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Review

Vascular pathology and osteoarthritis

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There is mounting evidence that vascular pathology plays a role in the initiation and/or progression of the major disease of joints: osteoarthritis (OA). Potential mechanisms are: episodically reduced blood flow through the small vessels in the subchondral bone at the ends of long bones, and related to this, reduced interstitial fluid flow in subchondral bone. Blood flow may be reduced by venous occlusion and stasis or by the development of microemboli in the subchondral vessels. There are several likely effects of subchondral ischaemia: the first of these is compromised nutrient and gas exchange into the articular cartilage, a potential initiator of degradative changes in the cartilage. The second is apoptosis of osteocytes in regions of the subchondral bone, which would initiate osteoclastic resorption of that bone and at least temporarily reduce the bony support for the overlying cartilage. It may be important to recognize these potential aetiological factors in order to develop more effective treatments to inhibit the progression of OA.

Key words: Osteoarthritis, Blood vessels, Subchondral bone, Venous stasis, Hypertension, Hypercoagulability, Hypoxia, Osteocyte viability, Osteoclast.

Introduction

This review examines the evidence supporting the concept that vascular pathology might play a role in the initiation and/or progression of the major disease of joints: osteoarthritis (OA). Although OA is characterized by progressive degenerative damage to articular cartilage, there are, as the name suggests, significant changes in the bone of affected joints. Bone changes in established OA include subchondral cysts, sclerosis and osteophyte formation. However, the detection of changes in the subchondral bone by MRI, even in early OA [1] have led to the suggestion that OA may arise as a bone disorder, affecting bone structure and remodelling, in addition to, or perhaps rather than, a disease affecting articular cartilage directly [2, 3]. More likely, OA has multiple aetiologies, which converge to produce the recognized manifestations of joint pain and stiffness and degeneration of articular cartilage. Genetic and environmental risk factors for OA [4–7], such as increased weight, female sex, joint dysplasias and malalignment and injury, clearly contribute to the establishment and progression of this condition. However, lack of understanding of the underlying cause(s) for OA mean that treatments remain largely palliative, with joint replacement an option in end-stage disease. Although cartilage itself is avascular, there is reasonable accumulated evidence that vascular problems may underlie the development of osteoarthroses.

Blood flow and bone

Bone is a highly vascular structure and the vasculature is intimately involved in all aspects of its growth, repair and metabolism [8]. The blood supply to bones serves both the marrow and the calcified bone tissue and these two tissue types are functionally interdependent with respect to haemopoiesis and bone modelling and remodelling [9]. The vascular supply of bone has multiple arterial inlets and venous outlets, comprising, in the case of long bones, four arterial inputs, the nutrient artery, periosteal arteries, metaphyseal arteries and epiphyseal arteries [10–12]. The work of Rhinelander and coworkers [13, 14] underlined the intimate relationship that exists between the vasculature and sites of bone turnover. Parfitt [15] has written persuasively on the role of blood vessels as key agents in coupling bone resorption and bone formation. Blood vessels are strategically located for participation in the coupling of these processes and the elegant work of Moller *et al.* [16] showed blood vessels intimately associated with trabecular bone and more particularly at sites of bone resorption. Barou *et al.* [17] found a significant relationship in rats between vessel number and bone formation rate.

The subchondral regions of long bones are particularly highly vascularized, suggesting high nutrient requirements [18]. Higher rates of bone blood flow are also associated with increased rates of bone remodelling [19]. However, the 'backup' system of nutrient and periosteal arteries is not present at the epiphyseal regions of long bones because of the joint cartilage at this site. Therefore, the epiphyses and articular surfaces are particularly at risk of circulatory insufficiency [11, 20]. Compromised blood flow in the subchondral bone for any reason could have deleterious effects on the bone, but, because of the likely importance of the subchondral bone to supply nutrition to the avascular articular cartilage [18], also has implications for the integrity of the cartilage.

Bone blood flow and osteocyte viability

Blood flow in bone accomplishes a number of functions. These include the exchange of oxygen and nutrients and metabolic waste, with bone interstitial fluid, which is of primary importance for osteocytes buried in the bony matrix. Although osteoblasts and osteoclasts have clear roles in episodes of bone remodelling, osteocytes are the most numerous cells in bone and their essential ongoing roles in bone health, metabolism and adaptation to loading are becoming increasingly recognized [21]. Firstly, osteocytes have a key role in mechanosensing by bone, likely mediated by interstitial fluid flow travelling along osteocyte lacunae, which is in turn driven by both mechanical loading of bone and pulsatile blood flow [12, 22]. Secondly, osteocytes are ideally located to detect and respond to microdamage in the calcified bone matrix [23], enabling them to exert important control over bone resorption and formation. The regulation of bone formation by osteocytes is at least partly accomplished by their secretion of the negative regulator of BMP/wnt signalling, sclerostin [24]. The initiation of targeted resorption by osteocytes is expanded on subsequently. Thirdly, recent work points to a broader role for osteocytes in systemic mineral metabolism [25].

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Bone remodelling is accomplished by the co-ordinated action of osteoclasts and osteoblasts. The initiating event for sites of bone remodelling is not known, but it seems likely that these sites are targeted and the basis of this targeting may be regions of loss of osteocyte viability, as reviewed by Noble [26]. It has been shown conclusively, using intravital imaging, that osteocyte viability is compromised by ischaemia, and that osteocyte death leads to resorption of the dead bone segment [27]. Depriving bone of mechanical loading and thus reducing diffusion of interstitial fluid rapidly induces osteocyte hypoxia [28–30]. Consistent with this, serum starved osteocytes have an increased rate of apoptosis *in vitro*, which can be largely overcome by subjecting these cells to fluid shear stress [31], which stimulates expression of the cell pro-survival molecule, Bcl-2 [31]. Thus, osteocytes are able to detect mechanical signals in the form of fluid flow, and, importantly, appear to be dependent upon fluid flow for their viability. Bone matrix microdamage has also been shown to induce osteocyte apoptosis [26]. In bone, the initial response to apoptotic osteocytes appears to be catabolic, with rapid recruitment and differentiation of osteoclast precursors [28–34]. The cascade of events, beginning with osteocyte signalling and leading to bone renewal, has been elegantly summarized by Parfitt [35].

Vascular pathology and OA

Bone marrow oedema

How might vascular pathology translate into the disease symptoms of OA? From the above, inadequate fluid flow around osteocytes due to any cause, for example limb unloading or venous stasis or small vessel occlusion, may sequentially result in osteocyte apoptosis, attraction of osteoclasts and excavation of the non-viable bone. Repeated episodes of this process at the ends of affected long bones could lead to altered remodelling and bone morphology. In the extreme, there could be partial or total collapse of the subchondral bone, as seen in avascular necrosis (AVN). Evidence that such events may occur in subchondral bone has come with the advent of high resolution magnetic resonance imaging (MRI) of the joints. Areas of subchondral bone that appear bright on MRI are commonly observed in both established OA and in early OA and in individuals with painful joints [36]. These are thought to correspond to areas of bone marrow oedema (BMO), which occurs idiopathically or in response to bone trauma [36]. Longitudinal studies have shown that BMO is a potent risk factor for structural deterioration in knee OA [37–41]. Enlargement of these bone marrow lesions has been strongly associated with increased cartilage loss [38]. Conversely, a reduction in the extent of bone marrow abnormalities on MRI is associated with a decrease in cartilage degradation [39]. It has recently been shown that subchondral cysts, characteristic of established and severe OA, arise from regions of BMO [41].

The origin of BMO is not known but it may be secondary to episodes of ischaemia, perhaps exacerbated by reperfusion injury, as elegantly modelled by Winet and coworkers [28, 42]. Interestingly, similar MRI-defined BMO areas have been described in stress fractures [43], where their origin has been proposed to be due to the generation of intramedullary pressures exceeding peak arterial pressure during strenuous exercise [44]. In this scenario, the bone tissue would suffer from ischaemia caused by reduced blood flow during exercise and reperfusion injury post-exercise. Although it is not possible to histologically investigate BMO in patients in early OA, several studies have sought to correlate the MRI findings with histology in more severe diseases. Regions of BMO in end-stage OA patients at knee replacement were more likely to exhibit oedema, bone necrosis and trabecular abnormalities than control sites [45]. In another study, BMO in early non-traumatic AVN of the hip showed areas of oedematous marrow, empty osteocyte lacunae and woven bone, indicating increased bone formation [46]. There is thus some evidence that an important early correlate of OA, BMO, is associated with both bone necrosis and cartilage degeneration. There are multiple possible causes of BMO and its occurrence due to local ischaemia remains to be proven. Likewise, whether BMO is an initiating event in OA, or drives the progression of OA, remains to be determined. The recent acquisition of tools to probe early events in subchondral bone in OA should deliver rapid advances in our understanding of the natural history of this condition.

Consequences of subchondral bone ischaemia

If subchondral bone ischaemia is a causal factor in OA development, there are several possible consequences. Firstly, nutrients and oxygen supply from the subchondral bone to the overlying articular cartilage would be reduced from regions of ischaemia. Imhof *et al*. [18] have described the dense subchondral vasculature in close proximity to the cartilage and the micro-channels that penetrate the subchondral mineralization zone and permit communication between the bone and the cartilage. These authors have further claimed that more than 50% of the glucose, oxygen and water requirements of cartilage are provided by perfusion from the subchondral vessels [47]. In addition, inspection of the osteo-chondral junction of long bones reveals that osteocytes and osteocyte canaliculi, which are also likely conduits of nutrients, are intimately associated with the articular cartilage. Indeed, experimental interruption of contact between articular cartilage and subchondral bone in baboons resulted in degeneration of the cartilage [48]. Interestingly, osteoblasts from OA subchondral bone, but not control bone, produced changes in articular chondrocytes that were consistent with a catabolic influence by the osteoblasts upon the cartilage [49]. This suggests that communication between the bone and cartilage components at the osteo-chondral junction could be important in health and disease.

What is the evidence that ischaemic episodes in the subchondral bone might lead to increased bone resorption? As stated above, there is histological and biochemical evidence of increased bone turnover in subchondral bone containing BMO [46, 50]. In addition, increased subchondral bone remodelling, detected by bone scans, has been well described in established OA, where it has been reported to predict joint space narrowing [51]. Whether the increased bone turnover is cause or effect cannot be determined in human OA, however, several animal models of OA are interesting in this regard. In the rat anterior cruciate ligament transection model (ACLT) of OA, increased subchondral bone resorption is associated with early development of cartilage lesions, which precedes significant cartilage thinning and sub-chondral bone sclerosis [52]. Significantly, treatment with the anti-resorptive bisphosphonate, alendronate, in that model suppressed both subchondral bone resorption and the later development of OA symptoms in the knee joint [53]. The authors concluded that subchondral bone remodelling plays an important role in the pathogenesis of OA. In the dog model of ACLT, calcitonin reduced the levels of circulating bone turnover markers and the severity of OA lesions [54]. In discussion of similar results in calcitonin-treated dogs with ACLT, Behets *et al*. [55] commented that loss of subchondral bone trabeculae could contribute to cartilage breakdown by enhancing cartilage deformation upon joint loading. An alternative explanation for the results of these studies is that the anti-resorptive agents acted directly on chondrocytes and in neither study was there direct evidence of a vascular cause for the increased bone turnover. The human data are consistent with the animal models, without being definitive. Although they show, for example, increased bone turnover markers in patients with progressive knee OA compared with those with non-progressive OA [56], there are clearly multiple factors contributing to this, such as osteoporosis [57] and vitamin D [58] and vitamin K deficiency [59].

The above data support an important role for increased turnover of the subchondral bone in OA. The question to be addressed is whether this could be secondary to episodic ischaemia, in turn due to vascular pathology, in the subchondral bone. As detailed subsequently, the literature contains abundant evidence of venous stasis, hypertension and altered coagulability in human OA and in animal models of OA (summarized in Fig. 1).

Venous stasis

Reduced arterial inflow and obstruction of the venous outflow have been shown to impair bone blood flow and to lower the cellular nutrient and oxygen supply [60]. Impaired venous circulation (venous stasis) and consequent decreased outflow of blood, especially from the articular ends of long bones, resulting in increased intra-osseous pressure, has been proposed as a causal factor in osteonecrosis [61]. Although a long bone has multiple feeding and draining vessels, once the big veins, for example, the femoral vein, is blocked or experimentally ligated, or the muscle veins are collapsed by a tourniquet or perhaps poorly functional as is the case with varicose veins, the ability of the system to drain the blood is compromised. Accordingly, patients with severe degenerative OA of the hip reportedly have impaired venous drainage from the juxtachondral cancellous bone across the cortex. Arnoldi [62] showed that increasing the intra-articular pressure in rabbits increased intra-osseous pressure. This is because the drainage veins from the ends of the long bones in general emerge within the joint capsule. For example, the drainage veins from the femoral neck emerge at the edge of the cartilage and are initially within the joint capsule. Thus, even small increases in articular pressure are sufficient to collapse these thin walled vessels and block the flow of blood. These findings suggest that increased intra-articular pressure, produced by obesity or intra-articular inflammation, could be one of the mechanisms for producing intra-osseous hypertension in OA, either as a primary event in the disease or as an exacerbating factor. Consistent with the animal data, intra-osseous hypertension has also been reported in the femur of patients with OA of the knee [63].

The concept of venous stasis was further developed by Cowin and colleagues [61]. Venous stasis of whatever cause will result in more blood remaining in the organ and being rerouted to the remaining functional vessels. These vessels will expand in size to accommodate the increased vascular resistance and as a consequence the vascular pressure will increase. This is also accompanied by an increased filtration flux across the vessel wall, which causes the extravascular pressure to rise because bone is a relatively rigid compartment. Since the pressure in the system is increased in venous congestion, differences generated by the blood pulse and thus interstitial fluid flow, are also reduced in the mineralized matrix.

Since blocked or compromised venous drainage will decrease interstitial fluid flow, the supply of nutrients and oxygen to the bone and the removal of waste products will be reduced, which is extremely deleterious to osteocytes. It has been reported that an osteocyte left without nutrient exchange for 4 h will die [64] and bone ischaemia for more than 6 h causes significant osteonecrosis [65]. Pedersen *et al*. [66] reported that hypoxia of the subchondral bone was present in hips with OA and hips with non-traumatic necrosis. Identical signs of subchondral medullary and trabecular necrosis were found in both conditions. The loss of fluid flow in osteocyte lacunae will not only remove the ability of osteocytes to detect loading [67] but it is likely that osteocytes depend upon loading and flow-induced cellular deformation for their viability [31].

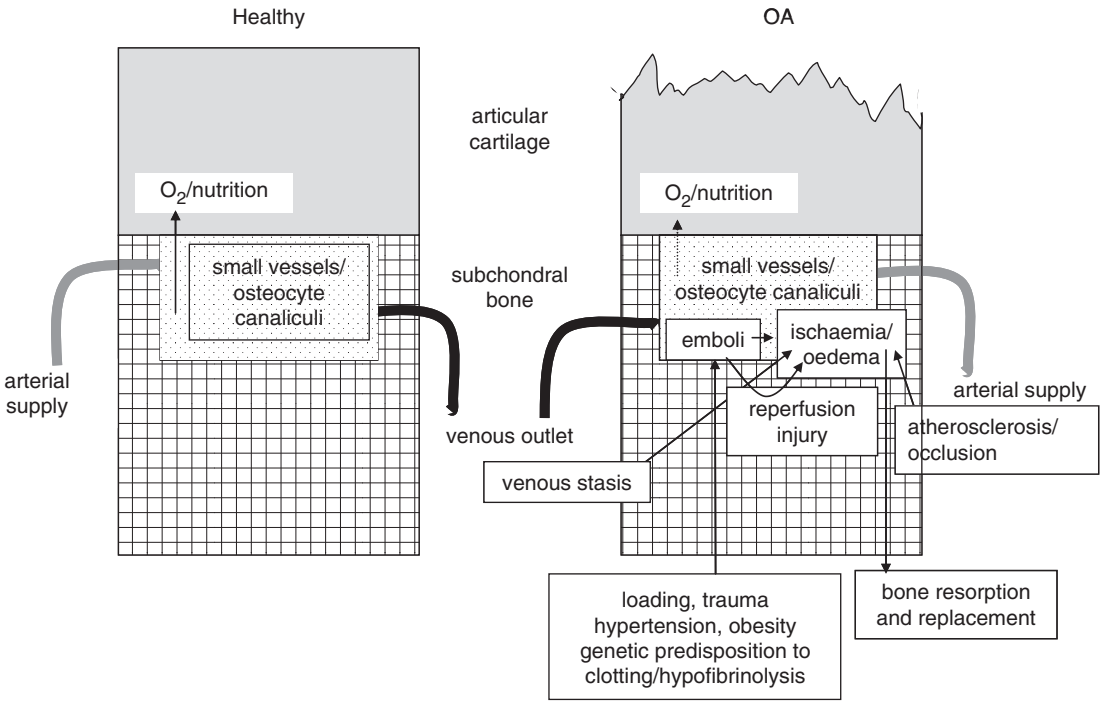

FIG. 1. Role of the subchondral vasculature in the initiation and/or progression of OA. The left panel shows a representation of healthy articular cartilage overlying the subchondral trabecular bone. In addition to structural support and absorption of shock offered by the subchondral bone, its small vessels and probably the interstitial bone fluid in osteocyte canaliculi, provide important nutrition to the cartilage. The right panel shows some cartilage erosion, as seen in OA. Typically, the subchondral bone would also be altered in OA, with areas of BMO, increased bone turnover, and sclerosis. BMO may be due to episodes of ischaemia, perhaps due to occlusion of the supply vessels by atherosclerosis, or venous stasis due to loading and/or increased intra-articular pressure, or to embolus formation in the small vessels of the subchondral bone. The latter could be due to trauma, obesity or increased propensity to clot, perhaps exacerbated by reperfusion injury, at sites where blood flow has been lost and then recovers into hypoxic tissues. One result of local ischaemia in the bone may be to deny the overlying cartilage of nutrition, causing catabolic and reparative events in the cartilage. Osteocyte death in areas of bone affected by hypoxia will also be targeted for resorption and replacement, increasing subchondral bone turnover. The support to the articular cartilage and the shock absorption provided by the subchondral bone may be compromised during episodes of bone repair, leading to articular cartilage damage.

Thus, episodes of venous stasis in OA may lead to loss of osteocyte viability in regions of the bone. This is likely to be especially the case in the highly vascular subchondral region of long bones. Venous stasis may also result in a decrease in nourishment to the overlying cartilage, as proposed by Imhof *et al*. [18]. Loss of osteocyte viability in the subchondral bone would lead to increased bone turnover in order to repair damaged and necrotic bone tissue, which in turn may result in altered architecture of the subchondral bone and perhaps to articular degeneration because of compromised structural support for the cartilage.

Hypertension

Patients with end-stage hip OA exhibit a high prevalence of vascular-related comorbidities [68] and a causal link between the progression of OA and atheromatous vascular disease has recently been proposed [69]. This may be reflective of the higher incidence of hypertension and other vascular conditions with ageing, however, generalized osteoarthrosis was found to be significantly more common in older males with high than with low diastolic blood pressure [70]. Osteoarthrosis of the knee in females was more frequent in hypertensive cohorts, independent of obesity [68], although many of these patients were overweight or obese. Weinberger *et al*. [71] reported that patients with OA commonly had symptoms associated with hypertension and heart disease, consistent with evidence linking OA to potentially preventable health problems such as obesity, hypertension and heart disease and independent of trauma. The implication is that by reducing the burden of cardiovascular disease there may also be positive benefits for the development of OA.

It is clear that uncontrolled hypertension is a strong risk factor for cardiovascular diseases, cardiovascular accidents and numerous other end-organ morbidities. There is evidence that these consequences of hypertension relate to an impaired capacity for vascular growth and angiogenesis, which is in turn due to endothelial cell damage or dysfunction [72–74]. Although the endothelia of different vascular beds differ and the characteristics of the bone microvasculature are not well understood, a likely unifying feature of all vascular beds is a reduced capacity to synthesize nitric oxide (NO) in a hypertensive environment [75]. Other vascular factors, such as vascular endothelial growth factor (VEGF) may be involved in the pathogenesis of hypertension, although their role in OA has received only preliminary attention [76, 77].

Hypercoagulability and hypofibrinolysis

Coagulation abnormalities have been described in patients with hip osteonecrosis. A variety of pre-disposing factors and generalized disease states have been associated with ON of the femoral head, including excessive corticosteroid usage, alcoholism, haemoglobinopathies, Gaucher's disease, pregnancy, hyperbaric exposure, autoimmune diseases [78] and hip trauma. Intravascular coagulation, activated by a variety of underlying diseases, has been postulated as the common link leading to ischaemic insult, intra-osseous thrombosis and bone necrosis. Korompilias *et al*. [79] examined patients with hip ON for the presence of thrombophilic disorders to assess whether their presence is associated with an increased risk of ON. Only 17% of patients had an entirely normal thrombotic profile and the authors speculated that ON may result from repetitive thrombotic or embolic phenomena that occur in the vulnerable vasculature of the femoral head. In a rabbit model of steroid-associated femoral ON, micro-angiography of the subchondral bone showed clear evidence of thrombus-blocked and leaking blood vessels in this disorder [80]. Understanding of the relationship between hypercoagulable states and ON may allow pharmacological intervention to prevent this process.

While there is currently little consensus that OA is aetiologically related to ON, Cheras *et al*. [81] and Ghosh and Cheras [82] have reviewed the literature, and reported their own data, in support of the concept that changes in coagulability of the blood might also pre-dispose to OA. Cheras *et al*. [83] observed intra-osseous intravascular lipid and thrombosis, particularly in the venous microvasculature, in femoral heads from patients with degenerative OA and to a greater extent in ischaemic necrosis of bone, but not in non-osteoarthritic femoral heads. Thrombotic blockage of the microvasculature in the articular ends of long bones is therefore a potential mechanism of bone necrosis and subsequent OA. Notably, an early study of femoral heads from OA patients showed frequent widespread loss of osteocyte viability and led to the suggestion that episodic osteocyte death and bone collapse in idiopathic OA of the hip could be a cause rather than a result of the arthritis [83]. It is also possible that the bone remodelling induced in this process results over time in at least some of the joint abnormalities described as causal for primary OA, particularly of the hip [4].

Potentially accounting for the observations in OA bone microvasculature, a study by Cheras *et al*. [81] revealed significant differences between an OA group and the control group in fibrinogenic and fibrinolytic parameters and lipid profiles. The data are consistent with hypercoagulability, hypofibrinolysis and increased fibrin generation in OA. In a follow-up study, Cheras *et al*. [83] and Ghosh and Cheras [82] described findings in a relatively young group of subjects (49 ± 10 yrs) with a comparatively recent diagnosis of OA, performed with the aim of identifying potential markers that could help differentiate OA from non-OA subjects. The results of this study reveal a combination of increased pro-coagulant factors, as well as significant hypofibrinolysis, as also reported also by Glueck *et al*. [84] in patients with ischaemic necrosis of bone. Impaired fibrinolysis and hyperlipidaemia are associated with a tendency to venous thrombosis. The authors proposed that the coagulation and lipid abnormalities described in this study support a possible relationship with the occurrence of OA and ischaemic necrosis of bone. Interestingly, the coagulability changes found in early OA individuals were also associated with evidence of increased bone turnover [82]. Ghosh and Cheras [82] also described a dog study, in which large breed dogs with radiologically confirmed hip OA were given subcutaneous calcium pentosan polysulphate (CaPPS). Pre-treatment platelet aggregability was increased compared with a control group. Interestingly, CaPPS treatment normalized thrombotic parameters and the dogs showed clinical improvement with respect to their OA symptoms. Qualitatively similar results were seen in a 24-week study in human OA subjects treated with CaPPS, although interpretation of this study was complicated by a strong placebo response. It has not been determined whether hypercoagulability and hypofibrinolysis precede or cause OA, or whether they are a consequence of the disease. However, familial studies by Glueck *et al*. [84], in patients with ischaemic necrosis of bone, indicated that genetically linked hypofibrinolysis associated with raised PAI-1 may be a major cause of osteonecrosis. Similar familial studies in OA are indicated, in addition to prospective studies of individuals with hypercoagulability or hypofibrinolysis.

Concluding remarks

This review presents some of the accumulated information, which together will help to construct a testable hypothesis for vascular involvement, if not as a causal factor in OA, then as an agent of progression of this condition. Since the vasculature in question is that of the subchondral bone, the role of this bone in OA, with its attendant vasculature, cells and molecular signalling molecules, needs to be more intensively considered. There is a great deal yet to be learnt about the ways in which the bone and cartilage collaborate in normal bone turnover, and how pathology of the

vasculature might affect this. However, a substantial platform of knowledge, summarized here, will enable more informed study, and hopefully treatment options, in OA, which constitutes such a heavy burden of disease in our ageing populations.

Rheumatology key messages

- Disruption of blood flow in subchondral bone may reduce nutrient diffusion to articular cartilage in OA.
- Ischaemia in subchondral bone may produce osteocyte death, bone resorption and articular damage in OA.

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