adults, participants from large epidemiological cohorts such as the Manitoba BMD[87] cohort, the Study of Osteoporotic Fractures[88] and the Bone Microarchitecture International Consortium.

A small study of 176 middle-aged and older adults in Canada demonstrated that DXA FEA estimates hip strength (failure load, Newtons and stiffness[89]). Larger studies indicate that estimated femoral strength (failure load and Newtons) or fracture-risk indices (which combine bone geometry, density and simulated load-to-strength ratios to approximate fracture likelihood) show correlations with hip-fracture risk. This association has been observed in the Manitoba BMD Registry in Canada (13,978 participants) in whom femoral neck DXA-based FEA derived fracture-risk indices predicted hip, major osteoporotic fracture and non-hip major osteoporotic fracture independently of DXA BMD, FRAX or hip-axis length with a hazard ratio per standard deviation for hip fracture of 1.26 (95% CI 1.07, 1.48 adjusted for age, sex, FRAX and hip-axis length)[87]. In a study of 1,941 participants in the UK and USA (with 668 incident hip fractures) the hazard ratio for hip fracture per standard deviation decrease in FEA parameter was 2.21 (95% CI 1.95–2.50) for finite element strength and 2.04 (95% CI 1.79–2.32) for femoral neck BMD[88], performing similarly (if not slightly better) than DXA.

Quantitative CT (QCT)-based FEA of the spine and hip is associated with larger effect sizes for fracture prediction. Across these studies,

vertebral compressive strength was approximately 20–40% lower in individuals with incident fractures than in men without an incident vertebral fracture (for example, reductions of ~37% (ref. 90) and ~20–25% (ref. 91)). Furthermore, correlations with incident fractures remained robust even after controlling for volumetric bone mineral density (vBMD). The concept of 'fragile bone strength' thresholds has been proposed for the hip and spine. These thresholds indicate the limit at which fractures are more likely to occur (spine ≤ 4,500 N in women and ≤ 6,000 N in men; hip: ≤ 3,000 N in women and ≤ 3,500 N in men). These values were derived from a 5-year case–control study of 1,110 women and men, > 65 years of age, from the AGES-Reykjavik cohort[92], and were validated in a prospective cohort study in the USA[91]. Although these thresholds are not yet ready for routine clinical decision making, they represent an attempt to translate FEA findings into a clinically usable tool. These QCT FEA studies demonstrate that bone-strength modelling can predict hip fractures[92] and vertebral fractures[91,92] independently of BMD; however, it does not appear to markedly exceed the performance of FRAX and BMD.

High-resolution peripheral quantitative computed tomography (HR-pQCT) provides a 3D assessment of cortical and trabecular bone microarchitecture at peripheral sites (including the distal radius and tibia), and FEA can be used in the context of this imaging modality (currently mainly used in a research context). Analysing HR-pQCT using FEA has shown reasonable performance in fracture association in a nested case–control study (STRAMBO cohort)[93] and fracture prediction in cohort studies (OFELY cohort)[94]. In a UK study (Hertfordshire cohort) FEA-derived measurements did not improve fracture prediction beyond conventional HR-pQCT parameters of volumetric density and trabecular and cortical features[95].

The Bone Microarchitecture International Consortium has collated large prospective datasets with analyses suggesting that cortical and trabecular microarchitecture-related strength surrogates predict incident fracture independently of DXA BMD and FRAX, with analyses indicating consistent discrimination across older age subpopulations and enabling development of HR-pQCT-based risk tools and phenotypes[91,96–98]. Across life-course cohorts, associations between earlier fracture history and later microstructural or strength deficits further support a mechanistic link between bone microarchitecture and fragility, while also highlighting that the risk of fracture in older age might be influenced by factors in early life[93,99,100]. Micro-FEA based on HR-pQCT adds a new level of detail by looking at both strength and microarchitecture in the peripheral skeleton at the radius and/or tibia. In a large, prospective study in Switzerland of 740 postmenopausal women, the prediction of incident fractures was improved by adding radius microstructure or failure load to femoral neck aBMD after 5 years of follow-up (AUC for major osteoporotic fractures improved from 0.695 to 0.760 (P = 0.022))[96]. Adding FRAX BMD to radius microstructure or failure load also improved predictive performance (AUC improved from 0.714 to 0.759 (P = 0.015)). However, it should be noted that the fracture prediction performance of radius microstructure or failure load was attenuated after adjusting for ultra-distal radius aBMD[96]. Evidence also indicates that CT FEA strength at both thoracic and lumbar vertebrae can predict clinical vertebral fractures over 6.6 years of follow-up[101].

FEA, particularly if acquired via QCT or HR-pQCT, provides information on bone health, and the development of clinically relevant fracture risk thresholds could be a promising step towards these metrics becoming clinically usable tools. However, despite the advantage over DXA provided by the additional, skeletal structural detail, QCT and HR-pQCT are largely unavailable in clinical practice at present and are used mainly for research purposes. DXA FEA could therefore provide a pragmatic route forward for the implementation of this technology.

3D shape modelling

3D-Shaper is a software application that reconstructs a 3D model of the proximal femur from a standard 2D DXA image by fitting a statistical shape and density model derived from QCT scans.

Secondary characteristics, including estimates of trabecular, cortical and integral vBMD, cortical thickness and geometric parameters, can then be derived from the 3D model. These bone microarchitecture data are acquired without an additional radiation burden, unlike QCT. Several studies have evaluated the association between 3D-Shaper parameters and the key outcome of fracture risk.

In a study of the Japanese Population-based Osteoporosis cohort (n = 1,331 women), 3D shape modelling of femoral neck trabecular vBMD predicted hip fracture (over approximately 20 years of follow-up) more accurately than femoral neck aBMD (AUC 0.748, 95% CI 0.695–0.801 versus AUC 0.70, 95% CI 0.64–0.76) but not more accurately than total hip aBMD. Prediction of fracture via aBMD was similar to femoral neck cross-sectional area (AUC 0.711, 95% CI 0.649–0.772) and cortical surface BMD (AUC 0.679, 95% CI 0.615–0.743)[102].

In a Spanish case–control study of women with hip fracture (n = 64) and age-matched healthy individuals (n = 64), discriminative ability was higher for trabecular vBMD (AUC 0.742, 95% CI 0.654–0.824; OR 2.85, 95% CI 1.78–4.56, P < 0.001) and integral vBMD (AUC 0.732, 95% CI 0.626–0.807; OR 2.74, 95% CI 1.72–4.38, P < 0.001) than for femoral neck aBMD (AUC 0.686, 95% CI 0.590–0.770; OR 2.05, 95% CI 1.36–3.10, P < 0.001). Similar to the study in Japan, total hip aBMD performed better than femoral neck aBMD (AUC 0.712, 95% CI 0.622–0.792; odds ratio 2.49, 95% CI 1.60–3.88)[103].

In a retrospective cohort in the USA (n = 775 women), the performance of 3D DXA varied for different ethnic groups. In white women, total hip trabecular vBMD (odds ratio 2.10, 95% CI 1.50–2.90) and cortical surface BMD (odds ratio 1.80, 95% CI 1.30–2.50) were associated with any fracture (vertebral or non-vertebral), whereas in Black women, neither measure was associated with fracture (trabecular vBMD, odds ratio 1.10, 95% CI 0.80–1.40; cortical surface BMD, odds ratio 1.10, 95% CI 0.90–1.40). However, in Black women, femoral neck cortical thickness was associated with prior fracture (odds ratio 1.40 per standard deviation decrease, 95% CI 1.00–1.90, P = 0.04) after adjustment for age, glucocorticoid use and aBMD T score; this association was not observed in white women[104].

In a Swiss population-based cohort (n = 796), independent associations of trabecular vBMD (hazard ratio 1.48, 95% CI 1.11–1.96), total vBMD (hazard ratio 1.46, 95% CI 1.10–1.93) and cortical surface BMD (hazard ratio 1.36, 95% CI 1.01–1.82) with major osteoporotic fractures were observed after adjustment for aBMD, over approximately 6 years of follow-up[105]. By contrast, a Spanish case–control study (n = 530) reported no statistically significant associations between 3D-Shaper parameters and hip fracture status[106].

In a Dutch, cross-sectional study (n = 471), associations were reported for hip fracture for aBMD (odds ratio 2.44, 95% CI 1.89–3.13), trabecular vBMD (odds ratio 2.33, 95% CI 1.81–2.94) and cortical surface BMD (odds ratio 1.75, 95% CI 1.38–2.22). For any fracture, the corresponding associations were aBMD (odds ratio 1.59, 95% CI 1.40–1.75), trabecular vBMD (odds ratio 1.59, 95% CI 1.43–1.79) and cortical surface BMD (OR 1.43, 95% CI 1.28–1.59)[107].

Findings from a large, community-based cohort study in Rotterdam (n = 5,000 adults) followed for 6.8 years provides further evidence: trabecular and cortical measures derived from 3D-Shaper were associated with both hip and any-type fractures, with hazard ratios comparable with those for aBMD[107]. The parameters were highly correlated, and when trabecular and cortical indices were modelled together, trabecular vBMD remained associated with fracture whereas cortical measures did not. AUCs for all metrics were closely aligned[107].

These data indicate that trabecular and integral vBMD from 3D-Shaper could offer improved hip-fracture discrimination over conventional aBMD in several populations, although results vary by ethnicity, fracture site and patient populations.

Artificial intelligence in fracture and bone mineral density detection

AI refers to computational systems designed to execute functions typically dependent on human cognitive processes, including pattern recognition and complex decision making[108]. In the field of osteoporosis, AI efforts have predominantly centred on computer vision-driven, image-based diagnostic approaches.

Computer vision is the automated extraction and interpretation of features from digital images, and this technology has the potential to rapidly advance the practice of musculoskeletal medicine, including osteoporosis. This tool is primarily used for opportunistic BMD prediction from routinely performed imaging and identifying vertebral fractures on images acquired for other clinical purposes. Routine medical imaging often contains elements of the skeleton and thereore provides an opportunity to assess bone health. For many years this clinical assessment has been in the form of the radiologist report, which would state 'bone appears osteopenic'. Now, however, supervised machine-learning models have been developed by taking datasets of routine medical images (plain radiographs, CT scans and MRI scans) labelled with BMD measures (taken from DXA scans performed proximal in time to the imaging study) and training an algorithm to predict BMD from the appearance of the routine medical image[109–111].

One such model (Rho) was developed in Canada on 67,000 pairs of plain radiographs (including chest, lumbar spine, thoracic spine, pelvis, hand and knee) and had an AUC of 0.80–0.89 for discrimination between 'normal' and 'low BMD' (including osteopenic- and osteoporotic-level BMD, BMD T score < −1.0)[112]. In a study of clinical deployment, Rho had a positive predictive score of 75% for T score −1.0 and 78% of primary care physicians said that they would use it to guide the care of their patients[113]. A study of spinal radiographs from the Canadian Multicentre Osteoporosis Study cohort showed that incorporation of Rho-predicted BMD into FRAX major osteoporotic fracture prediction had similar discriminative ability (measured by C index) to FRAX with DXA-BMD (P = 0.36) and superior discrimination to FRAX with no measurement of BMD (P < 0.004). In terms of accuracy (Brier score) FRAX Rho was superior to using FRAX without a measure of BMD (P < 0.05), but FRAX with a DXA-measured BMD was more accurate than FRAX with a Rho-measured BMD (P < 0.05)[114].

The Osteo Signal tool, developed in South Korea, was trained on pairs of routinely performed chest radiographs and DXA and aimed to identify osteoporosis alone (BMD T score ≤ −2.5) using an internal dataset of 13,026 scans and an external dataset of 1,089 scans. Discriminative performance for this osteoporosis screening tool was AUC 0.91 (95% CI 0.90, 0.92) internally and AUC 0.88 (95% CI 0.85, 0.90) externally[111]. Following this initial model, an osteopenia tool (OsPenScreen) has been developed and has a discriminative performance of AUC 0.95 (95% CI 0.94, 0.97) after exclusion of people with osteoporosis[115].

Other similar tools have been developed[116] using physics models rather than a supervised machine-learning approach[20,117,118].

Glossary

3D shape modelling
A computational approach that reconstructs three-dimensional features of bone shape and density from two-dimensional imaging data.

Areal bone mineral density
(aBMD). Bone mineral density measured over a projected two-dimensional area, most commonly using DXA.

Area under the curve
(AUC). A measure of model discrimination that summarizes how well a test or prediction model distinguishes between individuals with and without a given outcome.

Artificial intelligence
(AI). Computational methods that perform tasks such as pattern recognition or prediction using data-driven algorithms.

Bone microarchitecture
The internal structural organization of trabecular and cortical bone that contributes to bone strength independently of bone density alone.

Computer vision
A branch of AI that extracts and interprets information from digital images.

Dual-energy X-ray absorptiometry
(DXA). A low-dose X-ray imaging technique used to measure bone mineral density and diagnose osteoporosis.

Finite element analysis
(FEA). A computational modelling method that estimates how bone responds to mechanical loading and can be used to infer bone strength or fracture susceptibility.

FRAX
A fracture risk-assessment tool that estimates the 10-year probability of major osteoporotic fracture and hip fracture using clinical risk factors, with or without bone mineral density.

High-resolution peripheral quantitative computed tomography
(HR-pQCT). A high-resolution imaging technique that provides 3D assessment of bone density and microarchitecture at peripheral skeletal sites such as the radius and tibia.

Opportunistic screening
The use of imaging or clinical data obtained for another purpose to identify individuals who may be at an increased risk of disease.

Quantitative ultrasound
(QUS). A radiation-free technique that assesses skeletal properties using the interaction of sound waves with bone.

Radiofrequency echographic multi-spectrometry
(REMS). An ultrasound-based technology that analyses raw radiofrequency signals from axial skeletal sites to estimate bone status and fracture-related fragility.

Trabecular bone score
(TBS). A texture-derived measure obtained from lumbar spine DXA images that provides indirect information about trabecular microarchitecture.

Volumetric bone mineral density
(vBMD). Bone mineral density expressed per unit volume, enabling separate assessment of trabecular and cortical compartments.

One such example (Ibex Bone Health) analyses routinely acquired single-energy radiographs to estimate bone thickness and related indices of bone strength. Here, a routinely performed, single-energy (rather than dual-energy) X-ray is performed, and quantitative X-ray is used to extract the composition and thickness of the tissues. This assessment of bone health is achieved by aligning a simulated model image (with known material parameters) with the actual radiograph image to predict the derived bone parameters[119]. These parameters include bone thickness that strongly correlates with aBMD at the distal third of the radius from similar site radiographs (R^2 0.88; 95% CI 0.85, 0.90)[120]. Furthermore, applying quantitative X-ray to pelvic radiographs can discriminate patients categorized as having 'normal DXA' from those with 'non-normal DXA' (AUC 0.89; 95% CI 0.84, 0.94)[114].

A particular clinical gap addressed by AI is the under-recognition of vertebral fractures, approximately one-in-five are missed in standard radiology reports[121,122]. Automated vertebral fracture-detection systems have demonstrated substantial gains in sensitivity and efficiency in real-world hospital settings. A systematic review of 79 studies, 40 of which were included in a quantitative meta-analysis, confirmed that AI-based vertebral fracture detection achieved strong diagnostic performance across both osteoporotic and non-pathological compression fractures[123].

One such deep-learning algorithm has been trained (using over 12,000 CT scans) to identify vertebral compression fractures on CT scans of the chest and abdomen, using three board-certified neuroradiologists to provide the ground truth for model training. This algorithm achieved a good discriminative performance (AUC 0.97; 95% CI 0.96–0.99), accuracy (93.7%), sensitivity (95.2%) and specificity (92.9%)[124]. The performance of this model appeared to be maintained when exposed to an external, real-world dataset of 100 CT scans (sensitivity 92.3% and specificity 91.7%)[125] and in a high-risk cancer population (n = 1,556 scans, positive predictive value 87%)[126].

The development and diagnostic performance of these tools represent only one aspect of their use; successful implementation in clinical practice must also account for heterogeneity in institutional information governance and information-technology infrastructure. A harmonized framework for the opportunistic identification of vertebral fractures has been proposed[127].

Substantial progress has been made towards the deployment of the now established tools for the opportunistic prediction of BMD and the opportunistic identification of vertebral fractures. The next steps are for healthcare institutions to facilitate the efficient incorporation of these tools into clinical workflows.

Clinical integration, limitations and future directions

Despite their differing technical approaches and stages of maturity and regulatory approval, these technologies share several challenges that will determine their clinical impact.

Issues with standardization include variation in acquisition protocols, software versions, device-specific outputs and thresholds for risk interpretation[23,128,129]. Access and implementation are also inconsistent, influenced by equipment availability, operator training and reimbursement structures, which, in some cases, have limited uptake beyond specialist centres or research settings.

Although the validation literature is expanding, performance can be variable across populations and care settings, and external validation and prospective implementation data remain limited for several modalities[130,131]. Potential issues also exist around the diversity of the populations used to produce the original models of these tools.

Many studies only quote performance metrics (including AUC) and calibration parameters should be added to understand more about the operation of discriminative tools across the totality of the population. Furthermore, meaningful clinical adoption will depend on successful integration into existing imaging pathways and frameworks for treatment decision making, focusing on alleviating, rather than increasing, the pressure on existing resources (such as DXA availability).

Future research should include elements of implementation science, together with further, large, prospective studies (particularly in the context of the more novel tools) to investigate the use of these technologies in fracture-risk prediction and improving patient outcomes. The geographic spread of availability and regulatory clearance of these technologies is still growing, but availability remains limited in some low-income and middle-income countries, which highlights issues of health inequity that need to be addressed. This will be essential if single-component and non-ionizing bone assessment tools are to move to consistent and equitable use in fracture-risk assessment and osteoporosis care[129].

Conclusions

A range of emerging single-component tools can complement established approaches to fracture risk assessment, including DXA-derived BMD and multi-component fracture prediction tools. Collectively, these methods provide information on skeletal fragility that is not fully captured by aBMD alone. Among them, TBS and REMS are the most established in current practice, whereas FEA, 3D shape modelling and quantitative ultrasound remain promising but are at different stages of clinical development. AI adds further potential, particularly through the opportunistic use of routinely acquired imaging, but its place in everyday care is still evolving. Promising data support the idea that these technologies can detect fracture-related skeletal features, and the next steps for many are to see them standardized and validated across populations and incorporated pragmatically and repeatably into clinical pathways.

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Author contributions

G.H., N.R.F. and M.O. wrote the manuscript. All authors researched data for the article, contributed substantially to discussion of the content and reviewed and/or edited the manuscript before submission.

Competing interests

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Additional information

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Review criteria This narrative review was based on literature identified through initial searches of PubMed/MEDLINE for articles published in English up to 30 October 2024. Search terms included "osteoporosis", "fragility fracture", "fracture risk assessment", "dual-energy X-ray absorptiometry", "trabecular bone score", "finite element analysis", "3D shape", "quantitative ultrasound", "radiofrequency echographic multispectrometry" and "artificial intelligence", alone and in combination. Relevant original-research articles, narrative reviews, and meta-analyses were considered. Additional references published after 2024 were identified through the bibliographies of relevant articles and the authors' knowledge of the literature. Selection was guided by relevance to the development, validation and clinical application of these tools in fracture-risk assessment.

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