Mini-Review

The role of genetic and epigenetic factors in determining the risk of spinal fragility fractures: new insights in the management of spinal osteoporosis

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Abstract: Osteoporosis predisposes patients to spinal fragility fractures. Imaging plays a key role in the diagnosis and prognostication of these osteoporotic vertebral fractures (OVF). However, the current imaging knowledge base for OVF is lacking sufficient standardisation to enable effective risk prognostication. OVF have been shown to be more prevalent in Caucasian patient cohorts in comparison to the Eastern Asian population. These population-based differences in risk for developing OVF suggest that there could be genetic and epigenetic factors that drive the pathogenesis of osteoporosis, low bone mineral density (BMD) and OVF. Several genetic loci have been associated with a higher vertebral fracture risk, although at varying degrees of significance. The present challenge is clarifying whether these associations are specific to vertebral fractures or osteoporosis more generally. Furthermore, these factors could be exploited for diagnostic interpretation as biomarkers [including novel long non-coding (lnc)RNAs, micro (mi)RNAs and circular (circ)RNAs]. The extent of methylation of genes, alongside post-translational histone modifications, have shown to affect several interlinked pathways that converge on the regulation of bone deposition and resorption, partially through their influence on osteoblast and osteoclast differentiation. Lastly, in addition to biomarkers, several exciting new imaging modalities could add to the established dual-energy X-ray absorptiometry (DXA) method used for BMD assessment. New technologies, and novel sequences within existing imaging modalities, may be able to quantify the quality of bone in addition to the BMD and bone structure; these are making progress through various stages of development from the pre-clinical sphere through to deployment in the clinical setting. In this mini review, we explore the literature to clarify the genetic and epigenetic factors associated with spinal fragility fractures and delineate the causal genes, pathways and interactions which could drive different risk profiles. We also outline the cutting-edge imaging modalities which could transform diagnostic protocols for OVF.

Keywords: Osteoporosis; spinal fragility fractures; biomarkers; genomics; proteomics; epigenetics

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Introduction

Spinal fragility fractures stemming from osteoporosis have been shown to be more prevalent in Caucasians relative to Eastern Asian populations. For example, the prevalence of osteoporotic vertebral fractures (OVF) is much higher in Italian Caucasian in comparison to Hong Kong Chinese women (1), and osteoporotic fracture prevalence is more than 50% lower in the elderly Chinese in comparison with a European cohort (2). The differences in prevalence are important and should be taken into account in order to optimise diagnostic protocols, such as those based on T-score values, for different groups with varying risks for developing fragility fractures (3). One of the difficulties with the current knowledge base is that there is a lack of a defined standard for OVF risk prognostication through imaging (4). As such, there is an ongoing search for factors that can protect the vertebrae from osteoporosis or promote their healing process; as well as for quantitative and qualitative measures of disease monitoring useful in the context of a comprehensive clinical-radiological workup. As the global burden of low bone mineral density (BMD) and the disability-adjusted life years attributed to this phenomenon are growing each year, even in countries with good protective measures, this poses a significant challenge to improving outcomes for patients (5). We carried out a narrative literature review to synthesize novel discoveries across relevant and recent articles in the PubMed database with no language restriction. With a focus on spinal fragility fractures, we clarify the potential genetic and epigenetic risk factors that could be contributing to the different incidence and prevalence across different populations (*Figure 1*), and make use of this opportunity to outline the advancements in diagnostic approaches, including novel biomarkers and state-of-the-art imaging modalities.

Genetic factors

Genetic causes of osteoporosis have been extensively investigated; however, less is known about those specifically causing OVF (8). One of the key contributors to a higher rate of spinal osteoporotic fractures in western countries could be the occurrence of mutations in specific genetic loci conveying higher susceptibility to the Caucasian population (or vice versa, a lower risk in East Asian cohorts). For instance, one of the hallmarks of osteoporosis is low BMD, and several genetic loci have been implicated in genome-wide association studies (GWAS) showing a strong association with low BMD, and in some cases a direct correlation with the occurrence of vertebral fractures (9). Unfortunately, many of these studies do not make a clear distinction in different fracture phenotypes and examine them altogether; however spinal fractures are clinically different and could be affected by different genetic loci.

So far only two GWAS focused specifically on vertebral osteoporotic fractures (*Table 1*) (13). A GWAS of a Dutch cohort in the Rotterdam Study found that a single nucleotide polymorphism (SNP) at the 16q24 locus mapping to *FOXC2* was associated with a higher vertebral fracture risk, but when this SNP was evaluated through a meta-analysis covering 14 more studies this association, although confirmed, was not significant (10). These data point to one of the first challenges in investigating these genetic loci: the wide heterogeneity in the definition of the fractures included across multiple studies (8). The second study identified a locus on chromosome 2q13, which was significantly associated with vertebral fractures. Of note, such locus was not known from previous studies to affect BMD: hence we could argue that the correlation demonstrated by the authors could highlight an independent mechanism of susceptibility to osteoporosis (12). This is an interesting point because a significantly larger quantity of loci has been found with associations with BMD at various sites: a recent effort found at least 15 fracture loci (not specific to the spine), all of which were already associated with BMD, nonetheless the effect of the SNPs was smaller on the fracture risk than on BMD itself (14). All those aspects ultimately indicate that many factors can influence the different incidence and prevalence of spinal osteoporotic fractures around the world. In terms of GWAS specific to the Eastern Asian population, the *JAG1* gene has been found to be associated with increased BMD in lumbar vertebrae in a female Hong Kong cohort of patients; its levels of expression (based on the increased BMD conferred to those with a specific SNPs) could be a potential factor for fragility fracture pathogenesis (15).

Another aspect to consider is peak bone mass, increases in which have been shown to reduce the fracture risk at the population level (16). The bone mass gain in children could act as a protective factor from future osteoporosis; in children, the genes *IZUMO3* and *RBFOX1* have been associated in a GWAS with BMD of the lumbar spine in a site-specific manner (17). In addition, a non-coding variant near the *EN1* locus was found with whole genome sequencing and showed age-specific effects; it was associated with a decreased risk of fracture and, when conditionally

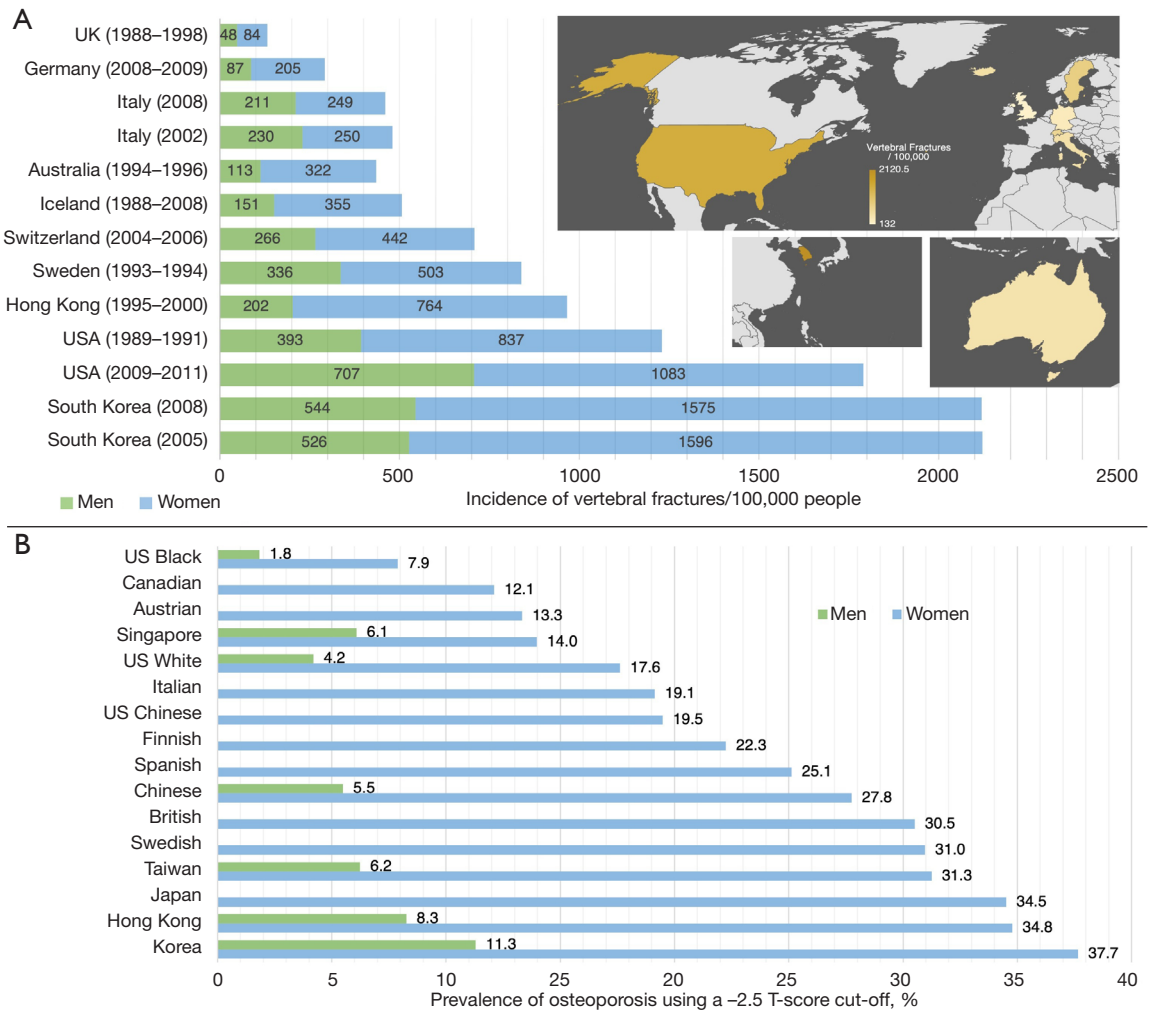

Figure 1 The incidence and prevalence of osteoporosis across the world. (A) The incidence rates of vertebral fractures per 100,000 people in various countries and regions worldwide, standardised to age (6). Due to the methodologies of the studies summarised in this paper, it is possible that the incidence/prevalence of osteoporosis and related fragility fractures is overestimated in populations from certain Asian countries and regions. (B) The estimated prevalence of osteoporosis in different populations using the standard –2.5 T-score cut-off (7). Note that using the same T-score for each country's or region's population may not be appropriate for diagnosing osteoporosis (see *Figure 2* and discussion).

lost in a mouse model, led to low bone mass (18). *EN1* and *RANKL* both displayed age-specific effects and suggest that either peak bone mass or peak BMD are the consequence of some of the signalling pathways in early life, and that the consequences of these expression patterns remains throughout life (19). It is possible, therefore, that the focus should be more on acquiring peak bone mass in childhood as well as preventing bone resorption and osteopenia as a protective measure against osteoporotic fractures. However, there are no studies comparing the peak bone mass of Caucasian versus Asian children, and the difference in peak bone mass seen between women of European and South Asian background was no longer significant when adjusting for weight and height (20).

An additional approach to unveil the genetic basis of OVF could be to consider genes conveying protective traits to bone health. In this way, studying disorders and rare mutations that are associated with a high bone mass (which will reduce bone fragility and fracture risk), could also help clarify the differences between populations. In sclerosteosis,

the *LRP* family of genes have been suggested to increase signalling in the WNT/β-catenin pathway and confer this increase in bone mass (21). Indeed, this pathway is indicated in epigenetic regulation of osteoblast differentiation (*Table 2*). Conversely, an insight into the risk factors for osteoporotic fractures could be gained by studying the hallmarks of inherited osteolysis disorders in which bone undergoes spontaneous and rapid lysis and resorption (30). Some disorders in this family of conditions are hereditary and the causative mutation have been identified, such as the *MAFB* gene in multicentric carpotarsal osteolysis syndrome (31). Some, like the non-hereditary Gorham-Stout disease (GSD), also known as phantom bone disease, display the involvement of pathways such as the mTOR, PTEN and RANKL. mTOR contributes to changes in angiogenic and osteoclast signalling and leads to the replacement of bone with vascular or connective tissue (32). Indeed, the mTOR inhibitor sirolimus has successfully been used to treat a number of patients with GSD (33). Alternatively, the RANK-ligand inhibitor denosumab could be a useful anti-resorptive agent. In a very small study, it was shown to increase BMD and reduce fractures in Japanese children with osteogenesis imperfecta with osteoporosis (34), whereas in a very large study of 7,868 post-menopausal women with osteoporosis, it decreased the risk of radiographic vertebral fracture by 68% (35).

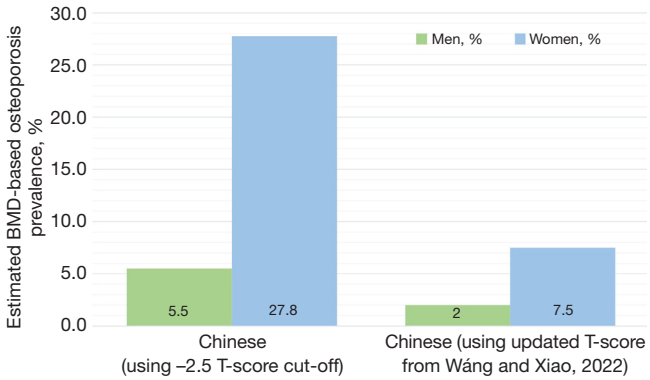

Figure 2 The importance of using cut-off point T-scores that are more clinically appropriate to define osteoporosis in the Chinese population. On the left side we see prevalence estimates when using the standard –2.5 T-score cut-off compared to the prevalence estimates when using a more updated and clinically relevant methodology on the right-hand graph—see Wáng and Xiao, 2022 for methodology (7). As the T-score of ≤–2.5 was utilised mainly to align with hip osteoporosis/fragility fracture in older Caucasian women, these adjustments are important to improve international comparison of disease burden (52,73). BMD, bone mineral density.

Whilst there is evidence for aberrant activity of certain genetically-encoded pathways, genetic risk factors that were identified in Europeans did not improve the prediction of fracture rate in Chinese populations (36). By contrast, 20% of the BMD variation in the genetic studies can be explained by the more common genetic variants [as opposed

Table 1 Genetic factors associated with spinal fragility fractures

Gene	Locus	Relevance	Bibliography
FOXC2	Ch 16; q24	• Highly expressed in bone tissue and codes for a transcription factor • Contributes to osteoblast differentiation via Wnt/β-catenin signals • Associated with other non-random vertebral birth defects (VACTERL association) (11)	Oei *et al.* 2014, (10)
SLC20A1 or *TLL*	Ch 2; q13	• Uncertainty if the SNP here is associated with *TLL* or *SLC20A1—SLC20A1* is involved in mineralisation whilst *TLL* is involved in neuronal development and injury signalling • *SLC20A1* codes for a sodium-phosphate symporter which regulates phosphate transport in osteoblasts • *SLC20A1* not previously associated with BMD or fractures • No association when compared for association with volumetric vertebral BMD—suggesting a novel, independent pathway for vertebral fracture independent of BMD	Alonso *et al.* 2018, (12)

Many other factors have been associated with low BMD, here we focus only on those that are spinal fracture specific. VACTERL, vertebral, ano-rectal, cardiac, tracheo-esophageal, renal, and limb; SNP, single nucleotide polymorphism; BMD, bone mineral density.

Table 2 Epigenetic factors associated with spinal fragility fractures

Epigenetic factor families	Genes and pathways involved	Bibliography
DNA methylation	• *BMP2, RUNX2, OSX*	Zhang *et al.* 2011, (22); Cao *et al.* 2018, (23)
	• Wnt/β-Catenin, OPG/RANKL/RANK pathways	
Histone acetylation	• *OPN, OCN, ALP, OSX, RUNX2*	Piao *et al.* 2013, (24); Xu *et al.* 2021, (25)
	• *SIRT1* and its downstream post-transcriptional pathways (p53, FoxOs, PPAR)	
Histone methylation	• Wnt/β-Catenin pathway, *BNMP2, RUNX2, OSX*—inhibit OB	Flowers *et al.* 2010, (26)
	• *DLX, HOX* promotes OB	
lncRNAs	• *RUNX2*, *SBP2* and Wnt/β-Catenin, RANK/RANKL/OPG pathways to promote OB	Li *et al.* 2020, (27)
	• P38 MAPK and BMP/TGF-β to inhibit OB	
miRNAs	• NF-κB, PI3K/AKT pathways promote OB	Letarouilly *et al.* 2019, (28)
	• OSX, TCF, Wnt, MARK pathways inhibit OB	
circRNAs	• Act on a variety of miRNA targets which subsequently act on the above-mentioned pathways	Dou *et al.* 2016, (29)

Many other factors have been associated with low BMD, here we focus only on those that are spinal fracture specific. OB, osteoblast differentiation; (lnc)RNAs, long non-coding RNAs; (mi)RNAs, micro RNAs; (circ)RNAs, circular RNAs; BMD, bone mineral density.

to risk factors like body mass index (BMI) or age which contribute only 8%] (37), suggesting that genetic factors do play some significant role in the disease process (12). Therefore, while we know by fact that different genetic loci can be implicated in specific populations, the lack of direct comparison between Chinese and Caucasian populations partly limits our inferences on prevention strategies.

Epigenetic factors

A healthier lifestyle (as calculated by the healthy lifestyle scores which includes smoking, BMI, physical activity, diet, alcohol, sleep and anxiety) has been shown to be associated with greater BMD (38). Many other factors, such as vitamin D and calcium levels have been generally accepted and included in guidelines on prevention of osteoporosis and general bone health. However, apart from homocysteine levels, no other clinically relevant risk factors (such as rheumatoid arthritis, vitamin D, calcium intake, cardiovascular disease or diabetes) had a statistically significant effect on fracture risk (14).

The impact of lifestyle factors can be queried because of the finding that, over a 5-year follow-up period, Chinese Canadians retained more BMD than Caucasian Canadians (39). This suggests that, even upon immigration from one country or region to another, the lower risk of osteoporotic fractures seen in the Chinese population remains. Various epigenetic factors, which are involved in the regulation of almost all cells in the bone marrow, could for instance indicate that the decrease in bone mass seen in osteoporosis depends from the differentiation of precursor cells towards an adipocyte lineage as opposed to the bone-forming osteoblasts (28). The three key epigenetic regulators involved in this process are DNA methylation, histone modifications and regulatory action of non-coding (nc)RNA (*Table 2*, *Figure 3*) (25).

There are number of genes which, when methylated by DNA methyltransferases (DNMTs), up- or downregulate osteogenic differentiation, and by extension affect the risk of developing osteoporosis. In this way, methylation inhibitors like 5-Aza-C have been used to demethylate *DLX5* and *OSX* promoters, increasing the expression of markers of osteogenesis (40). These, among others like *RUNX2* (22) and *ESR1* (41), are genes that promote osteogenic differentiation when hypomethylated. Conversely, some pathways have the reverse effect and promote bone resorptive or osteoclastic differentiation when in a hypermethylated state, such as *RANKL* (part of the key OPG/RANKL/RANK signalling pathway), *SOST* (strongly correlated with fracture risk) (23,42) and *Alu* elements (43). The last of these, *Alu* elements, which contribute to variable splicing and transcription regulation were increased during periods of

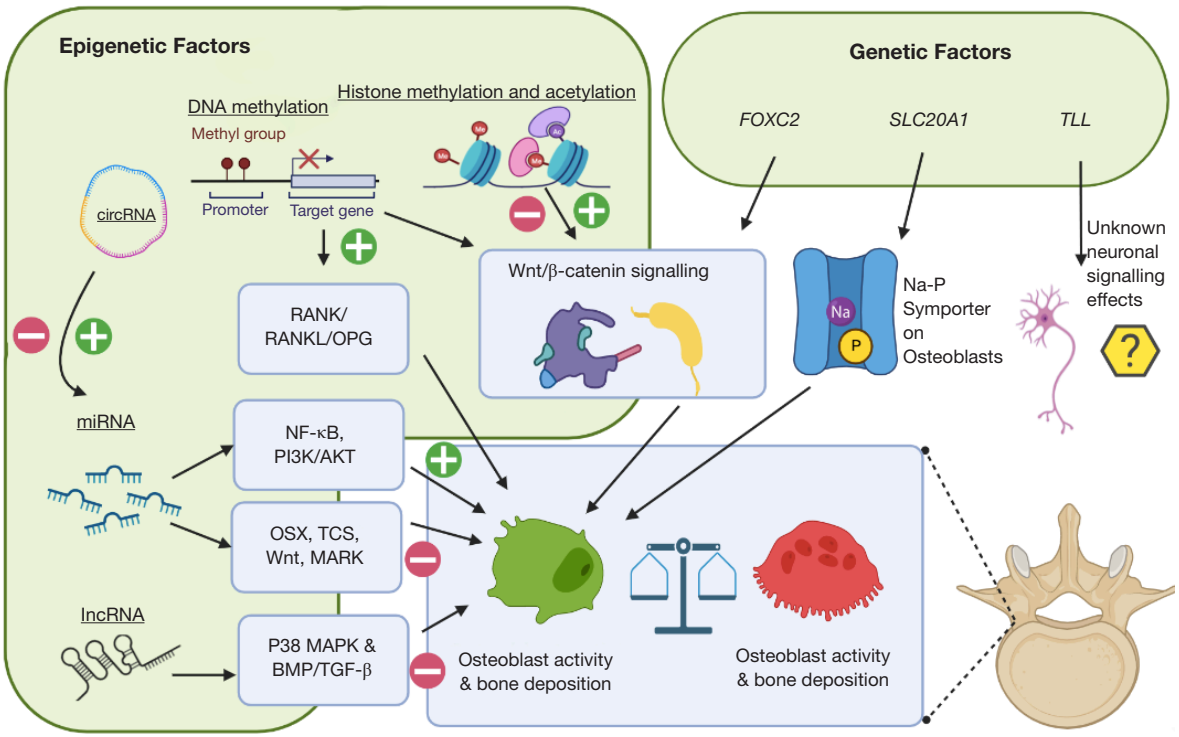

Figure 3 Summary of the epigenetic and genetic factors involved in balancing osteoblast and osteoclast activity in bone health and in osteoporosis. (lnc)RNAs, long non-coding RNAs; (mi)RNAs, micro RNAs; (circ)RNAs, circular RNAs; Na-P symporter, sodium-phosphate symporter.

rapid growth in children (44). This, much like peak bone mass, could be an early marker of future bone health and osteoporotic fracture risk, paving a potential new approach to risk stratification.

Other epigenetic factors that could influence osteoporotic fracture risk are related to post-translational histone modifications, through changes in acetylation or methylation. Acetylation levels are controlled by a balance of the action of a pro-acetylation and a de-acetylation enzyme, histone acetyltransferase (HAT) and a histone deacetylase (HDAC), respectively (24,25). Through inhibition studies, HDACs have been shown to regulate osteoblast differentiation, with some cross-over with genes affected by DNA methylation like *RUNX2* (45). Alternatively, histones can be methylated to different extents too. For example, the histone demethylase KDM5A exerts an effect on *RUNX2* and inhibits osteoblast differentiation, whereas another demethylase (26), JMJD3 targets *HOX* and promotes their differentiation (46). This variety shows how complex, and difficult, it may be to arrive at one pathway to stratify risk between different groups.

The last of the three families involved in epigenetic regulation are non-coding RNAs. These span in variety from long non-coding (lnc)RNAs and micro (mi)RNAs to circular (circ)RNAs (25). In osteoporotic postmenopausal women, several lncRNAs were found to regulate osteoclast differentiation, potentially contributing to osteoporosis by affecting mRNA expression (27,47). Their effects are varied: depending on the target genes, some promote, and some inhibit osteoblast differentiation. Furthermore, miRNAs regulate genes that affect osteogenic differentiation and they do so with even more variety [almost 40 have been identified (25)]. Lastly, the relatively novel circRNAs have proven their involvement in many aspects of genetic regulation, practically at each step by targeting miRNAs themselves (29); however, the contribution of circRNAs to bone metabolism and their direct relevance in osteoporotic fractures is not yet clear.

Biomarkers

Whilst environmental factors are difficult to characterise

and evaluate reliably, the elucidation of the pathways potentially contributing to osteoporotic fracture via genetic and epigenetic mechanisms suggests a potential ground for identification of useful biomarkers. This could enable more precise ways of comparing and estimating the burden of spinal fragility fractures between different populations.

Previously, conventional markers of bone metabolism and turnover would have been used; more recently, novel markers are being evaluated, such as the aforementioned miRNAs. Some of the biomarkers have mapped to specific populations: miR-133a was upregulated in those with low BMD in postmenopausal Caucasian women (48), whilst miR-194-5p elevation was correlated with T-scores in Chinese osteoporotic women (49).

What remains to be seen is if a comparison of one marker between different groups to evaluate whether they could partially explain the difference in risk of spinal fragility fractures. These miRNAs are also part of a wider drive of RNA therapies for various disorders, although bone-specific miRNAs are yet to enter clinical trials. Alternatively, novel genome-wide DNA methylation analysis could enable the characterisation of biomarkers of osteoporosis peripherally, in the blood.

Whilst some studies did not find significant methylation patterns in the blood (50), a study of methylation in whole blood samples of Canadian postmenopausal osteoporotic women showed that it is possibly to detect markers associated with osteoporosis in its early stages in white blood cells (51). However, as we are considering spinal fragility fractures, it is important to note that DNA methylation patterns vary between, and are specific to, different tissues; the blood may not reveal these markers effectively (25). Going forward, adjustments in the T-score cut-offs based on biomarkers could help improve characterisation of an individual's risk (52).

Imaging

In addition to biomarkers, innovative imaging approaches are being developed to better detect osteoporosis and subsequent vertebral fractures (*Table 3*). The aim is to achieve both earlier detection and to improve post-fracture screening. At present, the commonest modalities with the most data and experience are classical radiography for fracture detection and dual-energy X-ray absorptiometry (DXA) for BMD measurement. Despite its limitations in the overestimation of spinal BMD in older patients with sclerotic lesions which obfuscate the BMD value (54), DXA is still the current gold standard with several established guidelines (55). More recently, new data can be extracted from DXA images, including a trabecular bone score (TBS) which evaluates not just the BMD, but also the bone quality (56).

Quantitative computed tomography (QCT) scans can also be used in the assessment of the lumbar spine for spinal fragility fractures; they have several advantages over DXA. Overall, they are equal if not better at assessing BMD than DXA methods, however only in postmenopausal women (57). QCT has the advantage of generating a volumetric (rather than area-based) measurement of BMD (vBMD) and it can measure purely trabecular bone (which is more metabolically active than cortical bone and hence can be a better predictor of bone health and fracture risk than DXA). At present, DXA is still preferred for the spine over QCT because of the smaller radiation dose it delivers. Alternatively, QCT scanning could be carried out at the time of the injury (to prevent loss to follow-up) or as part of a 'opportunistic' screening programme in those being scanned for other reasons (58). More recently, high resolution peripheral QCT (HR-pQCT) scanners have been evaluated and showed greater spatial resolution. Whilst HR-pQCT is restricted to the peripheral skeleton, it shows a correlation with QCT values in the lumbar spine, suggesting it could be used to infer central BMD (59). In contrast to computed tomography (CT), the lack of ionising radiation is key advantage of magnetic resonance imaging (MRI) scanning. MRI has shown to perform just as well in imaging trabeculated bone as QCT and HR-pQCT (60). More recently, ultra-high-field MRI was used to show that vertebral bone microarchitecture changes are strongly correlated with parameters such as failure load and stress (61). Whilst high-resolution CT and MRI imaging can evaluate the microarchitecture of bone on a finer scale, their use is not yet established in practice—due to cost and practicality and the novelty of these approaches. By way of example, diagnosing patients with the WHO classification can only be done at present with BMD and T-scores obtained from DXA (62).

Looking to the future, several emerging technologies as well as novel sequences show promise for evaluating not just the bone structure and BMD, but also the bone quality (4). For example, measuring the bone marrow fat fraction (BMFF) with the modified Dixon MRI sequence predicted abnormal bone density (63), which has now improved further with deep learning integration (64). In another approach, MRI T2* mapping of vertebral bone marrow was used to differentiate between those with low-energy and high-energy traumatic vertebral fractures, potentially paving

Table 3 Advantages and disadvantages of various modalities for the diagnosis of spinal fragility fractures

Technique	Technique details and hallmarks	Advantages	Disadvantages
TBS	• Quantifies changes from adjacent pixels in grey-level texture	• Correlated with fracture risk in older males	• Cannot be used in isolation yet
	• Low TBS suggests increased fracture risk	• Complementary to BMD	• Age-dependent, and insensitive between 30–45 years
		• Derived from existing DXA scans	• Not a direct measure of bone microarchitecture
QCT	• Osteoporosis—vBMD <80 mg/cm^3	• Differentiates osteoporosis from other pathologies (e.g., tumour)	• Higher radiation dose (cf. DXA)
	• Severe osteoporosis—vBMD <80 mg/cm^3 + insufficiency fracture	• Not affected by scoliosis, weight, degeneration (cf. DXA)	
		• Ability to measure BMD in a specific volume (vBMD)	
HR-pQCT	• Assesses vBMD as well as trabecular vs cortical BMD	• Shows correlation with QCT values in spine, could be used to infer central BMD despite being a peripheral scan	• Restricted to the peripheral skeleton so not as useful for spinal fracture evaluation
	• Individual trabecula segmentation to quantify the ratio of rod-like to plate-like	• Can give very low effective dose and avoid radiosensitive organs	
Spectral CT and dual-energy CT	• Two oscillator elements with a photodiode providing spectral information	• Can differentiate tissue (e.g., water and fat) with material-specific values	• Higher radiation dose than QCT
MRI	• Changes in trabeculae from plate-like to rod-like associated vertebral disease risk (53)	• Avoids ionising radiation exposure	• Signal lacks standardisation
		• Can show early changes in bone marrow (cf. CT or X-ray)	• Direct signal not diagnostic
		• Can discern subtle fracture from other pathologies	
Novel MRI sequences	• BMFF by chemical shift for example with modified Dixon sequence	• Quantifies osteoporosis through bone architecture	• Cannot directly measure BMD
	• DWI for water diffusion	• Potential of effective integration with AI approaches in the future	• Practicalities—available technology and cost
	• Ultrashort TE for cortical bone		
Bone scintigraphy	• Radiotracer uptake increased in a linear pattern	• Cheaper than PET	• Is only able to provide 2D information
		• Allows bone metabolism visualisation (cf. X-ray/CT)	
SPECT, SPECT/CT and PET/MRI	• Hot spots with radioactive tracer uptake then computationally quantified	• Detect and differentiate different causes of secondary osteoporosis	• Cannot be used for primary osteoporosis diagnosis
		• Provides 3D information (cf. traditional scintigraphy)	• Should be combined with an existing QCT integrated scanner

TBS, trabecular bone score; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; QCT, quantitative computed tomography; vBMD, volumetric measurement of BMD (rather than area-based); HR-pQCT, high-resolution peripheral quantitative computed tomography; CT, computed tomography; MRI, magnetic resonance imaging; BMFF, bone marrow fat fraction; DWI, diffusion-weighted imaging; TE, time to echo; AI, artificial intelligence; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

a way for use in fracture risk evaluation (65). In terms of improvements on CT, novel spectral CT and dual-energy CT are also being evaluated as they are additionally able to better distinguish different tissues, however, their clinical value is still uncertain (4).

With regard to nuclear medicine bone scans, it is well known that they could answer different clinical questions, for instance they can be employed to monitor the response of compression fractures to therapy. These scans include bone scintigraphy, single-photon emission computed tomography (SPECT), SPECT/CT as well as positron emission tomography (PET)/MRI. Whilst nuclear bone scans can be used to differentiate between different causes of secondary osteoporosis, they are not used for the diagnosis of primary osteoporosis (4). Nevertheless, scintigraphy has been shown to detect a greater percentage of vertebral fractures than conventional radiography and, additionally, could also differentiate between old and new fractures (66).

Finally, in the pre-clinical sphere, vibro-acoustography (a technique based on ultrasound radiation) was able to differentiate between osteoporosis and control rodent groups; yet another potential future screening tool (67).

In summary, whilst radiographic and DXA scans are the norm for detecting vertebral fractures and evaluating BMD, they face competition from emerging adaptations to existing technologies like MRI and CT, with new sequences or new combined scanning protocols. The addition of artificial intelligence (AI) to these data sets will enable, in future clinical practice, the extraction of even richer data and the ability to predict fracture risk (68). Whilst the hunt for a biosignature of spinal fragility fractures or osteoporosis continues, the finding that HR-pQCT measurements of bone architecture and vBMD are heritable across a number of generations gives further incentive to look for specific signatures of reduced vBMD and try to elucidate the genetic and epigenetic factors contributing to them (69).

Lastly, it is important to consider that improving imaging techniques, potentially with the help of recent advances in nanomedicine with regards to techniques meant to optimize the of role of contrast media and radiotracers (70), which are directly translated from strategies to enhance the bioavailability of chemotherapics (71), is just one of the future hopes of early diagnosis in patients with osteoporosis. Identifying this condition early is just the beginning of a long and complex management course: equally important will be an efficient follow-up imaging to detect subsequent fragility fractures with a close comparison of previous imaging, even in those that have been treated medically or surgically with vertebroplasty (72).

Conclusions and future directions

The genetic and epigenetic landscape for spinal fragility fracture risk is being investigated, with several spine-specific loci linked to BMD and metabolism having been identified in GWAS studies. Only two loci have been found which directly associate with vertebral fracture risk. Studies comparing the prevalence of these loci in different populations are needed to understand if they underpin the risk differences, such as that existing between East Asian and Caucasian cohorts.

When analysing this risk, it is important to consider the particularities of how osteoporosis and fragility fracture prevalence and incidence are estimated across different countries or regions. For example, there is an argument to be made that using the traditional cut-off T-score of –2.5 is not appropriate in all populations; it can be argued that the population in certain Asian countries or regions has a different risk profile to Caucasian populations and hence should have their diagnostic cut-offs and modelling of fracture prevalence tailored more appropriately (73-75). Using the –2.5 cut-off score can therefore greatly overestimate the prevalence of osteoporosis and make projections about fragility fractures seem inflated (73). It is therefore important to analyse the methodology used to project these figures (6,76,77). Whilst in *Figure 1A* we highlight the incidence of fragility fractures (a directly measurable quantity), the projections used in prevalence estimates for osteoporosis can be flawed if they use the –2.5 T-score cut-off in populations where this may not be appropriate (*Figure 1B*). Recently, more appropriate T-score cut-offs for several Asian populations have been suggested to more appropriately represent the burden of osteoporosis and vertebral fractures in those countries (*Figure 3*) (7,73,78). In addition, the incidence rates reported in different regions are clearly highly affected by the healthcare systems in place there, particularly relating to access to healthcare and appropriate diagnostic investigations.

Lifestyle factors, whilst widely discussed as being important for general bone health, do not reach the same statistical significance to explain these variations. However, epigenetic factors are being elucidated extensively, and are showing promise both in understanding risk profiles, at detecting risk peripherally in the blood as biomarkers, but also as potential future therapies. This information will

help clinicians in obtaining a better diagnosis and enable tighter treatment monitoring; advancements in imaging techniques and data extraction from existing scans will further accelerate the exiting translational path for patients harbouring OVF.

In terms of potential future directions of research, there is a current pertinent needed for an integrated multi-omics approach that can bring together the various advances from imaging and (epi)genomics that we have highlighted in order to generate a practical tool for clinicians to improve management and outcomes for patients (11,53,79). The benefit of this would be two-fold; first it can decrease the necessity for duplicating research efforts, and secondly it would bring together what are at present a complex interplay of various factors. Rather than interpreting these various genetic and epigenetic factors, biomarkers and imaging findings in isolation, an integrated approach requiring an international effort could be particularly useful.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-513/coif). MG serves as an unpaid editorial board member of *Quantitative Imaging in Medicine and Surgery*. The other authors have no conflicts of interest to declare.

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