Hypertension meets osteoarthritis — revisiting the vascular aetiology hypothesis

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Abstract

Osteoarthritis (OA) is a whole-joint disease characterized by subchondral bone perfusion abnormalities and neovascular invasion into the synovium and articular cartilage. In addition to local vascular disturbance, mounting evidence suggests a pivotal role for systemic vascular pathology in the aetiology of OA. This Review outlines the current understanding of the close relationship between high blood pressure (hypertension) and OA at the crossroads of epidemiology and molecular biology. As one of the most common comorbidities in patients with OA, hypertension can disrupt joint homeostasis both biophysically and biochemically. High blood pressure can increase intraosseous pressure and cause hypoxia, which in turn triggers subchondral bone and osteochondral junction remodelling. Furthermore, systemic activation of the renin–angiotensin and endothelin systems can affect the Wnt–β-catenin signalling pathway locally to govern joint disease. The intimate relationship between hypertension and OA indicates that endothelium-targeted strategies, including re-purposed FDA-approved anti-hypertensive drugs, could be useful for treating OA.

[H1] Introduction

Osteoarthritis (OA) is a prevalent disease that affects 500 million people worldwide[1], and is not only a leading cause of chronic pain and disability in older adults, but is also a risk factor for cardiovascular events and all-cause mortality[2-4]. OA is no longer thought of as a simple wear-and-tear problem affecting articular cartilage, but rather as a whole-joint disorder subject to interactions between a variety of local and systemic risk factors. The prevalence of knee OA has doubled since the mid-20th century[5], alongside expanding populations of older individuals and those with obesity. However, neither ageing nor obesity can entirely explain this phenomenon. Therefore, interest is

growing in metabolic syndrome and its individual components (high blood pressure in particular) as emerging independent risk factors for OA[6,7].

Metabolic syndrome is a cluster of at least three out of the following five conditions: central obesity, high blood pressure (hypertension), hyperglycaemia (often in the form of type 2 diabetes), high cholesterol and low high-density lipoprotein levels. Among these conditions, hypertension and type 2 diabetes are often present in patients with knee OA[8]. After adjustment for body weight or body mass index (BMI), no statistically significant association exists between any of these conditions and the occurrence of OA, with the exception of hypertension[9]. These results suggest that vascular pathologies such as hypertension are likely to be important factors in the pathogenesis of metabolic syndrome-associated OA.

Indeed, vascular dysfunction has already been implicated in the pathogenesis of OA[10]. Emerging evidence is revealing a close association between vascular pathologies and OA in both load-bearing joints (such as the knee) and non-load-bearing joints (such as the joints of the hand)[11]. In a cross-sectional analysis of 254 patients with OA, 63% of patients with knee OA and 40% of patients with hand OA had hypertension[12]. By contrast, Mendelian randomization analysis of data from the UK Biobank has suggested a causal association between low blood pressure and knee OA[13], making a strong case to revisit the interactions between blood vessels and other tissues in joint homeostasis and disease. In this Review, we outline the main findings that link blood pressure and OA from both an epidemiological and a molecular perspective. We also discuss current and emerging therapeutics that target the endothelium and how these might be used in the management of OA.

[H1] Epidemiology of hypertension and OA

As a frequently encountered comorbidity in knee OA[14], hypertension confers a high risk of OA progression and a worse outcome for surgical joint replacements[15,16]. However, whether the contribution of hypertension to OA initiation and joint deterioration is biased by potential confounding factors such as BMI is uncertain. Furthermore, contradictory results have been reported regarding the relationship between hypertension and knee OA[9,13,17] (Table 1). Higher systolic blood pressure (above 112mmHg) and pulse pressure (above 39 mmHg), but not diastolic blood pressure, were associated with radiographic knee OA in one study that retrieved data from the Osteoarthritis Initiative[17]. Yet in another study that retrieved data from the same database, an increase in diastolic blood pressure from baseline was associated with more heterogenous cartilage T2 values on MRI scans at 48 months in patients with knee OA, indicating increased cartilage

degeneration[18]. By contrast, both diastolic and systolic blood pressure were associated with symptomatic knee OA, but not with radiographic knee OA, in data from the Framingham Osteoarthritis Study[9].

Systematic reviews and meta-analysis of pooled evidence has been performed to decipher the relationship between hypertension and OA[6]. As reported, hypertension increased the odds of developing radiographic knee OA by 101% , but of developing symptomatic knee OA by only 49%[6]; another recent meta-analysis also reported stronger association between hypertension and radiographic knee OA (with increased odds of 89%) than symptomatic knee OA (with increased odds of 39%)[19]. These findings could indicate a closer relationship between hypertension and structural damage in knee OA, than between hypertension and joint pain. Notably, a high degree of inter-study heterogeneity was detected when the link between hypertension and radiographic knee OA was explored[6]. Potential confounding factors such as sex, BMI and ethnicity could affect the relationship between hypertension and knee OA. However, only a few studies have provided sex-specific associations, including showing OA to be more prevalent among women than men[9]. Ethnicity might be another factor that has caused variation in the results of previous studies. For example, a higher prevalence of comorbid hypertension and metabolic syndrome seems to exist in Asian patients with OA than in non-Asian patients with OA[6,20]. This finding might be attributed to the association of an angiotensin-converting enzyme (ACE) gene polymorphism (which is more common in some Asian populations) with knee OA as well as hypertension[21-24], which warrants further investigation. Given that most studies that have been performed were cross-sectional in nature, the causal relationship between hypertension and knee OA has yet to be confirmed.

The development of analytical techniques such as Mendelian randomization provides a powerful control for confounding and inverse causation[25]. This technique deploys genetic variants as instrumental variables to infer whether a risk factor causally affects a health outcome. By using this big data analytics tool, a 2019 study reported an inverse causal association of genetically-determined blood pressure with the risk of knee OA, hip OA and surgical joint replacements using data from the UK Biobank[13]. However, the results from the study suggest that low blood pressure is a risk factor for knee OA and high blood pressure is a consequence, rather the cause of knee OA. The conclusion of this study was almost conclusive[13]; yet, the findings were limited by the definition of OA that was used. The requirement of a hospital diagnosis of OA in this study implied that only symptomatic OA might have been captured. In addition, whether joint pain relates to intra-osseous blood pressure and perfusion in response to alteration of systemic blood pressure remains

controversial[26,27]. Moreover, the observation that structural joint damage on a plain radiograph correlates poorly with symptomatic severity in OA is well-established. Hence, a critical research gap on the causal relationship between blood pressure and both radiographic and symptomatic OA still exists that needs to be filled.

[H1] Joint vascularisation in health and OA

Although the concept of OA as a whole joint disorder has gained much popularity in the past decade, the exact role of the vascular system in joint homeostasis and disease is not fully understood. Experimentally, a reduction of blood flow in postnatal long bones leads to a loss of mineralized bone, whereas bisphosphonate treatment enhances both blood flow and vessel growth in bone[28]. However, these findings were obtained from studying metaphyseal bone and diaphyseal bone in mice under non-inflammatory and non-degenerative conditions. Microangiography of osteoarthritic subchondral bone tissue has revealed an increase in vascular volume and the number of blood vessels in a mouse model of post-traumatic OA, indicating angiogenesis[29]. Optical clearing of bone tissues has also enabled the identification of a previously unknown blood vessel type in cortical bone[30]. Comparatively, it remains technically challenging to visualize and analyse the vascular system and angiogenesis in the subchondral bone of animals and humans in three dimensions. Further exploration of techniques such as optical clearing of bone is warranted to gain insight into the role of the vasculature in the progression of disease.

Articular cartilage is avascular and devoid of nerve endings. The growth and maintenance of articular cartilage therefore heavily rely on the two adjacent tissues — subchondral bone and synovium. The superficial side of articular cartilage is separated from the synovium by a cavity filled with synovial fluid that is mainly produced by synovial cells, and to a lesser extent by chondrocytes[29]. Synovial fluid serves as a medium for chemical exchange between the highly vascularized synovium and the avascular cartilage. For example, nutrients and oxygen from synovial capillaries diffuse to the chondrocytes in the superficial zone of articular cartilage via synovial fluid[31,32]. In its deep zone, articular cartilage is separated from subchondral bone by a thin layer of calcified cartilage[30]. The subchondral bone has a crucial role in nourishing the overlying cartilage[33,34]; indeed, the calcified cartilage is permeable to small molecules such as glucose and nitric oxide[35,36]. The presence of bone-derived proteins within articular cartilage further strengthens the idea of functional biochemical communication and interaction between bone and cartilage tissues[37]. Such interaction could be augmented through microcracks at the interface between bone and cartilage[38,39,40], through which

subchondral bone blood vessels can invade the calcified cartilage layer during the development of OA.

[H2] Synovial vasculature

Synovium is highly vascularized, with both fenestrated and continuous capillaries, which are present in relative proportions depending on the anatomical location in the joint[41]. The density of capillaries in synovium also varies according to the location of the synovium within the joint cavity and the depth below the synovial surface[41]. Capillaries are usually located superficially, and their density is high over areolar tissue and adipose tissue and low over tendons[42]. By contrast, lymphatic vessels are mainly located in the deep regions of the synovium[43]. The close proximity to the joint cavity and the fenestration of capillaries in the synovial microcirculation facilitates the exchange of molecules into the synovial fluid and the provision of nourishment to articular cartilage[44].

Modification of the synovial vascular network is a hallmark of the arthritic joint (Fig. 1). OA synovium is characterized by an increase in microvessel density and endothelial cell proliferation[45,46], and by a decrease in lymphatic vessel density[43]. Synoviocytes isolated from the inflamed areas of OA synovium exhibit high angiogenic potential and have increased expression of vascular endothelial growth factor (VEGF) compared with synoviocytes from adjacent non-inflamed areas[46-48]. VEGF promotes synovial angiogenesis via VEGF receptor 2 (VEGFR2), which is highly expressed by endothelial cells and synoviocytes[48]. Notably, the degree of synovial angiogenesis seems to relate to the severity of synovitis in OA, rather than to the severity of cartilage damage or symptoms[45,49].

[H2] Subchondral bone vasculature

Subchondral bone comprises a subchondral trabecular meshwork and a cortical bone plate, which is separated from the calcified cartilage by the cement line. Trabecular bone of the epiphysis is highly vascularized, containing capillaries and a sinusoidal network[50,51]. In the hematopoietic bone marrow of the femoral head, microvessels are sinusoidal in form, whereas in the adipose bone marrow the microvessels are similar to capillaries in other tissues[50]. Cortical bone is penetrated by cavities of different sizes that can be extensions of the marrow space, cylindrical canals containing marrow cells and, occasionally, a blood vessel, or small vascularized channels[52]. These small channels (10-30μm in diameter) are surrounded by concentric layers of bone that contain thin-walled blood vessels, and are the primary conduit for vessels in the subchondral bone[52]. These vascular channels, which contain blood vessels, sympathetic nerves, osteoclasts and osteoblasts[53-55], nourish the calcified

cartilage and the deep layers of the non-calcified cartilage, and govern remodelling at the osteochondral junction[52,53].

Subchondral bone undergoes constant remodelling in response to either physiological or pathological mechanical loading. In the early stages of OA, the cortical plate becomes thinner with less trabecular bone owing to an increase in osteoclast activity and bone turnover rate[56]. In later stages of OA, the subchondral cortical plate becomes thick and sclerotic, whereas the trabecular bone remains osteopenic[56]. Alongside this remodelling process, increased vascularization in the subchondral bone during OA has been well documented in both animals[29] and humans[57].

As bone is a mechanoresponsive tissue, angiogenesis is coupled with osteogenesis under mechanical stimuli during bone modelling and remodelling[58]. During bone repair in mice, osteoblast-derived VEGF regulates osteoblast differentiation and bone formation[59], and osteoblasts can also secrete angiogenic factors in response to mechanical stimuli[60]. Similarly, osteoclast-derived platelet-derived growth factor BB (PDGF-BB) stimulates angiogenesis in subchondral bone in mice and contributes to OA development[61]. Given that aberrant mechanical loading occurs in OA joints as a consequence of cartilage damage, then corresponding vascular modification would be anticipated to take place. Markedly, in a proposed new histological scoring system, subchondral angiogenesis is one of the criteria that must be taken into account to quantify remodelling of the subchondral bone in mouse models of OA[62]. This marks the recognition of vascular role in OA assessment and evaluation, implying the importance of angiogenic-osteogenic coupling in disease progression.

In addition to angiogenesis in the subchondral bone, vascular penetration is also observed in human OA at the tidemark that separates the non-calcified from the calcified cartilage[54,63] (Fig. 1). Vascular invasion is accompanied by the expression of matrix metalloproteinases (MMPs) and by the depletion of proteoglycans from the surrounding extracellular matrix in cartilage[54]. In addition, vascular channels at the osteochondral junction in OA enable the infiltration of sensory and sympathetic nerve endings that express nerve growth factor and that can generate pain sensation[55,64]. The number of vascular invasion incident has been associated with the severity of cartilage damage and clinical symptoms[45,54]. Indeed, inhibition of angiogenesis could successfully preserve joint integrity and reduce pain in various experimental models of OA[65]. These findings emphasize the importance of joint vascularization in joint homeostasis and disease.

Notably, angiogenic vessels in OA subchondral bone have a unique molecular phenotype and are known as type H vessels[66]. These blood capillaries are characterized by their high expression of both CD31 and endomucin, and were initially described in the metaphysis of young mice[67]. The proportion of type H vessels is maximal after birth and declines in adult and aged mice[67,68]. Type H vessels express large quantities of pro-osteogenic factors and recruit osterix-expressing osteoprogenitor cells, thereby coupling angiogenesis with osteogenesis[67]. The formation of type H vessels also involves preosteoclast-derived PDGF-BB[69]. Interestingly, preosteoclast-derived PDGF-BB can stimulate type H vessel development in the subchondral bone of mice after the induction of OA by destabilization of the medial meniscus[61]. Mice that specifically overexpress PDGF-BB in preosteoclasts develop spontaneous OA and are characterized by an increase in H type vessels and nerve endings in the subchondral bone, whereas the specific deletion of PDGF-BB in preosteoclasts provokes the opposite effects[61]. VEGF-A secreted by chondrocytes is also involved in type H vessel formation in OA[70], and a proposed crosstalk between endothelial cells and hypertrophic chondrocytes is thought to promote osteogenesis[71].

[H1] Hypertension and the joint environment

Given the pivotal roles of alterations in local vascular function and neoangiogenesis in the pathophysiology of OA, the effects of systemic vascular homeostasis on joint health and disease are of great interest. Although not fully understood, systemic vascular pathologies, and hypertension in particular, might contribute to joint disorders both biophysically and biochemically.

[H2] Perfusion abnormalities and ischemia

Hypertension might impair subchondral bone perfusion by altering both fluid flow and intraosseous pressure. Pulse pressure linearly correlates with intraosseous pressure, and intraosseous pressure is negatively associated with intraosseous blood flow[72-74]. Therefore, hypertension could potentially contribute to the reduced blood perfusion that occurs in local joint tissues in OA[10], despite compensatory extensive angiogenesis (Fig. 1). Moreover, structural and functional changes in the hypertensive heart could contribute to cardiac arrhythmias that disturb blood flow to the limbs[75].

Bone perfusion abnormalities, characterized by a reduction in both arterial inflow and venous outflow, have indeed been documented in human knee OA[76]. An increase in intraosseous pressure following venous occlusion in hip OA has also been known for a long time[73,77]. In a 2018 study, dynamic contrast-enhanced MRI was used to assess the kinetics of bone perfusion in knee OA[76]. This study revealed a slow clearance of contrast agent in subchondral bone, indicating a reduction of

venous outflow in osteoarthritic knees. The patients in this study also showed a limited arterial inflow[76]. Reduction in blood flow could lead to subchondral bone ischemia and apoptosis of osteocytes that, in turn, initiates osteoclast-mediated bone resorption[78]. In a mouse model of post-traumatic OA, the disruption of blood flow was detected by power Doppler imaging post-destabilization of the medial meniscus, and was associated with the severity of joint damage[79]. In a guinea pigs with spontaneous OA, decreased venous outflow in the medial tibial plateau both preceded and was co-localized with cartilage degradation and subchondral bone thickening[80]. Observation from both animals and humans further strengthen the notion of the intimate relationship between blood perfusion and joint destruction.

[H2] Hypoxia

Disruption of local blood flow could also trigger a cascade of responses at both a molecular and a cellular level. In OA, both the synovial fluid and the synovium are similarly characterized by a decrease in the partial pressure of oxygen (pO_2)[79,81] (Fig. 1). Interestingly, the importance of circulatory insufficiency relative to synovial tissue metabolism has been highlighted in an effort to explain this observation[82]. The reported link between synovial blood flow and intra-articular hydrostatic pressure could explain the inverse relationship between synovial fluid volume and pO_2[81,83]. In mice with destabilization of the medial meniscus-induced OA, synovial pO_2 (as measured by photoacoustic imaging) progressively decreased with the development and the progression of OA[79]. Synovial hypoxia negatively correlated with cartilage damage, but was positively associated with synovial blood flow[79]. Similar features have also been noted in the subchondral bone in human OA; the increased intraosseous pressure found in patients with hip OA is associated with a decreased subchondral pO_2 and an increase in lactate concentration[84].

[H2] Impaired nutrition supply

Hypertension-induced perfusion abnormalities cause nutrient deprivation to both bone and cartilage, which ultimately affects their homeostasis[85]. Indeed, osteocytes can only survive nutrient depletion for four hours in an experimental setting[86], and six hours of bone ischemia is sufficient to cause osteonecrosis[87].

Subchondral bone perfusion supplies at least 50% of the necessary glucose and oxygen to overlying cartilage[32]. Apart from being a building block for proteoglycan, a major component of cartilage extracellular matrix, glucose also regulates catabolic and anabolic gene expression in chondrocytes[88,89]. Changes to the glucose concentration in the extracellular matrix can impair insulin

growth factor 1-mediated anabolism in chondrocytes, leading to joint pathologies[90]. In a hypoxic environment, the expression of glucose transporter 1 by chondrocytes is upregulated, enabling a more rapid uptake of glucose[91]. However, the intake of nutrients in such an anaerobic environment favors glycolysis, which produces acidic lactate as an end product and further acidifies the cartilage environment[92]. Importantly, acidification of the extracellular matrix can alter the synthesis of matrix molecules[93]. The energy depletion caused by the switch to glycolysis is also associated with increased production of nitric oxide, as found in osteoarthritic joints[92].

[H1] Hypertension and joint structure

Hypertension increases intraosseous stress and causes perfusion abnormalities in joint tissues[73,74]. The resulting physical stress and hypoxic stress could be detrimental to joint homeostasis by dysregulating bone remodelling, altering the osteochondral junction and provoking inflammation (Fig. 2), and could also explain the comorbid presentation of hypertension and OA, particularly radiographic OA. Clinically, measures of bone quality such as bone mineral density are closely associated with blood flow[28,94]. Researchers have also documented the response of osteocytes and their progenitor cells towards changes in fluid shear stress in both intracellular and extracellular ways[95,96]. Fluid shear stress increases the expression of MMPs and the secretion of osteogenic signalling factors such as nitric oxide and prostaglandins by mesenchymal stem cells, which then triggers the downstream activation of transforming growth factor-β (TGFβ) and cGMP-dependent protein kinase signalling pathways[96,97]. Prolonged exposure of TGFβ was found to trigger OA-like changes in murine knee despite the transient effect on promoting chondrogenesis[98]. In a cGMP-dependent manner, nitric oxide has also shown to upregulate MMPs, which further contributes to cartilage destruction[99].

[H2] Osteonecrosis

When bone ischemia and a hypoxic environment are sustained, osteocytes will inevitably undergo apoptosis, which can initiate osteoclast-mediated bone resorption and even lead to osteonecrosis (Fig 2a). Apoptotic osteocytes are present in the subchondral bone of patients with OA[100]. In murine studies, apoptotic osteocytes could stimulate neighboring osteocytes to release receptor-activator of NFκB ligand (RANKL), which induces osteoclast activation[101,102]. In horses with spontaneous equine carpal post-traumatic OA, RANKL expression was increased in the subchondral bone and was linked to increased osteoclast density[103]. In vitro, the secretion of RANKL by the osteocytic MLO-Y4 cell line can be stimulated by hypoxia and favours the differentiation of RAW264.7 cells into osteoclasts[104]. Conversely, conditional knockout of RANKL in osteocytes in mice with surgically

induced OA reduces the differentiation of osteoclasts and inhibits the growth of sensory nerves into the subchondral bone and pain hypersensitivity[105].

Macrophage colony-stimulating factor (M-CSF) is another essential cytokine for osteoclastogenesis[106]. M-CSF is secreted by osteoblasts and can direct osteoclast differentiation, thereby promoting bone resorption. Administration of M-CSF can induce bone resorption in wild-type rats and restore bone resorption function and reverse disease phenotypes in mice with osteopetrosis[107,108]. Interestingly, an increase in M-CSF was observed in primary cultured osteoblasts from rats with spontaneous hypertension and was accompanied by loss of bone mass in the animals[109]. High amounts of circulating IL-6 have also been documented in both human and rodents with hypertension[110,111]. IL-6 can stimulate osteoclast formation in the presence of M-CSF[112], suggesting that inflammation in hypertension might aggravate osteonecrosis in OA via interaction between IL-6 and M-CSF.

Recently, a 2020 study has shown that damage-associated molecular patterns (DAMPs) released by necrotic osteocytes can be detected by C-type lectin domain family 4 member E (also known as MINCLE) on osteoclasts, which then induces the differentiation of osteoclasts and triggers bone loss[113]. In patients with osteonecrosis, MINCLE was highly expressed in areas of high osteocyte death and correlated with the expression of markers of osteoclast activity[113]. Although a role has not yet been reported for MINCLE in OA, DAMPs are known to be involved in the pathogenesis of OA[114].

[H2] Bone marrow oedema

When a joint is mechanically unstable (for example, after anterior cruciate ligament (ACL) injury[115,116]), the subchondral bone can exhibit a bone bruise (an oedema-like change on MRI scans) known as a bone marrow lesion (BML)[117]. In patients with OA, BMLs are characterized by highly vascularized sclerotic bone tissue with poor mineralization[118,119], and the size of BMLs is inversely proportional to the venous outflow, as measured by dynamic contrast enhanced MRI[27]. Presence of BMLs is strongly associated with increased cartilage erosion and more severe joint pain in patients with knee OA[120,121]. However, it remains controversial whether BMLs resolve or enlarge as OA develops[122,123]. Cystic lesions can develop alongside cartilage loss in both rats with post-traumatic OA and humans with knee OA[124,125]. Some investigators have also suggested that BMLs could be a consequence of ischemia reperfusion injury[126]. Arterial pressure could conceivably promote capillary oedema, resulting in increased intramedullary pressure and creating a phenomenon that is proposed

to be equivalent to BMLs[126]. These results suggest that vascular perfusion and pressure could be determinants of BMLs.

[H2] Bone sclerosis

Although patients usually experience temporal bone loss in the early stages of OA, at later stages of disease, bone mass actually increases[127]. The exact mechanism of subchondral bone thickening following the initial osteopenic changes is unclear, but hypertension-associated alterations in bone remodelling could account for the sclerotic changes in subchondral bone.

As previously mentioned, pre-osteoclasts secrete PDGF-BB, which stimulates type H vessel development in subchondral bone[61,69]. Type H endothelial cells are capable of inducing osteoblastic differentiation, which could lead to increased bone formation[67]. In addition, osteoclast-mediated bone resorption releases active TGFβ1, which stimulates the recruitment of mesenchymal stromal cells that further differentiate into osteoblasts, thus contributing to subchondral bone sclerosis in OA[29]. Notably, the differentiation of bone marrow mesenchymal stromal cells into osteoblasts can also be stimulated directly by hypoxia[128]. In this context, hypertension-induced hypoxia could aggravate bone sclerosis.

Despite the increase in mass, sclerotic bone is often under-mineralized[129,130]. This impaired mineralization might be linked to an increase in expression of the Wnt antagonist Dickkopf 2 (DKK2). Upregulation of TGFβ1 in osteoarthritic human osteoblasts could stimulate DKK2, a well-known inhibitor of bone mineralization[130]. Thus, the poor mineralization of sclerotic bone might be attributable to changes in Wnt signalling, which is indeed a critical link between hypertension and OA that will be discussed further in later part of this Review.

[H2] Osteochondral junction modification

In OA, increased hydraulic conductance has been recorded at the bone–cartilage interface[124]. The pathological remodelling of subchondral bone and vascular invasion into the osteochondral junction is thought to explain the increased ability of biochemical factors to cross the osteochondral junction[131,132] (Fig. 2b). These factors, produced by the damaged bone in OA, can stimulate cartilage degradation[133], particularly by inducing catabolic changes in chondrocyte phenotypes[134]. Considering the increased intraosseous pressure and osteochondral junction modification that occurs in OA, conveyance of molecules from the bone to the cartilage might also be accelerated, thus further

facilitating cartilage damage[135,136]. This process could be aggravated by hypertension as intraosseous pressure correlates with blood pressure[73].

[H2] Joint effusion

Joint effusion is associated with both radiographic severity and pain in OA[137,138]. It might result from an increase in the production of synovial fluid and from abnormalities in synovial fluid drainage in OA. Indeed, an association has been noted between joint effusion and a low density of lymphatic vessels in the synovium in patients with OA[43]. Synovial oedema is probably also related to an increased vascular permeability of the synovial capillaries[139]. For example, an increased ratio of proteins in the synovial fluid over the serum occurs in patients with OA compared with healthy individuals[140]. Immunohistochemical analysis has also revealed an overexpression of the water channel aquaporin 1 in synovitis contributed to joint swelling and synovial oedema formation in rheumatoid arthritis[141]. Notably, hypertension provokes aquaporin 1 overexpression and activation in aortic endothelial cells in rats[142], suggesting that upregulation of aquaporin 1 could lead to an increase in hydraulic conductance in OA.

Capillary endothelial cells from the synovium of patients with OA contain more Weibel-Palade bodies (WPBs) than the synovium of healthy individuals[143]. WPBs store the adhesive glycoprotein von Willebrand factor, the leukocyte adhesion molecule P-selectin and numerous other pro-inflammatory, angiogenic or vasoactive factors, including IL-8, angiopoietin 2, endothelin 1 (ET1) and osteoprotegerin. The exocytosis of WPBs is tightly regulated by a wide range of physiological signals (hormones and growth factors, thrombin, histamine and mechanical stress) and pathological signals (bacterial toxins)[144-146]. Notably, hypertensive stretch stimulates the exocytosis of WPBs in a mechanism dependent of VEGFR2[147]; hence, hypertension could aggravate synovitis in this context (Fig. 2c).

Exocytosis of endothelial WPBs could also be triggered by hypoxia[148], thereby promoting the secretion of pro-inflammatory cytokines. Hypoxic environment also induces the expression of endothelin converting enzyme (ECE1) and ET1, factors that stimulate the degranulation of WPBs[149,150]. A local amplification loop of ET1 production and secretion is then sustained. The excessive ET1 stimulates the production of pro-inflammatory factors and triggers catabolic metabolism of articular cartilage, as well as synovial thickening, in a mechanism that involves a positive feedback loop of reactive oxygen species (ROS) production[151-153].

[H1] Shared molecular pathways

As previously mentioned, hypertension and OA share some basic mechanistic pillars at the tissue, cellular and molecular levels, which largely converge on vasoconstrictors such as the renin–angiotensin system (RAS) and endothelin system[154,155] (Fig 3). Furthermore, the canonical Wnt–β-catenin pathway has been implicated in both cardiovascular and skeletal diseases[156]. Drugs that target these shared molecular pathways have the potential to demonstrate dual cardio-protective and chondro-protective effects. Further investigation into these shared molecular pathways could lay a foundation for the development of a unified strategy for a variety of age-related pathologies, such as hypertension and OA, in older adults.

[H2] Renin–angiotensin system

RAS has a central role in blood pressure regulation, particularly for short-term changes[154]. High circulating level of RAS component, angiotensin II, was observed in hypertensive patients[157]. Although first identified in the circulatory system, RAS components also exert tissue-specific functions, which are termed local RAS[158]. In the skeletal system, local RAS is particularly important for chondrocyte hypertrophy.

Local RAS expression is found in both human and mouse chondrocytes[159,160]. Although the upregulation of RAS components is greater in synovial fluid from patients with rheumatoid arthritis than in that from patients with OA, ACE expression correlated with concentrations of VEGF and MMP13 in individuals with either type of arthritis[161]. These results suggest a possible role for RAS in synovial angiogenesis, as well as in cartilage destruction. At a cellular level, RAS components are involved in different stages of chondrocyte differentiation; however, the respective roles of type 1 angiotensin II receptor (AT1) and AT2 remain controversial. In rats with OA with extensive chondrocyte hypertrophic differentiation, the amount of *AGTR1* mRNA (encoding AT1) was increased, while that of *AGTR2* was reduced[162]. Although the exact roles of the two receptors remain to be elucidated, the findings to date give solid support to the idea of interaction between local RAS and chondrocyte hypertrophy. A study in mice also found that RAS components were expressed exclusively in hypertrophic chondrocytes, and not in chondrocytes in hyaline cartilage[160]. Both infusion of angiotensin II and activation of AT2 induced the upregulation of hypertrophy-related genes such as *RUNX2* and *MMP13* in the ATDC5 chondrogenic cell line[163]. Similarly, in vitro administration of the hypertrophy stimulant IL-1β could also initiate expression of AT1 and AT2 on human articular chondrocytes[159]. Contradictory to current understanding, the induced hypertrophic differentiation by angiotensin II protects cells from apoptosis. The anti-apoptotic genes *Bcl2* and

Bcl2l1 were overexpressed in angiotensin II-induced hypertrophic chondrocytes in mice[164], contradicting the idea that angiotensin II promotes cell death via activation of AT2. However, the exact mechanisms involved remain unclear.

In addition to cartilage homeostasis, angiotensin II also has a role in bone remodelling via interaction with RANKL. In the vascular system, angiotensin II activates RANKL, which then accelerates calcium deposition[151]. Vascular calcification reduces vessel elasticity and thereby aggravates systolic hypertension in a vicious cycle[165,166]. In the skeletal system, angiotensin II can induce RANKL expression in osteoblasts, which can then activate osteoclasts and initiate bone remodelling, resulting in aberrant structural changes in OA[167,168].

[H2] Endothelin system

In addition to RAS, the endothelin system is a potent vasoconstrictor that helps to control vascular tone; and has been implicated in human hypertension[169]. Notably, angiotensin II is an important transcriptional inducer for ET1, and infusion of angiotensin II into normotensive rats enhances both ECE1 activity and renal ET1 concentrations[170].

The endothelin family consists of three isoforms, ET1, ET2 and ET3, which perform their biological functions as vasoconstrictors, mitogens or pro-inflammatory cytokines by activating two G protein-coupled receptors (ET_AR and ET_BR)[171]. Among the endothelins, ET1 is the predominant form in cardiovascular system and is an aggravating factor in endothelial dysfunction. ET1 is mostly produced by endothelial cells, and the counter-effect of the two receptors ensures precise control of vascular tone[171].

In addition to a role in vascular tone regulation, ET1–ET_AR interactions have also been implicated in articular cartilage degradation and OA development. Clinically, an increase in plasma and synovial ET1 concentrations correlates with the severity of knee OA[172]. Both ET1 and ET_AR are upregulated in all affected joint tissues in OA, including synovial fluid, synovium and articular cartilage[151,152,173-175]. ET1 in synovial fluid and synovium can stimulate the production of pro-inflammatory mediators such as IL-1β, IL-6 and IL-8, and can trigger catabolic metabolism of articular cartilage, as well as synovial thickening[151,152]. When used at similar concentrations to that present systemically and locally in patients with knee OA, ET1 could directly stimulate osteoarthritic chondrocytes in vitro to produce MMP1 and MMP13, major enzymes involved in degrading the cartilaginous extracellular matrix[173,174]. Underlying mechanism might involve a positive feedback loop of ROS production that

activates the transcriptional factor AP1 and, in turn, increases ECE1 expression and ET1 synthesis[153]. Notably, intra-articular injection of an ET1 antagonist could attenuate articular cartilage degradation following ACL trauma in rat model, suggesting ET system as a potential therapeutic target for OA management[175].

[H2] Wnt–β-catenin signalling

The canonical Wnt–β-catenin signalling pathway governs a wide range of biological activities, and remarkably, the Wnt–β-catenin pathway is upregulated in both hypertensive individuals and in patients with OA[176,177].

A genome-wide association study has revealed a direct correlation between *WNT3* and pulse pressure[178]. Peripheral blood expression of *APC* and *TCF4*, another two genes associated with the Wnt signalling pathway, also showed associations with pulse-wave velocity and arterial stiffness independent of traditional cardiovascular disease risk factors in a population of men with African ancestry from Tobago[179]. Clinically, overexpression of low density lipoprotein receptor-related protein 6 (LRP6), a co-receptor for Wnt proteins, has also found in hypertensive individuals[180]. In fact, interactions between the Wnt–β-catenin pathway and RAS have been widely discussed in relation to cardiovascular diseases. A bioinformatic analysis revealed binding sites for the TCF–LEF family of transcription factors in all RAS genes, including those encoding angiotensinogen, renin, angiotensin-converting enzyme, AT1 and AT2[181]. As TCF–LEF transcription factors are part of the Wnt–β-catenin signalling pathway, these results imply that the Wnt–β-catenin pathway could trigger RAS activation. In addition, angiotensin II infusion can induce β-catenin expression and activation[182,183]. The intimate relationship between RAS and the Wnt–β-catenin pathway consolidates the importance of this pathway in vascular homeostasis.

The Wnt signalling pathway has also been extensively studied in skeletal development and degeneration[184]. Wnt signalling helps to maintain the balance between osteogenesis and chondrogenesis, as activation of Wnt promotes osteoblast differentiation while repressing chondrogenesis[185]. Wnt–β-catenin signalling also suppresses expression of the chondrogenic gene *Sox9* while enhancing expression of the hypertrophic genes *Runx2* and *Mmp13* in mice[185]. In addition, overexpression of Wnt genes and β-catenin have been documented in knee OA[177,186,187]. Moreover, Wnt antagonists have shown beneficial effect on cartilage homeostasis. DKK1 is a Wnt inhibitor that competes with Wnt ligands for to bind LRP5 and LRP6[188], thereby blocking the Wnt signalling cascade. A high serum concentration of DKK1 reduced the risk of hip OA in elderly women,

whereas an increased serum concentration of another Wnt antagonist, frizzled-related protein, also produced a modest reduction in the risk of hip OA[189]. Frizzled-related protein is a competitive antagonist of frizzled receptors, which are the main receptors for Wnt proteins. A single nucleotide polymorphism in *FRZB*, which encodes frizzled-related protein, increases susceptibility to OA[190,191]. Downregulation of this gene has been also observed in mechanically injured cartilage[187]. All of this evidence hints at the detrimental effect of Wnt–β-catenin pathway upregulation on cartilage homeostasis. Notably, ET1 inhibits DKK1 production in vitro in mouse osteoblasts, thereby activating Wnt signalling[192]. However, although mediation of the Wnt signalling pathway via suppression of Wnt inhibitors by ET1 has been postulated in chondrocytes, experimental proof is required.

[H2] Targeting shared molecular pathways

Given that local RAS contributes to various skeletal pathologies, including osteoporosis[193,194], rheumatoid arthritis[195,196] and possibly OA, treatments that target RAS components are being investigated. Aliskiren, a renin inhibitor that is approved for the treatment of hypertension has chondroprotective effects by attenuating IL-1, TNF and RUNX2 expression[197]. Aliskiren could inhibit chondrocyte hypertrophy, reduce local RAS expression and rescue cartilage destruction in rats with surgically induced OA[197]. Another FDA-approved treatment for hypertension, the ACE inhibitor captopril, has similar effects; captopril suppressed renin, ACE and angiotensin II expression in rats with surgically induced OA by altering the expression of AT1 and AT2[162]. The hypertrophic zone was greatly reduced by both treatment methods. Furthermore, captopril can preliminarily attenuate the increased expression of senescence markers that occurs in both the subchondral bone and articular cartilage in the deoxycorticosterone acetate salt models of hypertension and in spontaneously hypertensive rats[198].

In addition to chondroprotective effects, anti-hypertensive drugs can also reduce inflammation. Losartan (an AT1 blocker) and captopril can reduce joint pain and inflammation in rodents with RA[195,199] and rats with OA[162,197,198], respectively, suggesting the protective effect of anti-hypertensive drugs on joints was achieved by suppression of local RAS. However, administration of losartan exacerbated bone loss induced by angiotensin II in mice[168]. This phenomenon might be explained by the opposing roles of AT1 and AT2 in osteoblasts, as knockdown of *AGTR2* produced promising effects towards restoring angiotensin II-induced bone loss[168]. By contrast, the ACE inhibitor enalapril improved bone mass and hypertension simultaneously in mice[166], but only marginally in humans[200]. These findings suggest that the beneficial effect of RAS inhibition on joint homeostasis and function might be cell-type specific.

Although the exact role of the endothelin system in OA has yet to be fully defined, ET1 has been linked to chondrocyte hypertrophy and senescence. Preliminary published also demonstrated that mice with transgenically overexpressed endothelial ET1 have an activated ET system an exhibit an OA-like phenotype compared with their littermates, alongside hypertrophic changes in cartilage[201,202]. A 2020 study has also demonstrated that ET1 can induce cellular senescence in the murine chondrogenic cell line ATDC5, which could be rescued by ET_BR blockade[203]. Considering that the endothelin system is intertwined with RAS, these effects on chondrocyte fate were anticipated.

Downregulation of Wnt signalling has also been proposed as a strategy to preserve cartilage integrity in OA management[204]. A variety of Wnt signalling antagonists have been developed and evaluated, including antidepressants, microRNAs, herb extracts and enzymes[205]. These antagonists target components of the Wnt pathway and thereby supress the signalling cascade, resulting in a reduction in cartilage destruction. Notably, intra-articular injection of the small molecule Wnt inhibitor SM04690 had promising effects on cartilage rescue and in a phase II clinical trial for knee OA with no reported toxicity[206]. Verapamil, a calcium channel blocker generally used for hypertension treatment, has also shown a chondroprotective effect through suppression of the Wnt pathway. Verapamil is a potent *FRZB* activator in human OA chondrocytes, in which it was able to downregulate the Wnt pathway and thus inhibit chondrocyte hypertrophic differentiation[207]. Intra-articular injection of verapamil successfully inhibits β-catenin accumulation and OA progression in rats with post-traumatic OA[207]. All these evidence has provided preliminary proof of the idea of targeting shared pathways between hypertension and OA for cartilage protection. However, whether those molecules and drugs could rescue OA in a whole-joint manner by restoring also bone and synovial function and structure warrants further investigation.

[H1] Others anti-hypertensive drugs for OA

Despite decades of effort in OA research, a cure has not yet been discovered. Research into the causal relationship between hypertension and OA might open the door to development of disease-modifying OA drugs. Repurposing of FDA-approved drugs for hypertension has the potential for rapid clinical translation as toxicity and pharmacokinetic information for these drugs is readily available. In addition to the RAS, endothelin and Wnt antagonists discussed in the previous section, some other anti-hypertensive drugs have been trialled for the treatment of OA in various experimental models. Some have already shown promising chondroprotective effects and pain relief, whereas others are still being investigated. Among all of the anti-hypertensive drugs being

investigated, potassium-sparing diuretics and adrenergic antagonists are undergoing the most extensive research for their anti-inflammatory and pain relief effects in OA management.

[H2] Potassium-sparing diuretics

Diuretics are drugs that increase sodium and water excretion while retaining potassium reabsorption to prevent hypokalaemia. Diuretics can be further classified into two types: aldosterone antagonists (such as spironolactone and eplerenone), and epithelial sodium channel blockers (such as amiloride). By regulating ion balance and fluid retention, diuretics generally have mild anti-hypertensive effect and are often used for the treatment of resistant hypertension, which is unresponsive to medication[208].

[H3] Spironolactone. In patients with OA, low-dose spironolactone improved joint effusion and its associated pain with a higher efficacy than ibuprofen, a commonly used NSAID[209]. Remarkably, low-dose spironolactone (25mg daily) did not affect blood pressure in normotensive individuals[209], implying that this treatment might also be useful in normotensive OA patients. A large-scale clinical study is still needed to further investigate the efficacy of this treatment.

[H3] Eplerenone. Eplerenone, also known as mineralocorticoid receptor antagonist, is known to have beneficial effects in experimental models of obesity-related metabolic disorder[210]. Eplerenone also has protective effects on metabolic-associated OA joint lesions; in a rat model of obese spontaneous hypertensive heart failure, treatment with eplerenone also reduced cartilage degradation, osteophyte formation and synovial inflammation[211].

[H3] Amiloride. As well as being a diuretic, amiloride also serves as an acid-sensing ion channel blocker[212]. Abnormal activation of acid-sensing ion channels is usually accompanied by a drop in pH and inflammation, and can also contribute to cartilage erosion in joints in experimental models of rheumatoid arthritis and pain and disease progression in models of OA[212,213]. Amiloride inhibits acid-induced cartilage damage and restores type II collagen expression in rats with adjuvant-induced arthritis[212].

[H2] Adrenergic antagonists

Adrenergic antagonists are adrenergic receptor blockers that inhibit the action of adrenaline and thereby elicit potent anti-hypertensive effects. Adrenergic antagonists can be split into two main

types: alpha adrenergic antagonists (such as clonidine), and beta adrenergic antagonists (such as beta blockers).

[H3] Clonidine. In addition to its anti-hypertensive effects, clonidine is an effective analgesic that acts on the central nervous system. Systemic administration of clonidine was therefore found to be more effective against joint pain than intra-articular injection in a rat model of OA[214]. However, local intravenous anaesthesia seems to be enough to ameliorate joint pain in humans[215].

[H3] Beta blockers. Similar to clonidine, beta blockers also have anti-nociceptive effects. However, although one study reported a reduction in pain in patients with hip or knee OA following beta blocker use, another study has disproved the pain relief effect of this drug[216,217]. Therefore, the efficacy of beta blockers for joint pain is still an open subject for debate. Nevertheless, beta blockers can reduce ET1 synthesis in human endothelial cells, providing further explanation for the anti-hypertensive effect of the drug[218]. Given that increased concentrations of ET1 correlates with OA severity, evaluating the chondroprotective effects of beta blockers from the perspective of the endothelin family could provide novel insights into OA treatment.

[H2] Other therapies

As mentioned in section on targeting shared molecular pathways, the calcium channel blocker verapamil elicits protective effects on cartilage via inhibition of the Wnt signalling pathway[207]. The same study also reported the efficacy of other anti-hypertensive calcium channel blockers on Wnt signalling inhibition, including nifedipine; however, none of them successfully inhibited Wnt signalling[207]. By contrast, a beneficial effect of nifedipine on chondrocytes has been reported in another study[207,219]. From a metabolic perspective, nifedipine seems to promote the shift from oxidative respiration to glycolysis in chondrocytes. Although this alteration of nutritional pathway was accompanied by nitric oxide production, the drug showed a surprising stimulation of type II collagen and proteoglycan synthesis[219]. This finding feeds into the discussion about the role of nitric oxide, which most studies tend to agree has a catabolic effect on cartilage homeostasis[220].

[H1] Future directions

Interactions between body systems is a growing area for understanding pathogenesis and disease aetiology. Given the emerging evidence demonstrating a correlation between the vascular and skeletal systems[221], interventions that have multiple targets could be promising for chronic disease management. Beyond the epidemiological associations between hypertension and OA and the

shared role of physical inactivity and weight gain in both diseases, there seem to be direct links between these two diseases at the tissue or cellular level, as hypertension can initiate or promote the progression of OA. Therefore, it is conceivable that new therapies with both symptom alleviation and structural aims could be developed on the basis of these new pathophysiologic discoveries.

Reducing systemic blood pressure in hypertensive patients with OA should logically have an effect on local tissue and cell regulation by restoring the perfusion abnormalities of the synovial tissue that are responsible for hypoxia-triggered inflammation, improving the nutritional intake of cartilage owing to the reduction of subchondral bone ischemia induced by hypertension, and reducing intramedullary pressure, which can partly explain the pain that occurs in OA. As discussed in this Review, RAS, endothelin and Wnt signalling inhibitors, as well as some existing anti-hypertensive drugs, have already shown positive effects on joint health. The chondroprotective effect of these drugs provides hope for future use in OA treatment. Although it seems intriguing to control hypertension and OA simultaneously, safety issues related to systemically administered drugs need to be taken into account. Importantly, the shared pathological pathways might also be critical for other biological functions, which could be cell-type specific. More stringent safety assessment of intended therapeutics need to be used to prevent undesired adverse effects. Hence, specific treatments that target local vascular regulation could be considered. Intra-articular injection is an easy route of administration that could be considered as it is well-accepted by patients and that can be used to achieve high concentrations of a drug without any major risks or safety concerns.

While the contribution of hypertension to structural damage of joint is established and evidenced, the correlation between blood pressure and nociception remains controversial. In deoxycorticosterone acetate salt models of hypertension[222] and spontaneous hypertensive rat model[223], hypertension-associated hypoalgesia was observed, making the rats less sensitive to acute pain. Similar findings was obtained in human study, where hypertensive patients had higher pain tolerance than normotensive ones in acute pain stimulation tests[224,225]. However, such association between blood pressure and pain sensation reversed in patients with chronic pain. Studies have reported positive correlation between resting blood pressure and chronic low back pain[226,227]. The proposed mechanism causing alteration of blood pressure-relationship was endogenous opioid dysfunction in chronic pain condition[227]; yet another study did not agree to this notion[226]. The conflicting blood pressure-pain correlation in acute and chronic pain may explain heterogenic findings on association between hypertension and symptomatic OA, in which some studies reported positive correlations while some reported the opposite. Therefore, blood pressure-chronic pain

relationship warrants further investigation to help consolidate the association between hypertension and symptomatic OA.

Considering that there is currently no cure for OA and the preliminary success of rescuing experimental OA phenotypes using RAS, endothelin and Wnt signalling inhibitors and anti-hypertensive drugs, the preclinical development of these molecules for therapeutic purposes seems worth investigating.

[H1] Conclusions

Existing evidence supports hypertension as being one of the most common metabolic components associated with OA after adjustment for confounding factors. The biophysical and biochemical effects of hypertension on the synovium, subchondral bone and chondrocytes disturb joint homeostasis and could contribute to OA onset and progression. The presence of endothelial–skeletal crosstalk in the pathogenesis of OA emphasizes the potential role of systemic factors such as RAS, endothelins and Wnt signalling in disease management. Forthcoming therapeutic strategies should therefore employ macroscopic approaches that target systemic high blood pressure to resolve local diseases, in particular those with multifactorial aetiologies such as OA.

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Competing interests

The authors declare no competing interests.

Key points

- Epidemiologically, high blood pressure (hypertension) has been linked to radiographic and symptomatic knee osteoarthritis.
- At the tissue level, systemic hypertension leads to subchondral bone perfusion abnormalities and ischemia, which disrupts angiogenic–osteogenic coupling and impairs the integrity of the bone–cartilage functional unit.
- At a molecular level, systemic activation of the renin–angiotensin, endothelin and Wnt–β-catenin signalling pathways induces a phenotypical change in articular chondrocytes and triggers cartilage degradation.
- Anti-hypertensive medications that exhibit chondroprotective effects in preclinical studies warrant further investigation in patients with osteoarthritis and the frequently encountered comorbidity of systemic hypertension.

Figure 1. The vasculature and its changes in knee osteoarthritis.

Extensive angiogenesis occurs during knee osteoarthritis. Vascular endothelial growth factor (VEGF) is secreted by various tissues, including the synovium, subchondral bone and cartilage, to promote vessel growth. At sites of aberrant bone remodelling, other angiogenic factor such as platelet-derived growth factor BB (PDGF-BB) is also secreted. Despite the increase in the number of vessels, local blood flow to the tissue decreases. Perfusion abnormalities including limited arterial inflow and venous outflow occur, possibly as a result of impaired vessel function and increased intraosseous pressure. The reduced blood flow hinders the supply of oxygen and nutrients to tissues, thus creating an environment of hypoxia and nutritional stress. The formation of highly fenestrated blood vessel and reduction of lymphatic vessel in osteoarthritic knee also affect synovial fluid drainage, resulting in joint effusion. PDGF-BB, platelet-derived growth factor BB; pO_2, partial pressure of oxygen.

Figure 2. Biophysical effects of hypertension on the joint at a cellular level.

Increased arterial pressure positively correlates with increased intraosseous pressure, while hypertension-induced perfusion abnormalities of vessels limit oxygen supply to joint tissues, creating a hypoxic microenvironment. **a**| Bone undergoes remodelling in response to mechanical changes, resulting in structural changes. Hypoxia triggers osteocyte necrosis. Necrotic osteocytes secrete damage-associated molecular patterns (DAMPs) that could bind to C-type lectin domain family 4 member E (MINCLE) on pre-osteoclast and stimulate their differentiation. Apoptotic osteocytes also induce secretion of receptor-activator of NFκB ligand (RANKL) from neighbouring osteocytes to activate osteoclasts, which initiate bone remodeling cascade by stimulating osteoblasts via transforming growth factor-β (TGFβ). **b**| The increased physical stress and pressure accelerates the exchange of chemicals (including matrix metalloproteinases (MMPs)) at the osteochondral junction that promotes cartilage catabolism. **c**| Physical stress increases aquaporin 1 expression in synovial micro-vessels, contributing to joint effusion and synovial oedema. Hypertensive stretch and hypoxia also aggravate synovial inflammation by promoting exocytosis of inflammatory cytokine-containing Weibel-Palade body (WPB) from endothelial cells. ET1, endothelin 1; MSC, mesenchymal stem cell; MINCLE, C-type lectin domain family 4 member E; RANKL, receptor activator of NFκB ligand; TGFβ, transforming growth factor-β; VEGF, vascular endothelial growth factor; VEGFR2, VEGF receptor 2; WPB, Weibel-Palade body.

Figure 3. Molecular pathways shared by hypertension and osteoarthritis.

Cartilage is avascular and hypoxic, making it less susceptible to direct physical stress and hypoxic stress brought about by hypertension. However, overactivated pathways in hypertension could affect chondrocyte fate. The renin–angiotensin system (RAS), endothelin system and the canonical Wnt–β-catenin pathway that are upregulated in hypertension induce chondrocyte hypertrophy and inflammatory response, contributing to joint catabolism. The three pathways are also interconnected. RAS components are transcriptional inducer of endothelin system components; endothelin can then suppress Dickkopf protein 1 (DKK1) synthesis and thereby activate the Wnt–β-catenin pathway; which in turn induce transcription of RAS components. Drugs targeting these shared pathways have shown both cardioprotective and chondroprotective effects, suggesting potential roles in the pathogenesis of both cardiovascular disease and joint disease. ATRs, angiotensin receptors; Ang II, angiotensin II; DKK1, Dickkopf protein 1; ET1, endothelin 1; ETRs, endothelin receptors; GSK3, glycogen synthase kinase 3; ILs, interleukins; LRP, low density lipoprotein receptor-related protein; MMPs, matrix metalloproteinases; RUNX2, Runt-related transcription factor 2; TCF, T cell factor.

Table 1. Studies investigating the relationship between hypertension and knee osteoarthritis.

Study (date)	Study design	Database used	Location (ethnicity)	OA classification	Odds ratio (95% CI)	Adjusted factors	Reference
Bagge et al. (1991)	CSS	NA	Sweden (Swedes)	Radiographic	0.96 (0.731.27)	BMI	[228]
Hart et al. (1995)	CSS	Chingford study	UK (NR)	Radiographic	1.28 (0.76-2.16)	BMI, Age	[229]
				Symptomatic	1.10 (0.53-1.26)		
Sowers et al. (1996)	CSS	Michigan Bone Health Study	USA (White)	Radiographic	6.51 (1.9-21)	NR	[230]
Kim et al. (2010)	CS	NA	Korea (NR)	Radiographic	2.74 (1.66-4.54)	Age, Educational level, BMI, Presences of osteoporosis, diabetes mellitus, exercise, smoking, alcohol consumption, occupation	[231]
				Symptomatic	2.17 (1.30-3.63)		
Reid et al. (2010)	CSS	Southern California American Indian Health Clinic [Data was collected	USA (American Indian, Alaska Native)	Hospital diagnosed	Women 8.46 (4.81–14.90)	Age	[232]
					Men 12.63 (5.25–30.37)		

		from this clinic]					
Inoue et al. (2011)	CSS	NA	Japan (NR)	Radiographic	Women 5.09 (3.38-7.67) Men 2.04 (1.08-3.84)	NR	[233]
Yoshimura et al. (2012)	CS	Research on Osteoarthritis Against Disability	Japan (Japan resident)	Radiographic	OA onset 2.74 (1.30-5.78) OA progression 1.54 (1.10-2.17)	Age, Gender, Alcohol consumption, Smoking, Resident region, BMI, presence of obesity, dyslipidaemia and impaired glucose tolerance	[234]
Han et al. (2013)	CC	National Health and Nutritional Examination Survey	Korea (Korean)	Hospital diagnosed	Male 0.710 (0.361, 1.397) Female 0.933 (0.653, 1.334)	Age, Exercise, Alcohol consumption, Smoking	[235]
Shin (2014)	CSS	National Health and Nutritional Examination Survey	Korea (Korean)	Radiographic	1.10 (0.89-1.36)	BMI, Age, Sex, Exercise, Alcohol consumption, Smoking, Income	[236]
Liu et al. (2015)	CSS	NA	China (Chinese)	Symptomatic	Women 1.42 (1.10-1.84) Men 1.48 (1.13-1.93)	NR	[237]
Li et al. (2016)	CSS	NA	USA (NR)	Radiographic	For stage 3 hypertension 6.749 (0.963-48.668)	NR	[238]
Kim et al. (2016)	CSS	National Health and Nutrition Examination Survey	Korea (Korean)	Radiographic & Symptomatic	1.26 (1.08-1.48)	BMI, Age, Sex, Exercise, Alcohol consumption, Smoking, Education, Income,	[239]

						occupation, mental health	
Niu et al. (2017)	CS	Framingham Study	USA (White)	Radiographic	Women 1.3 (0.8-2)	BMI, Age, Exercise, Alcohol consumption, Smoking, Education	[240]
					Men 1.3 (0.8-2.1)		
				Symptomatic	Women 1.7 (1.0-3.0)		
					Men 1.8 (1.0-3.4)		
Lo et al. (2017)	CS	Osteoarthritis Initiative	USA (African Americans, white Americans)	Radiographic	1.7 (1-2.6)	BMI, Age, Sex, Medication (NSAID use, antihypertensive, diabetic and cholesterol medication)	[241]
Zhang et al. (2017)	Meta-analysis	NA	NA	Radiographic	1.49 (1.26–1.77)	Sex, Study design, hypertension definition, Area	[6]
				Symptomatic	2.01 (1.28–3.15)		
Xie et al. (2017)	CSS	Xiangya Hospital Health Management Centre Study	China (Chinese)	Radiographic	1.23 (1.09-1.40)	Age, Exercise, Alcohol consumption, Smoking, Education	[242]
Yasuda et al. (2018)	CSS	NA	Japan (NR)	Symptomatic	3.44 (1.88-10.55)	BMI, Age, Muscle strength	[243]
Sanchez-Santos et al. (2019)	CSS	Chingford study	UK (NR)	Radiographic & Symptomatic	1.15 (0.63-2.11)	BMI, Age	[244]
Funck-Brentano et al. (2019)	CSS	UK Biobank	UK (white)	Hospital diagnosed	0.66 (0.57-0.77)	BMI, Age, Sex	[245]
Xie et al. (2020)	Meta-analysis	NA	NA	Radiographic	1.70(1.41-2.05)	NR	[7]
				Symptomatic	1.32 (1.19-1.48)		
Lo et al. (2021)	Meta-analysis	NA	NA	Radiographic	1.89 (1.40-2.54)	NR	[19]
				Symptomatic	1.39 (1.17-1.65)		

CC, case-control study; CS, cohort study; CSS, cross-sectional study; NA, not applicable; NR, not reported.

Glossary

T2 values

Values obtained in MRI scanning, providing information about the water content and organisation of collagen structure in cartilage.

Metaphyseal bone

The transition zone between the shaft and head of long bones; it is the location of the growth plate, which elongates and grows during bone development.

Diaphyseal bone

The midsection of long bones, composed of tubular cortical bone on the outside and a hollow bone marrow cavity on the inside.

Areolar tissue

A type of connective tissue with loosely organised fibre, allowing space for interstitial fluid to fill in for tissue nourishment.

Epiphysis

The two ends of long bones covered with articular cartilage that join adjacent bones

Weibel-Palade bodies

Storage granules in endothelial cells that can be released through exocytosis.

Hypokalaemia

A situation of electrolyte imbalance with low potassium in blood serum.