

## REVIEW

# Osteoarthritis and bone mineral density: are strong bones bad for joints?

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Osteoarthritis (OA) is a common and disabling joint disorder affecting millions of people worldwide. In OA, pathological changes are seen in all of the joint tissues including bone. Although both cross-sectional and longitudinal epidemiological studies have consistently demonstrated an association between higher bone mineral density (BMD) and OA, suggesting that increased BMD is a risk factor for OA, the mechanisms underlying this observation remain unclear. Recently, novel approaches to examining the BMD-OA relationship have included studying the disease in individuals with extreme high bone mass, and analyses searching for genetic variants associated with both BMD variation and OA, suggesting possible pleiotropic effects on bone mass and OA risk. These studies have yielded valuable insights into potentially relevant pathways that might one day be exploited therapeutically. Although animal models have suggested that drugs reducing bone turnover (antiresorptives) may retard OA progression, it remains to be seen whether this approach will prove to be useful in human OA. Identifying individuals with a phenotype of OA predominantly driven by increased bone formation could help improve the overall response to these treatments. This review aims to summarise current knowledge regarding the complex relationship between BMD and OA.

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## Introduction

The relationship between bone mineral density (BMD) and osteoarthritis (OA) has long been a subject of debate in the literature. Understanding this relationship has the potential to illuminate the role played by bone in the pathogenesis of OA, and may have important therapeutic implications. The aim of this review is to summarise the evidence to date supporting a positive association between systemic BMD and OA, including recent insights from studies using novel approaches, and to offer a perspective for the future.

## BMD and OA: the Epidemiological Evidence for an Association

As far back as the 1960s, it had been observed that features of OA were generally absent in femoral heads excised after hip fracture.<sup>1</sup> In 1972, Foss and Byers<sup>2</sup> studied a series of femoral heads excised either in the surgical treatment of hip fracture or total hip replacement for OA; they observed very few pathological changes of OA in the fracture specimens, whereas bone density appeared to be increased in the OA patients, as

assessed on radiographs of the second metacarpal. Since then, numerous studies have been published examining the relationship between systemic BMD and OA, and several authors have reviewed this topic.<sup>1,3,4</sup>

OA is recognised to be a heterogeneous disease that can be defined in different ways (for example, in terms of clinical symptoms, radiographic change or a combination of these features).<sup>5</sup> Despite this, epidemiological studies of the relationship between BMD and OA have almost exclusively defined OA radiographically, usually using a summary grading system such as the Kellgren–Lawrence grade.<sup>6</sup> Earlier studies were cross-sectional in design, comparing BMD (generally measured at the spine and/or hip) in OA cases with that in unaffected controls (**Table 1**). The hip and knee joints have been most studied, with several groups finding evidence of higher systemic BMD in those with OA at these joint sites in a variety of populations.<sup>7–11</sup> Higher BMD has also been reported in association with OA of the spine<sup>10,12</sup> and hand.<sup>9,10,13</sup>

A limitation of cross-sectional studies is that the direction of causality cannot be formally assessed. Features of OA such as

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**Table 1** Cross-sectional studies examining the association between BMD and OA using dual X-ray absorptiometry (DXA)

Reference	Population	Joint site (OA)	OA definition	Site of BMD measurement	Conclusions
Hart <i>et al.</i> <sup>10</sup>	Women from the UK Chingford study ( $n = 979$ hands and knees, $n = 579$ lumbar spine)	Knee, hand (1st CMCJ, DIPJs), lumbar spine	Radiographic (K&L grade $\geq 2$ )	Femoral neck and lumbar spine (L1–L4)	Lumbar spine BMD higher in OA cases vs controls (all joint sites). Femoral neck BMD higher in OA cases vs controls at CMC joint, knee, lumbar spine. Associations persisted on adjusting for spinal osteophytes.
Nevitt <i>et al.</i> <sup>7</sup>	4090 Caucasian women from the US Study of Osteoporotic fractures, mean age 71 years	Hip	Radiographic (definite osteophytes or narrowing, plus cysts or sclerosis)	Hip (femoral neck, Ward's triangle, trochanter, intertrochanteric), lumbar spine	Increased BMD at all sites in subjects with moderate–severe OA of either hip, increased BMD at femoral neck and lumbar spine in subjects with milder hip OA. Associations persisted on adjusting for vertebral body osteophytes/subchondral sclerosis. OA hips with osteophytes, but not isolated JSN, associated with increased BMD.
Peel <i>et al.</i> <sup>12</sup>	375 women aged 40–85 years from a UK primary care population	Spine	Radiographic (K&L grade $\geq 2$ )	Lumbar spine, femoral neck and total body	BMD increased at all sites in the OA group.
Burger <i>et al.</i> <sup>8</sup>	2745 men and women from the Rotterdam Study (Netherlands), mean age 69 years	Knee and hip	Radiographic (K&L grade $\geq 2$ )	Femoral neck	BMD 3–8% higher in the group with OA (not significant for knee OA in men, $P = 0.07$ ). In general, BMD increased according to the number of joint sites affected and increasing OA severity (K&L grade).
Sowers <i>et al.</i> <sup>9</sup>	573 Caucasian women from the Michigan bone health study, aged 24–45 years	Hand and knee	Radiographic (K&L grade $\geq 2$ )	Proximal femur, lumbar spine and total body	Total body BMD positively associated with highest OA grade at both hand and knee. Total body BMD associated with knee OA (K&L grade $\geq 2$ ).
Chaganti <i>et al.</i> <sup>11</sup>	3929 men from the US MrOS study	Hip	Radiographic (summary grade 0–4, OA defined as grade $\geq 2$ )	Lumbar spine, total hip, femoral neck, trochanteric	Higher DXA BMD at all sites in moderate/severe OA group vs mild/no OA. Volumetric BMD elevated at hip and L1 vertebra in the severe OA group.

Abbreviations: BMD, bone mineral density; CMCJ, carpometacarpal joint; DIPJ, distal interphalangeal joint; JSN, joint space narrowing; IRF, individual radiographic feature (of OA); K&L, Kellgren & Lawrence grade (summary grade for OA); OA, Osteoarthritis. This represents some key studies as selected by the authors, and is not exhaustive.

osteophytes and subchondral sclerosis, if present within the dual X-ray absorptiometry (DXA) field, might artefactually elevate BMD. The site of BMD assessment is important, as it is recognised that osteophytosis affects BMD measured at the spine to a much greater degree than at the hip.<sup>14,15</sup> It is therefore worth noting that strong positive associations between hip BMD and large joint OA have been observed in many studies,<sup>8,10,11</sup> and that the positive association between lumbar spine BMD and OA at both the hip and knee has been shown to persist after adjusting for the presence of spinal osteophytes.<sup>7,10</sup>

More recently, the temporal relationship between BMD and OA has been clarified in prospective studies (**Table 2**). Several longitudinal studies have shown higher BMD to be associated with a greater risk of developing subsequent radiographic knee OA,<sup>16–20</sup> although findings have not always been conclusive.<sup>17</sup> Although the populations studied have been predominantly female, there is also evidence of a positive association between BMD and incident knee OA in male populations.<sup>19,20</sup> A similar association between higher BMD and incident radiographic hip OA has been reported in postmenopausal women,<sup>21</sup> whereas Sowers *et al.*<sup>16</sup> found no evidence of a longitudinal association with hand OA in a population of pre- and peri-menopausal women.

The Kellgren–Lawrence grading system for radiographic OA has been criticised for an overemphasis on the osteophyte,<sup>22</sup> whereas in fact distinct radiographic OA phenotypes, with varying degrees of osteophytosis relative to other features such

as joint space narrowing (JSN, an indirect measurement of cartilage loss), can be delineated.<sup>23,24</sup> In studies in which these individual radiographic features of OA have been quantified separately, increased BMD has generally been reported to be more strongly associated with osteophytosis than JSN.<sup>7,17,18,21</sup> Indeed, only one longitudinal study to date has convincingly demonstrated a positive association between BMD and incident JSN at the knee.<sup>19</sup> Several possible explanations for this observation, both methodological and biological, can be postulated. A stronger association with osteophytes in this type of study may arise because radiographs are insensitive for the detection of JSN. Alternatively, it may be that individuals with high BMD are prone to develop either osteophytes alone (the clinical relevance of which is uncertain) or a hypertrophic phenotype of OA characterised by vigorous osteophytosis; the term ‘bone-formers’ has been coined to describe this.<sup>3,7,25</sup> The former hypothesis that osteophytes and JSN may have different relationships with BMD is made plausible by the observation that these two features appear to be associated with distinct genetic variants.<sup>26,27</sup> Interestingly, several recent studies using magnetic resonance imaging have actually reported a positive association between BMD and cartilage thickness/volume at the knee in healthy subjects,<sup>28–30</sup> raising the possibility that measurable cartilage loss could appear later on in the OA disease trajectory in individuals with higher BMD.

When interpreting the results of these studies, it is important to recognise the limited concordance between radiographic

**Table 2** Longitudinal studies examining the association between BMD and OA

Reference	Population	Follow-up period	Joint site (OA)	Incident OA definition	Site of BMD measurement	Conclusions
Sowers <i>et al.</i> <sup>16</sup>	482 women from the US Michigan Bone Health study, mean age 37.4 years	3 years	Knee and hand	Radiographic (K&L grade $\geq 2$ , from $< 2$ at baseline)	Femoral neck, lumbar spine and total body	BMD (Z-scores) greater at all three sites in women with incident knee OA, and no differences in baseline BMD in women with incident hand OA vs controls.
Zhang <i>et al.</i> <sup>17</sup>	473 women from the Framingham study, mean age 71 years	8 years	Knee	Radiographic (K&L grade $\geq 2$ , from $< 2$ at baseline)	Femoral neck	Trend towards increased incidence knee OA with increasing BMD, mainly via increased osteophytes. Inverse association between baseline BMD and knee OA progression, mainly via reduced risk of progressive JSN.
Hart <i>et al.</i> <sup>18</sup>	830 women from the Chingford cohort, mean age 54 years	48 months	Knee	Radiographic (grade $\geq 1$ osteophytes or JSN, from grade 0 at baseline)	Lumbar spine and femoral neck	BMD significantly higher at both sites in group with incident osteophytes, and trend towards higher BMD in group with incident JSN. Weak trend towards lower hip BMD in group with progressive osteophytes/JSN.
Hochberg <i>et al.</i> <sup>21</sup>	5242 women from the Study of Osteoporotic Fractures, mean age 71 years	8 years	Hip	Radiographic (minimum JSW $\leq 1.5$ mm, definite osteophyte or summary grade $\geq 2$ , where feature absent at baseline)	Forearm and total hip	Dose-response relationship between quartile of baseline BMD and incidence of radiographic hip OA (defined by osteophyte or Croft grade $\geq 2$ ). No association between BMD and incident hip OA defined by JSN alone.
Bergink <i>et al.</i> <sup>20</sup>	1403 men and women from the Rotterdam study, aged $> 55$ years	6 years	Knee	Radiographic (K&L grade $\geq 2$ in either knee, vs $< 2$ at baseline)	Femoral neck and lumbar spine	Odds of incident knee OA significantly higher in highest vs lowest quartiles of both femoral neck and lumbar spine BMD. Trend towards increased odds of knee OA progression with higher lumbar but not femoral BMD.
Nevitt <i>et al.</i> <sup>19</sup>	1754 men and women from the multicentre osteoarthritis study (MOST), mean age 63 years	30 months	Knee	Radiographic (K&L grade $\geq 2$ , from 0–1 at baseline)	Femoral neck and total body	Risk of incident knee OA increased with higher BMD in both genders. Higher femoral neck/total body BMD associated with increased risk of incident JSN and osteophytosis. No association between BMD and OA progression observed.

Abbreviations: BMD, bone mineral density; JSN, joint space narrowing; JSW, joint space width; K&L, Kellgren & Lawrence grade; OA, Osteoarthritis. This represents some key studies as selected by the authors, and is not exhaustive.

and symptomatic OA.<sup>31</sup> Lower prevalence estimates for symptomatic compared with radiographic OA in the general population reflect the fact that radiographic OA is not always accompanied by clinical disease.<sup>32</sup> Relatively few studies have examined the relationship between BMD and clinically relevant OA, although it has been reported that individuals with radiographic OA have similar degrees of BMD elevation independent of the presence of joint symptoms.<sup>7,10</sup>

### Controversies and Inconsistencies

Despite the weight of evidence that systemic BMD and radiographic OA are positively associated, some inconsistencies and areas of controversy remain. Cross-sectional investigations into the relationship between OA and bone turnover, which is generally inversely related to BMD owing to its role in bone loss,<sup>33</sup> have yielded conflicting findings. Levels of serum or urine bone turnover markers have been reported as both increased<sup>34</sup> and decreased<sup>12,16</sup> in individuals with radiographic OA of different joints compared with controls, with other studies reporting no association between bone turnover markers and radiographic OA severity.<sup>35</sup> Conversely, prospective studies suggest that higher rates of bone turnover may be related to more rapid OA progression. In the Chingford study

population, higher bone resorption markers were noted in postmenopausal women with progressive, but not stable, radiographic knee OA.<sup>36</sup> Similarly, Dieppe *et al.*<sup>37</sup> found increased uptake on bone scintigraphy (indicating increased bone turnover) to be associated with greater subsequent progression of JSN in a mixed-gender population with symptomatic knee OA.

Studies examining the relationship between OA and rates of bone loss, also inversely related to BMD, have reached similarly opposing conclusions, with bone loss in individuals with OA found to be reduced,<sup>16</sup> increased,<sup>8,38</sup> or variable depending upon the site of assessment of both OA and BMD.<sup>39</sup> In a longitudinal study, more rapid bone loss over an 8-year period was associated with an increased risk of progressive OA at the knee.<sup>17</sup> Findings from prospective studies that greater bone loss and turnover may be associated with more rapid OA progression would seem at odds with those discussed earlier, suggesting that higher, rather than lower, BMD is a risk factor for OA. One potential explanation is that OA develops over time in a phasic manner, with periods of active bone turnover corresponding with radiographic progression interspersed with quiescent phases in which bone turnover may be normal or reduced.<sup>23</sup> Furthermore, BMD changes occurring

in different subchondral bone regions in OA are not uniform. In particular, the cancellous bone underlying the thickened subchondral bone plate may become osteopaenic in OA,<sup>40</sup> as observed in studies reporting a decrease in DXA BMD in subchondral bone regions of osteoarthritic knees compared with controls,<sup>41</sup> a phenomenon attributed to 'stress-shielding'.<sup>42</sup> Another possibility is that the relationship of BMD with incident versus progressive OA may differ;<sup>17</sup> this concept will be discussed further below.

In addition, differences in bone size could confound the association between BMD and OA.<sup>43</sup> DXA scans measure areal BMD, which is affected by bone size.<sup>44,45</sup> Larger bones have increased volume in relation to their area; therefore, dividing bone mineral content by bone area to obtain apparent areal BMD will lead to an overestimation of BMD proportional to size. This is relevant, because several studies have observed increases in bone size in individuals with OA, both local to<sup>44-46</sup> and distant from<sup>47</sup> the affected joint. Measurement of volumetric BMD (vBMD) using quantitative computed tomography (QCT) avoids this problem. Abdin-Mohamed *et al.*<sup>48</sup> in 2009 used peripheral QCT to compare tibial vBMD in men and women from the Hertfordshire cohort study with and without radiographic knee OA. An increase in tibial cross-sectional area at the 38% slice and tibial cortical area at the 14% slice was found in men but not in women with OA; however, no difference in vBMD between the groups was found. In contrast, a much larger study by Chaganti *et al.*<sup>11</sup> including 2384 men from the US-based MrOS study found evidence of increased vBMD using QCT at the hip and lumbar spine in men with severe radiographic hip OA compared with controls. As such techniques become more widespread, it seems likely that more data on the relationship between OA and vBMD will emerge.

A positive association between BMD and OA would imply that individuals with OA should have a reduced risk of fracture; however, several studies have instead observed either no difference in fracture incidence between OA affected individuals and controls<sup>39,49</sup> or an increase in fracture risk,<sup>50</sup> although it should be noted that the type of OA definition used in these studies has varied. It has long been speculated that this may relate to an increased risk of falls in OA cases,<sup>50</sup> and indeed a recent large prospective study supported this hypothesis, showing that an association between (self-reported) OA and fracture was largely attenuated by adjusting for incident falls.<sup>51</sup>

Finally, and intriguingly, longitudinal studies have suggested that, in contrast to incident OA, progression of pre-existing OA may be inversely related to BMD. This finding was particularly striking in a paper by Zhang *et al.*<sup>17</sup> studying the Framingham population, in whom a clear association between increasing age-specific femoral neck BMD quartiles and reduced risk of knee OA progression over the 8-year study period was seen. Hart *et al.*<sup>18</sup> also observed a trend towards lower hip BMD in those with progressive knee OA versus non-progressors. In contrast, Nevitt *et al.*<sup>19</sup> failed to find any association between BMD at the femoral neck or whole body and knee OA progression. If an inverse association between BMD and OA progression does hold true, it may provide important insights into the role of bone in the pathogenesis of OA at different stages of the disease. However, it has also been proposed that this observation, rather than reflecting a true difference in risk factors for OA incidence and progression, represents an

epidemiological artefact resulting from aspects of the design of longitudinal studies of OA progression (see Zhang *et al.*<sup>52</sup> for a detailed discussion of this issue).

### OA in High Bone Mass Individuals: a Novel Approach

To date, the evidence for an association between BMD and OA is derived largely from studies in the general population; however, several conditions exist in which BMD is markedly elevated from relatively early in life. Studying OA in these individuals could potentially provide valuable insights into the BMD-OA relationship, particularly as it is clearer in this group that increases in BMD precede the onset of OA, consistent with a causal relationship. Until recently, data on OA in these high bone mass (HBM) conditions have been limited to case reports and case series. For example, early-onset OA has been reported in association with autosomal dominant osteopetrosis.<sup>53,54</sup> In contrast, sclerosteosis does not appear to be associated with degenerative arthritis,<sup>55</sup> and no increased risk of OA in association with activating mutations of *LRP5* has thus far been reported; however, the extreme rarity of these monogenic HBM conditions, coupled with the high prevalence of OA within the general population, may make any such association difficult to detect.

The UK-based HBM study represents the largest collection of individuals with extremely high BMD studied to date.<sup>56</sup> HBM index cases were initially identified through systematic screening of NHS DXA databases for BMD Z- and/or T-scores  $\geq +4$ , excluding scans with artefactual causes of BMD elevation, as previously described.<sup>56</sup> Further HBM cases were subsequently identified through DXA screening of first-degree relatives of index cases, resulting in recruitment of just over 350 cases with unexplained HBM.<sup>56</sup> We recently studied the prevalence and phenotype of OA in this HBM population. HBM individuals were found to have a higher prevalence of self-reported joint replacement and use of nonsteroidal anti-inflammatory drugs compared with unaffected family controls, implying an increased risk of OA as ascertained by clinical, as opposed to radiographic, end points.<sup>57</sup>

Recently, this work was extended to examine the relationship between HBM and radiographic OA phenotypes. An increased prevalence of radiographic hip OA was seen in HBM cases compared with a control group comprising both unaffected family members and general population controls. In line with findings in the general population with respect to BMD, the hip OA phenotype in HBM was characterised by bony features such as osteophytosis and subchondral sclerosis.<sup>58</sup> In contrast, when the individual radiographic features of OA were analysed separately, there was little evidence that HBM is associated with JSN. As HBM is associated with an increased prevalence of clinical OA (as demonstrated by our finding of higher rates of joint replacement<sup>58</sup>), this may imply an association between isolated osteophytosis and clinical symptoms such as pain in this population. However, accurate quantification of joint space width using plain radiographs is hampered by a number of methodological issues, and to what extent HBM leads to OA through osteophytosis independently of cartilage loss and JSN remains to be established.

Subsequent characterisation of knee OA in this group revealed a similar, osteophyte-predominant, radiographic OA phenotype.<sup>59</sup> One caveat is that HBM individuals tend to have a greater BMI,<sup>56</sup> which is well recognised as a risk factor for OA at

a number of sites, particularly the knee.<sup>60</sup> However, although greater BMI appeared to contribute to the association between HBM and knee OA, this association persisted after BMI adjustment,<sup>59</sup> and the relationship between HBM and hip OA appeared to be independent of BMI.<sup>58</sup> It should also be noted that although the HBM cases within this population displayed several clinical features suggestive of a mild skeletal dysplasia, no evidence was found of any significant gait abnormality compared with controls.<sup>56</sup>

We speculate that HBM individuals manifest a 'bone-forming' tendency, which contributes to their risk of OA. This is supported by the additional observation that HBM individuals also have a greater prevalence and severity of radiographic pelvic enthesophytes (bony spurs at tendon and ligament insertions).<sup>61</sup> Although the genetic basis for increased BMD in the majority of these HBM cases remains to be determined, and is the subject of ongoing studies, a genome-wide association analysis has shown overrepresentation of single-nucleotide polymorphisms (SNPs) that were previously shown to be associated with BMD variation in the general population.<sup>62</sup> It is hoped that whole-exome sequencing in this unique group, currently underway, could identify novel pathways with a role in both OA and bone mass regulation.

### Mechanisms, Including Recent Insights from Genetic Studies

Although the existence of an association between BMD and OA is now generally accepted, the mechanisms underlying this observation remain elusive. Many investigators have focussed on the role of subchondral bone in the cartilage loss that characterises most OA (see<sup>40</sup> for a recent review). In the 1970s, Radin and Rose<sup>63</sup> proposed that increased stiffness of subchondral bone might lead to articular cartilage degeneration through the mechanical effects of increased shear stress. However, subsequent studies using a variety of techniques at different stages of OA progression have revealed complex and opposing changes in apparent density, material density, and stiffness in osteoarthritic subchondral bone,<sup>64–66</sup> suggesting that this explanation is too simplistic.<sup>40,67</sup> Thinning of the articular cartilage from below, owing to reactivation of endochondral ossification at the bone–cartilage interface in OA joints resulting in tidemark duplication and advancement, may represent another important mechanism by which increased bone formation could drive the OA process.<sup>40,67</sup> The action of soluble mediators released from bone on the articular cartilage (and vice versa) has also been of interest (reviewed by Lories and Luyten<sup>67</sup>). Potentially important signalling pathways include the Wnt and bone morphogenetic protein pathways, and transforming growth factor  $\beta$ .<sup>67</sup>

Another potential mechanism that could underpin the observed association between BMD and OA is genetic pleiotropy—that is, the existence of genetic variants that contribute to both BMD variation and OA risk.<sup>26</sup> A recent paper by Yerges-Armstrong *et al.*<sup>69</sup> analysed associations between BMD SNPs, identified in a recent genome-wide association study meta-analysis,<sup>68</sup> and knee OA in two population cohorts. Knee OA was defined either radiographically as Kellgren–Lawrence grade  $\geq 2$  (definite osteophytes) or by the presence of a knee replacement. Four BMD-associated SNPs were found to be also associated with the presence of knee OA, although none reached conventional genome-wide significance levels. Two of

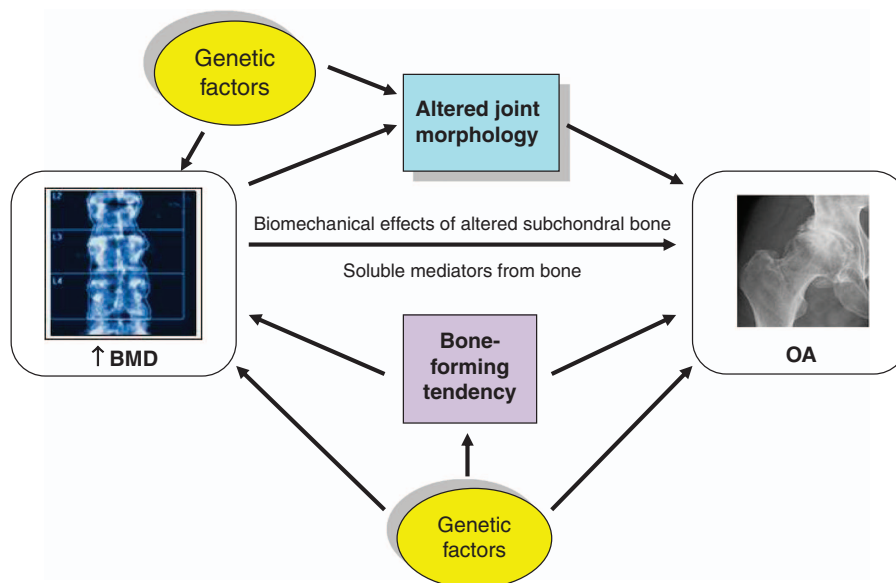
these variants are located near wnt signalling pathway genes, including one SNP (rs3736228) close to *LRP5*. The association of each of these SNPs with knee OA was in the hypothesised direction, with the higher BMD allele associated with increased knee OA risk. Earlier this year, an abstract by the same authors reported a similar analysis for radiographic hip OA, identifying only one variant with a nominal association with radiographic hip OA ( $P=0.03$ ); this SNP (rs7217932) is located near the *SOX9* gene that codes for part of the endochondral ossification pathway.<sup>70</sup> Similarly, as recently reviewed by Reynard and Loughlin,<sup>71</sup> some OA susceptibility genes have been shown to be associated with variation in BMD, and the functional annotations of OA susceptibility genes identified to date implicate bone-centred pathways such as skeletal development and morphogenesis, as well as osteoblast development/differentiation as playing a role in OA.

There are a number of potential mechanisms by which genetic variants associated with both BMD and OA could modify OA risk. The simplest of these is via increased BMD itself, termed 'mediated' pleiotropy.<sup>72</sup> Alternatively, BMD genes could directly influence other phenotypes that in turn increase the risk of developing OA ('biological' pleiotropy<sup>72</sup>), such as cartilage thickness or joint shape;<sup>73</sup> these characteristics have been termed 'endophenotypes', and their study could help clarify relevant mechanisms.<sup>74</sup> For example, a variant allele in the *DOT1L* gene has been associated with increased cartilage thickness (measured as joint space width) and a decreased risk of hip OA.<sup>75</sup> Another wnt pathway SNP has been found to influence hip morphology in women, and to modify the association between a particular morphological variant and radiographic hip OA.<sup>76</sup> Finally, bone-active OA susceptibility genes might be expected to directly increase the risk of developing phenotypes of OA characterised by bony features as a result of their effects on osteophyte formation and subchondral sclerosis. Potential mechanisms underlying the BMD-OA association are illustrated in **Figure 1**.

### Targeting Bone Turnover in the Treatment of OA

Extensive research has been performed with the aim of identifying agents that prevent structural progression in OA. In addition to directly targeting articular cartilage, which has yielded largely negative results, strategies have been developed to target adjacent tissues including bone. As reviewed by Roux and Richette,<sup>77</sup> antiresorptive agents, including bisphosphonates and cathepsin-K inhibitors, have demonstrated beneficial effects on structural progression in experimental animal models of OA, suggesting that treatments targeting bone may have a role in managing the disease. However, in humans, two randomised controlled trials of risedronate for knee OA failed to demonstrate a significant reduction in JSN over time,<sup>78,79</sup> and similarly a recent systematic review concluded that there was limited evidence that bisphosphonates are an effective treatment option for pain in OA.<sup>80</sup>

Following these negative studies, there has been a recent resurgence of interest in manipulating bone turnover for the treatment of OA following the publication of the SEKOIA trial of strontium ranelate for the treatment of knee OA.<sup>81</sup> This mixed-gender, multicentre study demonstrated a reduction in the progression of JSN in the treatment group over a 3-year period,<sup>81</sup> and as such it has been heralded as the first positive



**Figure 1** Schematic diagram illustrating some potential mechanisms underlying the association between BMD and OA.

disease-modifying OA drug trial. However, in contrast to the radiographic findings, a small beneficial effect on symptoms in this trial was confined to the group taking the higher (2 g per day) dose.<sup>81</sup> As discussed by Lafeber and van Laar<sup>82</sup> in their accompanying editorial, a number of questions remain to be addressed before strontium can be adopted clinically as a treatment for OA, and recent concerns regarding the cardiovascular safety of this drug may prove prohibitive in the patient group most in need;<sup>83</sup> nevertheless, these results lend further support to the concept of using pharmacotherapies targeting bone to treat OA.

A possible reason for the largely disappointing results of OA drug trials to date is failure to stratify potential participants by OA phenotype. As stated earlier, it is recognised that in any given patient with OA changes in different joint tissues (including cartilage, bone and synovium) may predominate.<sup>84</sup> Phenotyping OA, for example into hypertrophic versus atrophic variants based on the extent of bony change and osteophytosis visible radiographically,<sup>24,85</sup> attempts to identify these pathogenic subgroups. Many commentators now believe that the key to success in OA treatment may be rational targeting of treatments with a specific mode of action to patients with a relevant subtype of the disease.<sup>82,84,86</sup> However, at what point during the OA disease trajectory such treatments would prove most useful remains unclear.

## Conclusions

Novel approaches have recently shed new light on the relationship between BMD and OA. Genetic studies, and observations regarding OA in individuals with extreme HBM, have helped to highlight mechanisms that may be relevant in explaining the BMD-OA association. Such insights could potentially provide new avenues to be explored therapeutically. In addition, identifying individuals in whom OA is predominantly driven by changes in bone might improve response to treatment by providing a basis for therapeutic stratification.

## Conflict of Interest

The authors declare no conflict of interest.

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