Hypertension meets osteoarthritis — revisiting the vascular aetiology hypothesis

Karen Ching[1], *Xavier Houard*[2], *Francis Berenbaum*[2,3] *and Chunyi Wen*[1] ✉

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 in the treatment of OA.

Q1

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 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 the increased prevalence of knee OA. 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 HDL levels. Among these conditions, hypertension and type 2 diabetes are often present in patients with knee OA[8]. After adjustment for body weight or 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.

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[6,15]. However, whether the contribution of hypertension to OA initiation and joint deterioration is biased by

Q2 [1]*Department of Biomedical Engineering, The Hong Kong Polytechnic University, Hung Hom, Hong Kong, China.*
Q3 [2]*Sorbonne Université, INSERM, Centre de Recherche Saint-Antoine, Paris, France.*
Q4 [3]*Department of Rheumatology, Sorbonne Université, Saint-Antoine Hospital, Paris, France.*
✉*e-mail: chunyi.wen@polyu.edu.hk*

https://doi.org/10.1038/s41584-021-00650-x

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 ischaemia, which disrupts angiogenic–osteogenic coupling and impairs the integrity of the bone–cartilage functional unit.
- At the 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.

potential confounding factors such as BMI is uncertain. Furthermore, contradictory results have been reported regarding the relationship between hypertension and knee OA[9,13,16] (TABLE 1). Higher systolic blood pressure (above 112 mmHg) 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[16]. However, in another study that retrieved data from the same database, an increase in diastolic blood pressure from baseline was associated with more heterogeneous cartilage T2 values on MRI scans at 48 months in patients with knee OA, indicating increased cartilage degeneration[17]. 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-analyses of pooled evidence have been performed to decipher the relationship between hypertension and OA. In one systematic review[6], hypertension increased the odds of developing radiographic knee OA by 101% but of developing symptomatic knee OA by only 49%; another meta-analysis also reported a stronger association between hypertension and radiographic knee OA (with increased odds of 89%) than symptomatic knee OA (with increased odds of 39%)[18]. 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 in women than in 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 individuals of Asian ancestry with OA than in individuals of non-Asian ancestry with OA[6,19]. 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 with hypertension[20–23], 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 is yet to be confirmed.

Analytical techniques such as Mendelian randomization provide powerful control for confounding and inverse causation[24]. Mendelian randomization 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. Despite the strong conclusions of this study[13], the findings were limited by the definition of OA that was used. The requirement of a hospital diagnosis of OA in this study implies that only symptomatic OA might have been captured. In addition, whether joint pain relates to intra-osseous blood pressure and perfusion in response to alterations of systemic blood pressure remains controversial[25,26]. 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 and needs to be filled.

Joint vascularization 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[27]. 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[28]. Optical clearing of bone tissues has also enabled the identification of a previously unknown blood vessel type in cortical bone[29]. 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[28]. Synovial fluid serves as a medium for chemical exchange between the highly vascularized

T2 values
Values obtained in MRI scans that provide information about the water content and organization of the 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.

Table 1 | **Studies investigating the relationship between hypertension and knee osteoarthritis**

Study (date)	Study design	Cohort	Location (ethnicity)	OA classification	Odds ratio (95% CI)	Adjusted factors	Ref.
Bagge et al. (1991)	CSS	70-year-old people in Göteborg	Sweden (NR)	Radiographic	0.96 (0.73–1.27)	BMI	226
Hart et al. (1995)	CSS	Chingford Study	UK (NR)	Radiographic	1.28 (0.76–2.16)	BMI and age	227
				Symptomatic	1.10 (0.53–1.26)		
Sowers et al. (1996)	CSS	Michigan Bone Health Study	USA (white)	Radiographic	6.51 (1.90–21.00)	NR	228
Kim et al. (2010)	CS	NA	Korea (NR)	Radiographic	2.74 (1.66–4.54)	Age, educational level, BMI, presence of osteoporosis or diabetes mellitus, amount of exercise, smoking, alcohol consumption and occupation	229
				Symptomatic	2.17 (1.30–3.63)		
Reid et al. (2010)	CSS	Southern California American Indian Health Clinic	USA (Native American and Native Alaskan)	Hospital diagnosed	Women 8.46 (4.81–14.90) Men 12.63 (5.25–30.37)	Age	230
Inoue et al. (2011)	CSS	NA	Japan (NR)	Radiographic	Women 5.09 (3.38–7.67) Men 2.04 (1.08–3.84)	NR	231
Yoshimura et al. (2012)	CS	Research on Osteoarthritis/ Osteoporosis Against Disability (ROAD) Study	Japan (NR)	Radiographic	OA onset 2.74 (1.30–5.78) OA progression 1.54 (1.10–2.17)	Age, sex, alcohol consumption, smoking, resident region, BMI, presence of obesity, dyslipidaemia or impaired glucose tolerance	232
Han et al. (2013)	CC	Korean National Health and Nutritional Examination Survey	Korea (NR)	Hospital diagnosed	Women 0.93 (0.65–1.33) Men 0.71 (0.36–1.40)	Age, amount of exercise, alcohol consumption and smoking	233
Shin (2014)	CSS	Korean National Health and Nutritional Examination Survey	Korea (NR)	Radiographic	1.10 (0.89–1.36)	BMI, age, sex, amount of exercise, alcohol consumption, smoking and income	234
Liu et al. (2015)	CSS	NA	China (NR)	Symptomatic	Women 1.42 (1.10–1.84) Men 1.48 (1.13–1.93)	NR	235
Li et al. (2016)	CC	NA	USA (NR)	Radiographic	For stage 3 hypertension 6.75 (0.96–48.67)	NR	236
Kim et al. (2016)	CSS	Korean National Health and Nutrition Examination Survey	Korea (NR)	Radiographic and symptomatic	1.26 (1.08–1.48)	BMI, age, sex, amount of exercise, alcohol consumption, smoking, education, income, occupation and mental health	237
Niu et al. (2017)	CS	Framingham Study	USA (white)	Radiographic	Women 1.30 (0.80–2.00) Men 1.30 (0.80–2.10)	BMI, age, amount of exercise, alcohol consumption, smoking and education	9
				Symptomatic	Women 1.70 (1.00–3.00) Men 1.80 (1.00–3.40)		

Table 1 (cont.) | **Studies investigating the relationship between hypertension and knee osteoarthritis**

Study (date)	Study design	Cohort	Location (ethnicity)	OA classification	Odds ratio (95% CI)	Adjusted factors	Ref.
Lo et al. (2017)	CS	Osteoarthritis Initiative	USA (NR)	Radiographic	1.70 (1.00–2.60)	BMI, age, sex and medication use (NSAIDs, anti-hypertensive, diabetic and cholesterol medication)	16
Zhang et al. (2017)	Meta-analysis	NA	NA	Radiographic	2.01 (1.28–3.15)	Sex, study design, hypertension definition and area	6
				Symptomatic	1.49 (1.26–1.77)		
Xie et al. (2017)	CSS	Xiangya Hospital Health Management Centre Study	China (NR)	Radiographic	1.23 (1.09–1.40)	Age, amount of exercise, alcohol consumption, smoking and education	238
Yasuda et al. (2018)	CSS	NA	Japan (NR)	Symptomatic	3.44 (1.88–10.55)	BMI, age and muscle strength	239
Sanchez-Santos et al. (2019)	CSS	Chingford Study	UK (NR)	Radiographic and symptomatic	1.15 (0.63–2.11)	BMI and age	240
Funck-Brentano et al. (2019)	CSS	UK Biobank	UK (white)	Hospital diagnosed	0.66 (0.57–0.77)	BMI, age and sex	13
Xie et al. (2021)	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	18
				Symptomatic	1.39 (1.17–1.65)		

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

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[30,31]. In its deep zone, articular cartilage is separated from subchondral bone by a thin layer of calcified cartilage[29]. Subchondral bone plays a crucial role in nourishing the overlying cartilage[32,33]; indeed, the calcified cartilage is permeable to small molecules such as glucose and nitric oxide[34,35]. The presence of bone-derived proteins within articular cartilage further strengthens the idea of functional biochemical communication and interaction between bone and cartilage tissues[36]. Such interaction could be augmented through microcracks at the interface between bone and cartilage[37–39], through which subchondral bone blood vessels can invade the calcified cartilage layer during the development of OA.

Synovial vasculature

The synovium is highly vascularized, with both fenestrated and continuous capillaries present in relative proportions depending on the anatomical location in the joint[40]. The density of capillaries in the synovium also varies according to the location of the synovium within the joint cavity and the depth below the synovial surface[40]. Capillaries are usually located superficially and their density is high over areolar tissue and adipose tissue and low over tendons[41]. By contrast, lymphatic vessels are mainly located in the deep regions of the synovium[42]. 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[43].

Modification of the synovial vascular network is a hallmark of the arthritic joint (FIG. 1). The OA synovium is characterized by an increase in microvessel density and endothelial cell proliferation[44,45], and by a decrease in lymphatic vessel density[42]. Synoviocytes isolated from inflamed areas of the OA synovium exhibit high angiogenic potential and have increased expression of vascular endothelial growth factor (VEGF) compared with synoviocytes from adjacent non-inflamed areas[45–47]. VEGF promotes synovial angiogenesis via VEGF receptor 2 (VEGFR2), which is highly expressed by endothelial cells and synoviocytes[47]. 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[44,48].

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[49,50]. In the haematopoietic 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[49]. 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[51]. These small channels (10–30 μm 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[51]. These vascular channels, which contain blood vessels,

Areolar tissue
A type of connective tissue with loosely organized fibres that provides space for interstitial fluid to fill the tissue to provide nourishment.

Epiphysis
The ends of long bones that are covered with articular cartilage and join adjacent bones.

sympathetic nerves, osteoclasts and osteoblasts[52–54], nourish the calcified cartilage and the deep layers of the non-calcified cartilage and govern remodelling at the osteochondral junction[51,52].

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[55]. In later stages of OA, the subchondral cortical plate becomes thick and sclerotic, whereas the trabecular bone remains osteopenic[55]. Alongside this remodelling process, increased vascularization in the subchondral bone during OA has been well documented in both animals[28] and humans[56].

As bone is a mechanoresponsive tissue, angiogenesis is coupled with osteogenesis under mechanical stimuli during bone modelling and remodelling[57]. During bone repair in mice, osteoblast-derived VEGF regulates osteoblast differentiation and bone formation[58] and osteoblasts can also secrete angiogenic factors in response to mechanical stimuli[59]. Similarly, osteoclast-derived platelet-derived growth factor BB (PDGF-BB) stimulates angiogenesis in subchondral bone in mice and contributes to OA development[60]. Given that aberrant mechanical loading occurs in OA joints as a consequence of cartilage damage, then a 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 considered to quantify remodelling of the subchondral bone in mouse models of OA[61]. The inclusion of subchondral angiogenesis marks the recognition of a role for the vasculature 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[53,62] (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[53]. 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[54,63]. The number of vascular invasion incidents has also been associated with the severity of cartilage damage and clinical symptoms[44,53]. Indeed, the inhibition of angiogenesis successfully

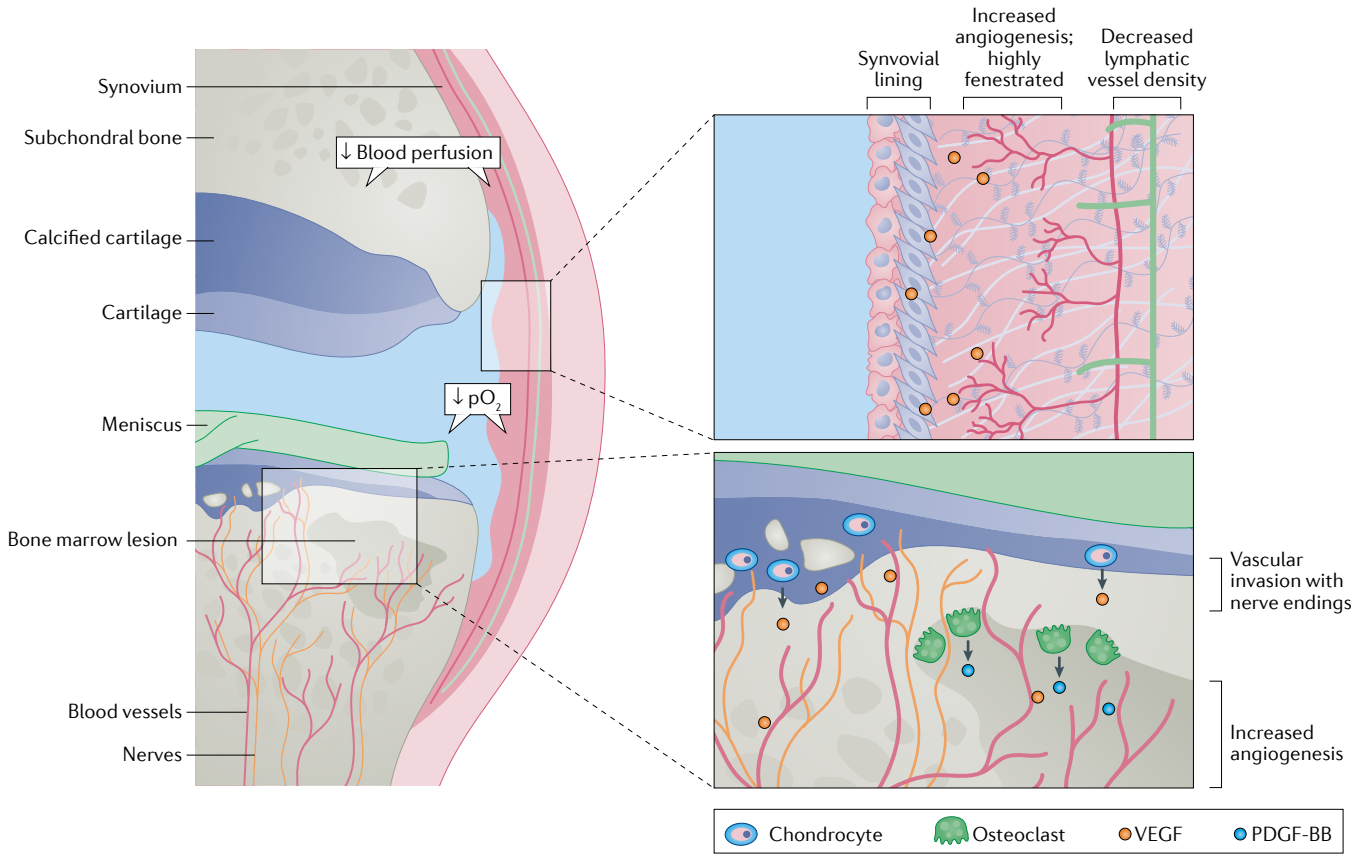

Fig. 1 | **The vasculature and its changes in knee osteoarthritis.** Extensive angiogenesis occurs during knee osteoarthritis. Vascular endothelial growth factor (VEGF) is secreted by various tissues, including the synovium, subchondral bone and cartilage, to promote vessel growth. At sites of aberrant bone remodelling, other angiogenic factors, such as platelet-derived growth factor BB (PDGF-BB), are 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 vessels and reduction in lymphatic vessel density in osteoarthritic knees also affect synovial fluid drainage, resulting in joint effusion. pO_2, partial pressure of oxygen.

preserves joint integrity and reduces pain in various experimental models of OA[64]. 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[65]. These blood capillaries are characterized by their high expression of both CD31 and endomucin and were initially described in the metaphysis of young mice[66]. The proportion of type H vessels is maximal after birth and declines in adult and aged mice[66,67]. Type H vessels express large quantities of pro-osteogenic factors and recruit osterix-expressing osteoprogenitor cells, thereby coupling angiogenesis with osteogenesis[66]. The formation of type H vessels also involves preosteoclast-derived PDGF-BB[68]. 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[60]. 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[60]. VEGFA secreted by chondrocytes is also involved in type H vessel formation in OA[69] and a proposed crosstalk between endothelial cells and hypertrophic chondrocytes is thought to promote osteogenesis[70].

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 particularly hypertension, might contribute to joint disorders both biophysically and biochemically.

Perfusion abnormalities and ischaemia

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[71–73]. 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[74].

Bone perfusion abnormalities, characterized by a reduction in both arterial inflow and venous outflow, have indeed been documented in human knee OA[75]. An increase in intraosseous pressure following venous occlusion in hip OA has also been known for a long time[72,76]. In a 2018 study, dynamic contrast-enhanced MRI was used to assess the kinetics of bone perfusion in knee OA[75]. 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[75]. Reduction in blood flow could lead to subchondral bone ischaemia and apoptosis of osteocytes that in turn initiates osteoclast-mediated bone resorption[77]. 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[78]. In guinea pigs with spontaneous OA, decreased venous outflow in the medial tibial plateau both preceded and was colocalized with cartilage degradation and subchondral bone thickening[79]. Observations from both animals and humans further strengthen the notion of the intimate relationship between blood perfusion and joint destruction.

Hypoxia

The disruption of local blood flow could also trigger a cascade of responses at both the molecular and cellular levels. In OA, both the synovial fluid and the synovium are similarly characterized by a decrease in the partial pressure of oxygen (pO_2)[78,80] (FIG. 1). Interestingly, the importance of circulatory insufficiency relative to synovial tissue metabolism has been highlighted in an effort to explain this observation[81]. The reported link between synovial blood flow and intra-articular hydrostatic pressure could explain the inverse relationship between synovial fluid volume and pO_2[80,82]. In mice with OA induced by the destabilization of the medial meniscus, synovial pO_2 (as measured by photoacoustic imaging) progressively decreased with the development and the progression of OA[78]. Synovial hypoxia negatively correlated with cartilage damage but was positively associated with synovial blood flow[78]. 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[83].

Impaired nutrition supply

Hypertension-induced perfusion abnormalities cause nutrient deprivation to both bone and cartilage, which ultimately affects their homeostasis[84]. Indeed, osteocytes can only survive nutrient depletion for 4 hours in an experimental setting[85] and 6 hours of bone ischaemia is sufficient to cause osteonecrosis[86].

Subchondral bone perfusion supplies at least 50% of the necessary glucose and oxygen to overlying cartilage[31]. 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[87,88]. Changes to the glucose concentration in the extracellular matrix can impair insulin growth factor 1-mediated anabolism in chondrocytes, leading to joint pathologies[89]. In a hypoxic environment, the expression of glucose transporter 1 by chondrocytes is upregulated, enabling a more rapid uptake of glucose[90]. However, the intake of nutrients in such an anaerobic environment favours glycolysis, which produces acidic lactate as an end product and further acidifies the cartilage environment[91]. Importantly, acidification of the extracellular matrix can alter the synthesis of matrix molecules[92]. The energy depletion caused by the switch to glycolysis is also associated with increased

production of nitric oxide as found in osteoarthritic joints[91].

Hypertension and joint structure

Hypertension increases intraosseous stress and causes perfusion abnormalities in joint tissues[72,73]. 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[27,93]. Researchers have also documented the intracellular and extracellular responses of osteocytes and their progenitor cells towards changes in fluid shear stress[94,95]. 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[95,96]. Prolonged exposure to TGFβ can trigger OA-like changes in the knees of mice despite its transient effect on promoting chondrogenesis[97] and nitric oxide upregulates MMPs in a cGMP-dependent manner, further contributing to cartilage destruction[98].

Osteonecrosis

When bone ischaemia 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

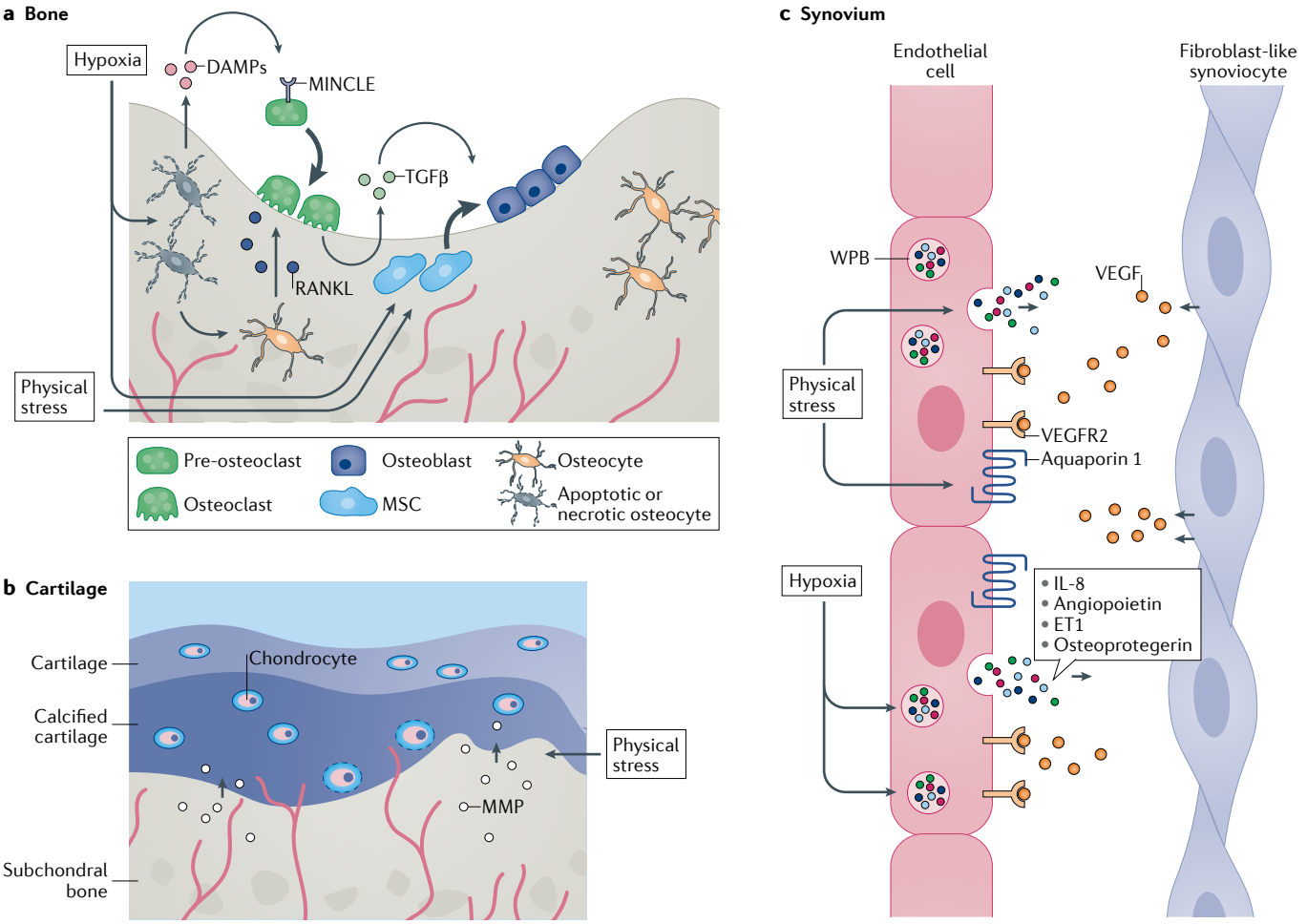

Fig. 2 | **Biophysical effects of hypertension on the joint at the cellular level.** Increased arterial pressure positively correlates with increased intraosseous pressure, while hypertension-induced perfusion abnormalities of vessels limit oxygen supply to joint tissues, creating a hypoxic microenvironment.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

with OA[99]. In murine studies, apoptotic osteocytes could stimulate neighbouring osteocytes to release receptor-activator of NF-κB ligand (RANKL), which induces osteoclast activation[100,101]. In horses with spontaneous equine carpal post-traumatic OA, RANKL expression was increased in the subchondral bone and was linked to increased osteoclast density[102]. 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[103]. 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[104].

Macrophage colony-stimulating factor (M-CSF) is another essential cytokine for osteoclastogenesis[105]. M-CSF is secreted by osteoblasts and can direct osteoclast differentiation, thereby promoting bone resorption. The 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[106,107]. Interestingly, an increase in M-CSF was observed in primary cultured osteoblasts from rats with spontaneous hypertension and was accompanied by a loss of bone mass in the animals[108]. High amounts of circulating IL-6 have also been documented in both human and rodents with hypertension[109,110]. IL-6 can stimulate osteoclast formation in the presence of M-CSF[111], suggesting that inflammation in hypertension might aggravate osteonecrosis in OA via an interaction between IL-6 and M-CSF.

Recently, a 2020 study has shown that damage-associated molecular patterns 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[112]. In patients with osteonecrosis, MINCLE was highly expressed in areas of high osteocyte death and correlated with the expression of markers of osteoclast activity[112]. Although a role has not yet been reported for MINCLE in OA, damage-associated molecular patterns are known to be involved in the pathogenesis of OA[113].

Bone marrow oedema

When a joint is mechanically unstable (for example, after anterior cruciate ligament injury[114,115]), the subchondral bone can exhibit a bone bruise (an oedema-like change on MRI scans) known as a bone marrow lesion (BML)[28]. In patients with OA, BMLs are characterized by highly vascularized sclerotic bone tissue with poor mineralization[116,117] and the size of BMLs is inversely proportional to the venous outflow as measured by dynamic contrast-enhanced MRI[26]. The presence of BMLs is strongly associated with increased cartilage erosion and more severe joint pain in patients with knee OA[118,119]. However, it remains controversial whether BMLs resolve or enlarge as OA develops[120,121]. Cystic lesions can develop alongside cartilage loss in both rats with post-traumatic OA and humans with knee OA[122,123]. Some investigators have also suggested that BMLs could be a consequence of ischaemia reperfusion injury[124]. Arterial pressure could conceivably promote capillary oedema, resulting in increased intramedullar pressure and creating a phenomenon that is proposed to be equivalent to BMLs[124]. These results suggest that vascular perfusion and pressure could be determinants of BMLs.

Bone sclerosis

Although patients usually experience temporal bone loss in the early stages of OA, at later stages of disease, bone mass actually increases[125]. 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[60,68]. Type H endothelial cells are capable of inducing osteoblastic differentiation, which could lead to increased bone formation[66]. 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[28]. Notably, the differentiation of bone marrow mesenchymal stromal cells into osteoblasts can also be directly stimulated by hypoxia[126]. In this context, hypertension-induced hypoxia could aggravate bone sclerosis.

Despite the increase in mass, sclerotic bone is often under-mineralized[127,128]. This impaired mineralization might be linked to an increase in expression of the Wnt antagonist Dickkopf 2 (DKK2). The upregulation of TGFβ1 in osteoarthritic human osteoblasts could stimulate DKK2, a well-known inhibitor of bone mineralization[128]. 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 this Review.

Osteochondral junction modification

In OA, increased hydraulic conductance has been recorded at the bone–cartilage interface[122]. 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[129,130] (FIG. 2b). These factors, produced by the damaged bone in OA, can stimulate cartilage degradation[131], particularly by inducing catabolic changes in chondrocyte phenotypes[132]. Considering the increased intraosseous pressure and osteochondral junction modification that occurs in OA, the transport of molecules from the bone to the cartilage might also be accelerated, thus further facilitating cartilage damage[133,134]. This process could be aggravated by hypertension as intraosseous pressure correlates with blood pressure[72].

Joint effusion

Joint effusion is associated with both radiographic severity and pain in OA[135,136] and could 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

Weibel–Palade bodies (WPB). Storage granules in endothelial cells that can be released through exocytosis.

Q7

and a low density of lymphatic vessels in the synovium in patients with OA[42]. Synovial oedema is probably also related to an increased vascular permeability of the synovial capillaries[137]. For example, an increased ratio of proteins in the synovial fluid over the serum occurs in patients with OA compared with healthy individuals[138]. Immunohistochemical analysis has also revealed an overexpression of the water channel aquaporin 1 in synovitis that contributes to joint swelling and synovial oedema formation in rheumatoid arthritis[139]. Notably, hypertension provokes aquaporin 1 overexpression and activation in aortic endothelial cells in rats[140], suggesting that the 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[141]. 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)[142–144]. Notably, hypertensive stretch stimulates the exocytosis of WPBs in a mechanism dependent on VEGFR2 (REF.[145]); hence, hypertension could aggravate synovitis in this context (FIG. 2c).

The exocytosis of endothelial WPBs could also be triggered by hypoxia[146], thereby promoting the secretion of pro-inflammatory cytokines. A hypoxic environment also induces the expression of endothelin-converting enzyme (ECE1) and ET1, factors that stimulate the degranulation of WPBs[147,148]; a local amplification loop of ET1 production and secretion is then sustained. The excessive ET1 stimulates the production of pro-inflammatory factors and triggers the catabolic metabolism of articular cartilage as well as synovial thickening in a mechanism that involves a positive feedback loop of reactive oxygen species production[149–151].

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[152,153] (FIG. 3). Furthermore, the canonical Wnt–β-catenin pathway has been implicated in both cardiovascular and skeletal diseases[154]. 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.

Renin–angiotensin system

RAS plays a central role in blood pressure regulation, particularly for short-term changes[152], and high circulating concentrations of the RAS component angiotensin II have been observed in individuals with hypertension[155]. Although first identified in the circulatory system, RAS components also exert tissue-specific functions, which are termed local RAS[156]. In the skeletal system, local RAS is particularly important for chondrocyte hypertrophy.

Local RAS expression is found in both human and mouse chondrocytes[157,158]. 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[159]. These results suggest a possible role for RAS in synovial angiogenesis as well as in cartilage destruction. At the 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[160]. 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[158]. 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[161]. Similarly, in vitro administration of the hypertrophy stimulant IL-1β could also initiate expression of AT1 and AT2 on human articular chondrocytes[157]. 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[162], 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 plays a role in bone remodelling via interaction with RANKL. In the vascular system, angiotensin II activates RANKL, which then accelerates calcium deposition[149]. Vascular calcification reduces vessel elasticity and thereby aggravates systolic hypertension in a vicious cycle[163,164]. 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[165,166].

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[167]. 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[168].

The endothelin family consists of three isoforms, ET1, ET2 and ET3, which perform their biological functions as vasoconstrictors, mitogens or pro-inflammatory

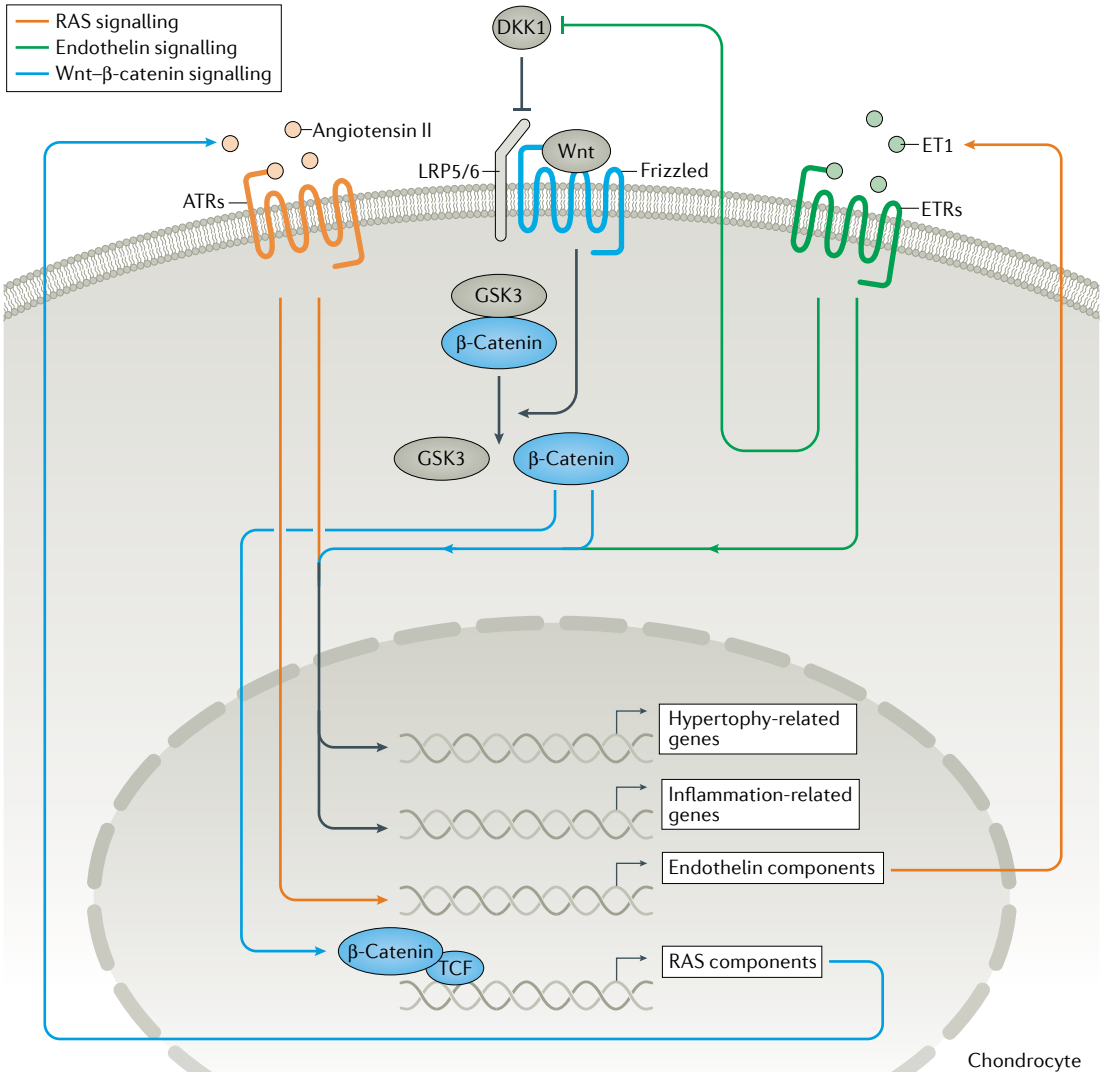

Fig. 3 | **Molecular pathways shared by hypertension and osteoarthritis.** Cartilage is avascular and hypoxic, making it less susceptible to direct physical stress and hypoxic stress brought about by hypertension than bone and the synovium. However, overactivated pathways in hypertension could affect chondrocyte fate. The renin–angiotensin system (RAS), endothelin system and canonical Wnt–β-catenin pathways, which are upregulated in hypertension, induce chondrocyte hypertrophy and an inflammatory response, contributing to joint catabolism. The three pathways are also interconnected. RAS components are transcriptional inducers of endothelin system components. Endothelin 1 (ET1) can suppress Dickkopf protein 1 (DKK1) synthesis and thereby activate the Wnt–β-catenin pathway, which in turn induces the 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; ETRs, endothelin receptors; GSK3, glycogen synthase kinase 3; LRP, LDL receptor-related protein; TCF, T cell factor.

cytokines by activating two G protein-coupled receptors (ET_AR and ET_BR)[169]. Among the endothelins, ET1 is the predominant form in the 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 the precise control of vascular tone[169].

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[170]. Both ET1 and ET_AR are upregulated in all affected joint tissues in OA, including synovial fluid, the synovium and articular cartilage[149,150,171–173]. ET1 in synovial fluid and the synovium can stimulate the production of pro-inflammatory mediators such as IL-1β, IL-6, and IL-8 and can trigger the catabolic metabolism of articular cartilage as well as synovial thickening[149,150]. When used in vitro at similar concentrations to those present systemically and locally in patients with knee OA, ET1 could directly stimulate osteoarthritic chondrocytes to produce MMP1 and MMP13, major enzymes involved in degrading the cartilaginous extracellular matrix[171,172]. Underlying mechanisms might involve a positive feedback loop of reactive oxygen species production

that activates the transcription factor AP1 and, in turn, increases ECE1 expression and ET1 synthesis[151]. Notably, intra-articular injection of an ET1 antagonist could attenuate articular cartilage degradation following anterior cruciate ligament trauma in a rat model, suggesting that the endothelin system could be a potential therapeutic target for OA management[173].

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 individuals with hypertension and in patients with OA[174,175].

A genome-wide association study has revealed a direct correlation between *WNT3* and pulse pressure[176]. 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[177]. Clinically, the overexpression of LDL receptor-related protein 6 (LRP6), a co-receptor for Wnt proteins, has also been found in individuals with hypertension[178]. In fact, interactions between the Wnt–β-catenin pathway and RAS have been widely discussed in relation to cardiovascular diseases. A bioinformatics analysis revealed binding sites for the TCF–LEF family of transcription factors in all RAS genes, including those encoding angiotensinogen, renin, ACE, AT1 and AT2 (REF.[179]). 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[180,181]. 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[182]. Wnt signalling helps to maintain the balance between osteogenesis and chondrogenesis as activation of Wnt promotes osteoblast differentiation while repressing chondrogenesis[183]. Wnt–β-catenin signalling also suppresses expression of the chondrogenic gene *Sox9* while enhancing expression of the hypertrophic genes *Runx2* and *Mmp13* in mice[183]. In addition, the overexpression of Wnt genes and β-catenin has been documented in knee OA[175,184,185]. Moreover, Wnt antagonists have shown a beneficial effect on cartilage homeostasis. DKK1 is a Wnt inhibitor that competes with Wnt ligands to bind LRP5 and LRP6 (REF.[186]), 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[187]. 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[188,189]. The downregulation of this gene has also been observed in mechanically injured cartilage[185]. 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[190]. However, although mediation of the Wnt signalling pathway via suppression of Wnt inhibitors by ET1 has been postulated in chondrocytes, experimental proof is required.

Targeting shared molecular pathways

Given that local RAS contributes to various skeletal pathologies, including osteoporosis[191,192], rheumatoid arthritis[193,194] and possibly OA, treatments that target RAS components are being investigated. Aliskiren, a renin inhibitor approved for the treatment of hypertension, has chondroprotective effects by attenuating IL-1, TNF and RUNX2 expression[195]. Aliskiren inhibited chondrocyte hypertrophy, reduce local RAS expression and rescue cartilage destruction in rats with surgically induced OA[195]. 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 (REF.[160]). The amount of hypertrophic cartilage was greatly reduced by both treatment methods. Furthermore, preliminary results suggest that captopril can attenuate the increased expression of senescence markers that occurs in both subchondral bone and articular cartilage in the deoxycorticosterone acetate salt model of hypertension and in spontaneously hypertensive rats[196].

In addition to chondroprotective effects, antihypertensive drugs can also reduce inflammation. Losartan (an AT1 blocker) and captopril can reduce joint pain and inflammation in rats and mice with experimental models of RA[193,197] and rats with experimental OA[160,195,196], respectively, suggesting that the protective effect of anti-hypertensive drugs on joints was achieved by suppression of local RAS. However, the administration of losartan exacerbated bone loss induced by angiotensin II in mice[166]. 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[166]. By contrast, the ACE inhibitor enalapril improved bone mass and hypertension simultaneously in mice[164] but only marginally in humans[198]. 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 is yet to be fully defined, ET1 has been linked to chondrocyte hypertrophy and senescence. Preliminary data have also demonstrated that mice with transgenically overexpressed endothelial ET1 have an activated endothelin system and exhibit an OA-like phenotype compared with their littermates as well as having hypertrophic changes in their cartilage[199,200]. 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[201].

Considering that the endothelin system is intertwined with RAS, these effects on chondrocyte fate were anticipated.

The downregulation of Wnt signalling has also been proposed as a strategy to preserve cartilage integrity in OA management[202]. A variety of Wnt signalling antagonists has been developed and evaluated, including antidepressants, microRNAs, herb extracts and enzymes[203]. 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[204]. Verapamil, a calcium channel blocker generally used for the treatment of hypertension, 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[205]. Intra-articular injection of verapamil successfully inhibits β-catenin accumulation and OA progression in rats with post-traumatic OA[205]. Taken together, these studies provide preliminary proof of the idea of targeting shared pathways between hypertension and OA for cartilage protection. However, whether these molecules and drugs could rescue OA in a whole-joint manner by restoring bone and synovial function and structure warrants further investigation.

Other 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 the development of disease-modifying OA drugs. The 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 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.

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 effects and are often used for the treatment of resistant hypertension that is unresponsive to medication[206].

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

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[207]. Remarkably, low-dose spironolactone (25 mg daily) did not affect blood pressure in individuals who are normotensive [207], implying that this treatment might also be useful in patients with OA who are normotensive. A large-scale clinical study is still needed to further investigate the efficacy of this treatment.

Eplerenone. Eplerenone, also known as mineralocorticoid receptor antagonist, is known to have beneficial effects in experimental models of obesity-related metabolic disorder[208]. 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[209].

Amiloride. As well as being a diuretic, amiloride also serves as an acid-sensing ion channel blocker[210]. 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[210,211]. Amiloride inhibits acid-induced cartilage damage and restores type II collagen expression in rats with adjuvant-induced arthritis[210].

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).

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[212]. However, local intravenous anaesthesia seems to be enough to ameliorate joint pain in humans[213].

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[214,215]. 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[216]. Given that increased concentrations of ET1 correlate with OA severity, evaluating the chondroprotective effects of beta blockers from the perspective of the endothelin family could provide novel insights into OA treatment.

Other therapies

As mentioned in the section on targeting shared molecular pathways, the calcium channel blocker verapamil elicits protective effects on cartilage via inhibition of the Wnt signalling pathway[205]. 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[205]. By contrast, a beneficial effect of nifedipine on chondrocytes has been reported in another study[205,217]. 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[217]. 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[218].

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[219], 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 based on these new pathophysiological discoveries.

Reducing systemic blood pressure in patients with OA and hypertension 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 ischaemia 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 considered. Importantly, the shared pathological pathways might also be critical for other biological functions, which could be cell-type specific. More stringent safety assessments 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 can be used to achieve high concentrations of a drug without any major risks or safety concerns.

Although the contribution of hypertension to structural damage in joints is established and supported by evidence, the correlation between blood pressure and nociception remains controversial. Hypertension-associated hypoalgesia has been reported in deoxycorticosterone acetate salt models of hypertension[220] and in rats with spontaneous hypertension[221], which makes the rats less sensitive to acute pain. Similar findings have been obtained in human studies, in which individuals with hypertension had a higher pain tolerance than individuals who are normotensive in acute pain stimulation tests[222,223]. However, such associations between blood pressure and pain sensation are reversed in patients with chronic pain; studies have reported a positive correlation between resting blood pressure and chronic low back pain[224,225]. The proposed mechanism causing alterations to the blood pressure relationship was endogenous opioid dysfunction in chronic pain conditions[225]; although another study did not agree with this notion[224]. The conflicting blood pressure–pain correlation in acute and chronic pain might explain the heterogeneity of findings related to the association between hypertension and symptomatic OA, where some studies have reported positive correlations whereas others the opposite. Therefore, the 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.

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.

1. Hunter, D. J., March, L. & Chew, M. Osteoarthritis in 2020 and beyond: a Lancet Commission. *Lancet* **396**, 1711–1712 (2020).
2. Kendzerska, T. et al. The longitudinal relationship between hand, hip and knee osteoarthritis and cardiovascular events: a population-based cohort study. *Osteoarthr. Cartil.* **25**, 1771–1780 (2017).
3. Haugen, I. K. et al. Hand osteoarthritis in relation to mortality and incidence of cardiovascular disease: data from the Framingham Heart Study. *Ann. Rheum. Dis.* **74**, 74–81 (2015).
4. Nuesch, E. et al. All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study. *BMJ* **342**, d1165 (2011).
5. Wallace, I. J. et al. Knee osteoarthritis has doubled in prevalence since the mid-20th century. *Proc. Natl Acad. Sci. USA* **114**, 9332–9336 (2017).

6. Zhang, Y.-M., Wang, J. & Liu, X.-G. Association between hypertension and risk of knee osteoarthritis: a meta-analysis of observational studies. *Medicine* **96**, e7584 (2017).
7. Xie, Y. et al. Metabolic syndrome, hypertension, and hyperglycemia were positively associated with knee osteoarthritis, while dyslipidemia showed no association with knee osteoarthritis. *Clin. Rheumatol.* **40**, 711–724 (2021).
8. Wen, C. Y. et al. Bone loss at subchondral plate in knee osteoarthritis patients with hypertension and type 2 diabetes mellitus. *Osteoarthr. Cartil.* **21**, 1716–1723 (2013).
9. Niu, J., Clancy, M., Aliabadi, P., Vasan, R. & Felson, D. T. Metabolic syndrome, its components, and knee osteoarthritis: The Framingham Osteoarthritis Study. *Arthritis Rheumatol.* **69**, 1194–1203 (2017).
10. Findlay, D. M. Vascular pathology and osteoarthritis. *Rheumatology* **46**, 1763–1768 (2007).
11. Hussain, S. M. et al. Vascular pathology and osteoarthritis: a systematic review. *J. Rheumatol.* **47**, 748–760 (2020).
12. Calvet, J. et al. High prevalence of cardiovascular co-morbidities in patients with symptomatic knee or hand osteoarthritis. *Scand. J. Rheumatol.* **45**, 41–44 (2016).
13. Funck-Brentano, T., Nethander, M., Moverare-Skrtic, S., Richette, P. & Ohlsson, C. Causal factors for knee, hip and hand osteoarthritis: a Mendelian randomization study in the UK Biobank. *Arthritis Rheumatol.* **71**, 1634–1641 (2019).
14. Singh, G. et al. Consequences of increased systolic blood pressure in patients with osteoarthritis and rheumatoid arthritis. *J. Rheumatol.* **30**, 714–719 (2003).
15. Jamsen, E., Peltola, M., Eskelinen, A. & Lehto, M. U. Comorbid diseases as predictors of survival of primary total hip and knee replacements: a nationwide register-based study of 96 754 operations on patients with primary osteoarthritis. *Ann. Rheum. Dis.* **72**, 1975–1982 (2012).
16. Lo, G. H. et al. Systolic and pulse pressure associate with incident knee osteoarthritis: data from the Osteoarthritis Initiative. *Clin. Rheumatol.* **36**, 2121–2128 (2017).
17. Ashmeik, W. et al. Association of blood pressure with knee cartilage composition and structural knee abnormalities: data from the Osteoarthritis Initiative. *Skelet. Radiol.* **49**, 1359–1368 (2020).
18. Lo, K., Au, M., Ni, J. & Wen, C. Association between hypertension and osteoarthritis: a systematic review and meta-analysis of observational studies. *J. Orthop. Transl.* https://doi.org/10.1016/j.jot.2021.05.003 (2021).
19. Gandhi, R., Razak, F., Tso, P., Davey, J. R. & Mahomed, N. N. Asian ethnicity and the prevalence of metabolic syndrome in the osteoarthritic total knee arthroplasty population. *J. Arthroplasty* **25**, 416–419 (2010).
20. Poornima, S., Subramanyam, K., Khan, I. A. & Hasan, Q. The insertion and deletion (I28005D) polymorphism of the angiotensin I converting enzyme gene is a risk factor for osteoarthritis in an Asian Indian population. *J. Renin Angiotensin Aldosterone Syst.* **16**, 1281–1287 (2015).
21. Hong, S. J. et al. Angiotensin converting enzyme gene polymorphism in Korean patients with primary knee osteoarthritis. *Exp. Mol. Med.* **35**, 189–195 (2003).
22. Lin, C. et al. Angiotensin-converting enzyme insertion/deletion polymorphism and susceptibility to osteoarthritis of the knee: a case-control study and meta-analysis. *PLoS One* **11**, e0161754 (2016).
23. Shehab, D. K. et al. Prevalence of angiotensin-converting enzyme gene insertion-deletion polymorphism in patients with primary knee osteoarthritis. *Clin. Exp. Rheumatol.* **26**, 305–310 (2008).
24. Smith, G. D. & Ebrahim, S. Mendelian randomization: prospects, potentials, and limitations. *Int. J. Epidemiol.* **33**, 30–42 (2004).
25. Arnoldi, C. C. et al. Intraosseous hypertension and pain in the knee. *J. Bone Joint Surg. Br.* **57**, 360–363 (1975).
26. Seah, S. et al. The relationship of tibial bone perfusion to pain in knee osteoarthritis. *Osteoarthr. Cartil.* **20**, 1527–1533 (2012).
27. Ramasamy, S. K. et al. Blood flow controls bone vascular function and osteogenesis. *Nat. Commun.* **7**, 13601 (2016).
28. Zhen, G. et al. Inhibition of TGF-β signaling in mesenchymal stem cells of subchondral bone attenuates osteoarthritis. *Nat. Med.* **19**, 704–712 (2013).
29. Grüneboom, A. et al. A network of trans-cortical capillaries as mainstay for blood circulation in long bones. *Nat. Metab.* **1**, 236–250 (2019).
30. Huber, M., Trattnig, S. & Lintner, F. Anatomy, biochemistry, and physiology of articular cartilage. *Invest. Radiol.* **35**, 573–580 (2000).
31. Imhof, H. et al. Subchondral bone and cartilage disease: a rediscovered functional unit. *Invest. Radiol.* **35**, 581–588 (2000).
32. Bashir, A., Gray, M. L., Boutin, R. D. & Burstein, D. Glycosaminoglycan in articular cartilage: in vivo assessment with delayed Gd (DTPA)(2-)-enhanced MR imaging. *Radiology* **205**, 551–558 (1997).
33. Malinin, T. & Ouellette, E. Articular cartilage nutrition is mediated by subchondral bone: a long-term autograft study in baboons. *Osteoarthr. Cartil.* **8**, 483–491 (2000).
34. Pan, J. et al. In situ measurement of transport between subchondral bone and articular cartilage. *J. Orthop. Res.* **27**, 1347–1352 (2009).
35. Arkill, K. & Winlove, C. Solute transport in the deep and calcified zones of articular cartilage. *Osteoarthr. Cartil.* **16**, 708–714 (2008).
36. Lajeunesse, D. & Reboul, P. Subchondral bone in osteoarthritis: a biologic link with articular cartilage leading to abnormal remodeling. *Curr. Opin. Rheumatol.* **15**, 628–633 (2003).
37. Lyons, T. J., McClure, S. F., Stoddart, R. W. & McClure, J. The normal human chondro-osseous junctional region: evidence for contact of uncalcified cartilage with subchondral bone and marrow spaces. *BMC Musculoskelet. Disord.* **7**, 52 (2006).
38. Sokoloff, L. Microcracks in the calcified layer of articular cartilage. *Arch. Pathol. Lab. Med.* **117**, 191–195 (1993).
39. Mori, S., Harruff, R. & Burr, D. Microcracks in articular calcified cartilage of human femoral heads. *Arch. Pathol. Lab. Med.* **117**, 196–198 (1993).
40. Knight, A. & Levick, J. R. Morphometry of the ultrastructure of the blood-joint barrier in the rabbit knee. *Q. J. Exp. Physiol.* **69**, 271–288 (1984).
41. Knight, A. & Levick, J. R. The density and distribution of capillaries around a synovial cavity. *Q. J. Exp. Physiol.* **68**, 629–644 (1983).
42. Walsh, D. et al. Lymphatic vessels in osteoarthritic human knees. *Osteoarthr. Cartil.* **20**, 405–412 (2012).
43. Levick, J. Microvascular architecture and exchange in synovial joints. *Microcirculation* **2**, 217–233 (1995).
44. Walsh, D. et al. Angiogenesis in the synovium and at the osteochondral junction in osteoarthritis. *Osteoarthr. Cartil.* **15**, 743–751 (2007).
45. Lambert, C. et al. Characterization of synovial angiogenesis in osteoarthritis patients and its modulation by chondroitin sulfate. *Arthritis Res. Ther.* **14**, R58 (2012).
46. Lambert, C. et al. Gene expression pattern of cells from inflamed and normal areas of osteoarthritis synovial membrane. *Arthritis Rheumatol.* **66**, 960–968 (2014).
47. Giatromanolaki, A. et al. The angiogenic pathway "vascular endothelial growth factor/fl-1(KDR)-receptor" in rheumatoid arthritis and osteoarthritis. *J. Pathol.* **194**, 101–108 (2001).
48. Haywood, L. et al. Inflammation and angiogenesis in osteoarthritis. *Arthritis Rheum.* **48**, 2173–2177 (2003).
49. Trueta, J. & Harrison, M. The normal vascular anatomy of the femoral head in adult man. *J. Bone Joint Surg. Br.* **35**, 442–461 (1953).
50. Morini, S., Pannarale, L., Conti, D. & Gaudio, E. Microvascular adaptation to growth in rat humeral head. *Anat. Embryol.* **211**, 403–411 (2006).
51. Clark, J. M. The structure of vascular channels in the subchondral plate. *J. Anat.* **171**, 105–115 (1990).
52. Lane, L. B., Villacin, A. & Bullough, P. The vascularity and remodelling of subchondral bone and calcified cartilage in adult human femoral and humeral heads. An age- and stress-related phenomenon. *J. Bone Joint Surg. Br.* **59**, 272–278 (1977).
53. Shibakawa, A. et al. The role of subchondral bone resorption pits in osteoarthritis: MMP production by cells derived from bone marrow. *Osteoarthr. Cartil.* **13**, 679–687 (2005).
54. Suri, S. et al. Neurovascular invasion at the osteochondral junction and in osteophytes in osteoarthritis. *Ann. Rheum. Dis.* **66**, 1423–1428 (2007).
55. Burr, D. B. & Gallant, M. A. Bone remodelling in osteoarthritis. *Nat. Rev. Rheumatol.* **8**, 665–673 (2012).
56. Harrison, M., Schajowicz, F. & Trueta, J. Osteoarthritis of the hip: a study of the nature and evolution of the disease. *J. Bone Joint Surg. Br.* **35**, 598–626 (1953).
57. Boerckel, J. D., Uhrig, B. A., Willett, N. J., Huebsch, N. & Guldberg, R. E. Mechanical regulation of vascular growth and tissue regeneration in vivo. *Proc. Natl Acad. Sci.* **108**, E674–E680 (2011).
58. Hu, K. & Olsen, B. R. Osteoblast-derived VEGF regulates osteoblast differentiation and bone formation during bone repair. *J. Clin. Invest.* **126**, 509–526 (2016).
59. Liu, C. et al. Osteoblast-derived paracrine factors regulate angiogenesis in response to mechanical stimulation. *Integr. Biol.* **8**, 785–794 (2016).
60. Su, W. et al. Angiogenesis stimulated by elevated PDGF-BB in subchondral bone contributes to osteoarthritis development. *JCI Insight* **5**, e135446 (2020).
61. Nagira, K. et al. Histological scoring system for subchondral bone changes in murine models of joint aging and osteoarthritis. *Sci. Rep.* **10**, 10077 (2020).
62. Bonde, H., Talman, M. & Kofoed, H. The area of the tidemark in osteoarthritis–a three–dimensional stereological study in 21 patients. *APMIS* **113**, 349–352 (2005).
63. Walsh, D. A. et al. Angiogenesis and nerve growth factor at the osteochondral junction in rheumatoid arthritis and osteoarthritis. *Rheumatology* **49**, 1852–1861 (2010).
64. Hamilton, J. L. et al. Targeting VEGF and its receptors for the treatment of osteoarthritis and associated pain. *J. Bone Miner. Res.* **31**, 911–924 (2016).
65. Cui, Z. et al. Halofuginone attenuates osteoarthritis by inhibition of TGF-β activity and H-type vessel formation in subchondral bone. *Ann. Rheum. Dis.* **75**, 1714–1721 (2016).
66. Kusumbe, A. P., Ramasamy, S. K. & Adams, R. H. Coupling of angiogenesis and osteogenesis by a specific vessel subtype in bone. *Nature* **507**, 323–328 (2014).
67. Langen, U. H. et al. Cell–matrix signals specify bone endothelial cells during developmental osteogenesis. *Nat. Cell Biol.* **19**, 189–201 (2017).
68. Xie, H. et al. PDGF-BB secreted by preosteoclasts induces angiogenesis during coupling with osteogenesis. *Nat. Med.* **20**, 1270–1278 (2014).
69. Lu, J. et al. Positive-feedback regulation of subchondral H-type vessel formation by chondrocyte promotes osteoarthritis development in mice. *J. Bone Miner. Res.* **33**, 909–920 (2018).
70. Watson, E. C. & Adams, R. H. Biology of bone: the vasculature of the skeletal system. *Cold Spring Harb. Perspect. Med.* **8**, a031559 (2018).
71. De Lorenzo, R. A., Ward, J. A., Jordan, B. S. & Hanson, C. E. Relationships of intraosseous and systemic pressure waveforms in a Swine model. *Acad. Emerg. Med.* **21**, 899–904 (2014).
72. Beverly, M. & Murray, D. Factors affecting intraosseous pressure measurement. *J. Orthop. Surg. Res.* **13**, 187 (2018).
73. Aaron, R. K. et al. Perfusion abnormalities in subchondral bone associated with marrow edema, osteoarthritis, and avascular necrosis. *Ann. N. Y. Acad. Sci.* **1117**, 124–137 (2007).
74. Lip, G. Y. H. & Coca, A. On behalf of the Task Force. Hypertension and cardiac arrhythmias. *Eur. Heart J.* **38**, 223–225 (2017).
75. Aaron, R., Racine, J., Voisinet, A., Evangelista, P. & Dyke, J. Subchondral bone circulation in osteoarthritis of the human knee. *Osteoarthr. Cartil.* **26**, 940–944 (2018).
76. Arnoldi, C. C., Linderholm, H. & Müssbichler, H. Venous engorgement and intraosseous hypertension in osteoarthritis of the hip. *J. Bone Joint Surg. Br.* **54**, 409–421 (1972).
77. Chan, P. M. B., Wen, C., Yang, W. C., Yan, C. & Chiu, K. Is subchondral bone cyst formation in non-load-bearing region of osteoarthritic knee a vascular problem? *Med. Hypotheses* **109**, 80–83 (2017).
78. Liu, Z. et al. Photoacoustic imaging of synovial tissue hypoxia in experimental post-traumatic osteoarthritis. *Prog. Biophy. Mol. Biol.* **148**, 12–20 (2019).
79. Lee, J. H. et al. Subchondral fluid dynamics in a model of osteoarthritis: use of dynamic contrast-enhanced magnetic resonance imaging. *Osteoarthr. Cartil.* **17**, 1350–1355 (2009).
80. Richman, A. I., Su, E. Y. & Ho, G. Jr. Reciprocal relationship of synovial fluid volume and oxygen tension. *Arthritis Rheum.* **24**, 701–705 (1981).
81. Falchuk, K., Goetzl, E. & Kulka, J. Respiratory gases of synovial fluids: an approach to synovial tissue circulatory-metabolic imbalance in rheumatoid arthritis. *Am. J. Med.* **49**, 223–231 (1970).

82. Geborek, P., Forslind, K. & Wollheim, F. Direct assessment of synovial blood flow and its relation to induced hydrostatic pressure changes. *Ann. Rheum. Dis.* **48**, 281–286 (1989).
83. Kiaer, T., Grønlund, J. & Sørensen, K. Subchondral pO_2, pCO_2, pressure, pH, and lactate in human osteoarthritis of the hip. *Clin. Orthop. Relat. Res.* **229**, 149–155 (1988).
84. Kiær, T., Dahl, B. & Lausten, G. S. The relationship between inert gas wash-out and radioactive tracer microspheres in measurement of bone blood flow: effect of decreased arterial supply and venous congestion on bone blood flow in an animal model. *J. Orthop. Res.* **11**, 28–35 (1993).
85. James, J. & Steijn-Myagkaya, G. Death of osteocytes. Electron microscopy after in vitro ischaemia. *J. Bone Joint Surg. Br.* **68**, 620–624 (1986).
86. Catto, M. Ischaemia of bone. *J. Clin. Pathol. Suppl.* **11**, 78–93 (1977).
87. Archer, C. W. & Francis-West, P. The chondrocyte. *Int. J. Biochem. Cell Biol.* **35**, 401–404 (2003).
88. Rosa, S. C. et al. Role of glucose as a modulator of anabolic and catabolic gene expression in normal and osteoarthritic human chondrocytes. *J. Cell. Biochem.* **112**, 2813–2824 (2011).
89. Mobasheri, A. et al. Glucose transport and metabolism in chondrocytes: a key to understanding chondrogenesis, skeletal development and cartilage degradation in osteoarthritis. *Histol. Histopathol.* **17**, 1239–1267 (2002).
90. Peansukmanee, S. et al. Effects of hypoxia on glucose transport in primary equine chondrocytes in vitro and evidence of reduced GLUT1 gene expression in pathologic cartilage in vivo. *J. Orthop. Res.* **27**, 529–535 (2009).
91. Mobasheri, A. et al. The role of metabolism in the pathogenesis of osteoarthritis. *Nat. Rev. Rheumatol.* **13**, 302–311 (2017).
92. Martín-Vasallo, P. et al. Sodium transport systems in human chondrocytes II. Expression of ENaC, Na^+/K^+/2Cl-cotransporter and Na^+/H^+ exchangers in healthy and arthritic chondrocytes. *Histol. Histopathol.* **14**, 1023–1031 (1999).
93. Tomlinson, R. E. & Silva, M. J. Skeletal blood flow in bone repair and maintenance. *Bone Res.* **1**, 311–322 (2013).
94. Wittkowske, C., Reilly, G. C., Lacroix, D. & Perrault, C. M. In vitro bone cell models: impact of fluid shear stress on bone formation. *Front. Bioeng. Biotechnol.* **4**, 87 (2016).
95. Liu, L., Yuan, W. & Wang, J. Mechanisms for osteogenic differentiation of human mesenchymal stem cells induced by fluid shear stress. *Biomech. Model. Mechanobiol.* **9**, 659–670 (2010).
96. Rangaswami, H. et al. Type II cGMP-dependent protein kinase mediates osteoblast mechanotransduction. *J. Biol. Chem.* **284**, 14796–14808 (2009).
97. Van Beuningen, H., Glansbeek, H., Van Der Kraan, P. & Van den Berg, W. Osteoarthritis-like changes in the murine knee joint resulting from intra-articular transforming growth factor-β injections. *Osteoarthr. Cartil.* **8**, 25–33 (2000).
98. Ridnour, L. A. et al. Nitric oxide regulates matrix metalloproteinase-9 activity by guanylyl-cyclase-dependent and -independent pathways. *Proc. Natl Acad. Sci. USA* **104**, 16898–16903 (2007).
99. Jaiprakash, A. et al. Phenotypic characterization of osteoarthritic osteocytes from the sclerotic zones: a possible pathological role in subchondral bone sclerosis. *Int. J. Biol. Sci.* **8**, 406–417 (2012).
100. Kennedy, O. D., Laudier, D. M., Majeska, R. J., Sun, H. B. & Schaffler, M. B. Osteocyte apoptosis is required for production of osteoclastogenic signals following bone fatigue in vivo. *Bone* **64**, 132–137 (2014).
101. Cheung, W. Y. et al. Pannexin-1 and P2X7-receptor are required for apoptotic osteocytes in fatigued bone to trigger RANKL production in neighboring bystander osteocytes. *J. Bone Miner. Res.* **31**, 890–899 (2016).
102. Bertuglia, A. et al. Osteoclasts are recruited to the subchondral bone in naturally occurring post-traumatic equine carpal osteoarthritis and may contribute to cartilage degradation. *Osteoarthr. Cartil.* **24**, 555–566 (2016).
103. Zhu, J. et al. HIF-1α facilitates osteocyte-mediated osteoclastogenesis by activating JAK2/STAT3 pathway in vitro. *J. Cell. Physiol.* **234**, 21182–21192 (2019).
104. Zhu, S. et al. Subchondral bone osteoclasts induce sensory innervation and osteoarthritis pain. *J. Clin. Invest.* **129**, 1076–1093 (2019).
105. Mun, S. H., Park, P. S. U. & Park-Min, K.-H. The M-CSF receptor in osteoclasts and beyond. *Exp. Mol. Med.* **52**, 1239–1254 (2020).
106. Felix, R., Cecchini, M. & Fleisch, H. Macrophage colony stimulating factor restores in vivo bone resorption in the op/op osteopetrotic mouse. *Endocrinology* **127**, 2592–2594 (1990).
107. Orcel, P., Feuga, M., Bielakoff, J. & De Vernejoul, M. Local bone injections of LPS and M-CSF increase bone resorption by different pathways in vivo in rats. *Am. J. Physiol. Endocrinol. Metab.* **264**, E391–E397 (1993).
108. Tiyasatkulkovit, W. et al. Impairment of bone microstructure and upregulation of osteoclastogenic markers in spontaneously hypertensive rats. *Sci. Rep.* **9**, 12293 (2019).
109. Chamarthi, B. et al. Inflammation and hypertension: the interplay of interleukin-6, dietary sodium, and the renin–angiotensin system in humans. *Am. J. Hypertens.* **24**, 1143–1148 (2011).
110. Zhang, W. et al. Interleukin 6 underlies angiotensin II-induced hypertension and chronic renal damage. *Hypertension* **59**, 136–144 (2012).
111. Kudo, O. et al. Interleukin-6 and interleukin-11 support human osteoclast formation by a RANKL-independent mechanism. *Bone* **32**, 1–7 (2003).
112. Andreev, D. et al. Osteocyte necrosis triggers osteoclast-mediated bone loss through macrophage-inducible C-type lectin. *J. Clin. Invest.* **130**, 4811–4830 (2020).
113. Millerand, M., Berenbaum, F. & Jacques, C. Danger signals and inflammaging in osteoarthritis. *Clin. Exp. Rheumatol.* **37**, 48–56 (2019).
114. Yao, J. et al. Deterioration of stress distribution due to tunnel creation in single-bundle and double-bundle anterior cruciate ligament reconstructions. *Ann. Biomed. Eng.* **40**, 1554–1567 (2012).
115. Yao, J. et al. Effect of tibial drill-guide angle on the mechanical environment at bone tunnel aperture after anatomic single-bundle anterior cruciate ligament reconstruction. *Int. Orthop.* **38**, 973–981 (2014).
116. Shabestari, M., Vik, J., Reseland, J. & Eriksen, E. Bone marrow lesions in hip osteoarthritis are characterized by increased bone turnover and enhanced angiogenesis. *Osteoarthr. Cartil.* **24**, 1745–1752 (2016).
117. Muratovic, D. et al. Bone matrix microdamage and vascular changes characterize bone marrow lesions in the subchondral bone of knee osteoarthritis. *Bone* **108**, 193–201 (2018).
118. Hunter, D. J. et al. Increase in bone marrow lesions associated with cartilage loss: a longitudinal magnetic resonance imaging study of knee osteoarthritis. *Arthritis Rheum.* **54**, 1529–1535 (2006).
119. Felson, D. T. et al. The association of bone marrow lesions with pain in knee osteoarthritis. *Ann. Intern. Med.* **134**, 541–549 (2001).
120. Link, T. M. et al. Osteoarthritis: MR imaging findings in different stages of disease and correlation with clinical findings. *Radiology* **226**, 373–381 (2003).
121. Kornaat, P. R. et al. Osteoarthritis of the knee: association between clinical features and MR imaging findings. *Radiology* **239**, 811–817 (2006).
122. Raynauld, J. P. et al. Correlation between bone lesion changes and cartilage volume loss in patients with osteoarthritis of the knee as assessed by quantitative magnetic resonance imaging over a 24-month period. *Ann. Rheum. Dis.* **67**, 683–688 (2008).
123. McErlain, D. D. et al. An in vivo investigation of the initiation and progression of subchondral cysts in a rodent model of secondary osteoarthritis. *Arthritis Res. Ther.* **14**, R26 (2012).
124. Winet, H., Hsieh, A. & Bao, J. Approaches to study of ischemia in bone. *J. Biomed. Mater. Res.* **43**, 410–421 (1998).
125. Intema, F. et al. In early OA, thinning of the subchondral plate is directly related to cartilage damage: results from a canine ACLT-meniscectomy model. *Osteoarthr. Cartil.* **18**, 691–698 (2010).
126. Wagegg, M. et al. Hypoxia promotes osteogenesis but suppresses adipogenesis of human mesenchymal stromal cells in a hypoxia-inducible factor-1 dependent manner. *PloS One* **7**, e46483 (2012).
127. Lajeunesse, D. The role of bone in the treatment of osteoarthritis. *Osteoarthr. Cartil.* **12**, 34–38 (2004).
128. Chan, T. F. et al. Elevated Dickkopf-2 levels contribute to the abnormal phenotype of human osteoarthritic osteoblasts. *J. Bone Miner. Res.* **26**, 1399–1410 (2011).
129. Hwang, J. et al. Increased hydraulic conductance of human articular cartilage and subchondral bone plate with progression of osteoarthritis. *Arthritis Rheum.* **58**, 3831–3842 (2008).
130. Pan, J. et al. Elevated cross-talk between subchondral bone and cartilage in osteoarthritic joints. *Bone* **51**, 212–217 (2012).
131. Westacott, C. I., Webb, G. R., Warnock, M. G., Sims, J. V. & Elson, C. J. Alteration of cartilage metabolism by cells from osteoarthritic bone. *Arthritis Rheum.* **40**, 1282–1291 (1997).
132. Priam, S. et al. Identification of soluble 14-3-3ε as a novel subchondral bone mediator involved in cartilage degradation in osteoarthritis. *Arthritis Rheum.* **65**, 1831–1842 (2013).
133. Weber, A., Chan, P. M. B. & Wen, C. Do immune cells lead the way in subchondral bone disturbance in osteoarthritis? *Prog. Biophys. Mol. Biol.* **148**, 21–31 (2019).
134. Goldring, S. R. & Goldring, M. B. Changes in the osteochondral unit during osteoarthritis: structure, function and cartilage–bone crosstalk. *Nat. Rev. Rheumatol.* **12**, 632–644 (2016).
135. Fernandez-Madrid, F., Karvonen, R. L., Teitge, R. A., Miller, P. R. & Negendank, W. G. MR features of osteoarthritis of the knee. *Magn. Reson. Imaging* **12**, 703–709 (1994).
136. Hill, C. L. et al. Knee effusions, popliteal cysts, and synovial thickening: association with knee pain in osteoarthritis. *J. Rheumatol.* **28**, 1330–1337 (2001).
137. Arnoldi, C. C., Reimann, I. & Bretlau, P. The synovial membrane in human coxathrosis: light and electron microscopic studies. *Clin. Orthop. Relat. Res.* **148**, 213–220 (1980).
138. Reimann, I., Arnoldi, C. C. & Nielsen, O. Permeability of synovial membrane to plasma proteins in human coxarthrosis: relation to molecular size and histologic changes. *Clin. Orthop. Relat. Res.* **147**, 296–300 (1980).
139. Mobasheri, A., Moskaluk, C. A., Marples, D. & Shakibaei, M. Expression of aquaporin 1 (AQP1) in human synovitis. *Ann. Anat.* **192**, 116–121 (2010).
140. Toussaint, J. et al. Chronic hypertension increases aortic endothelial hydraulic conductivity by upregulating endothelial aquaporin-1 expression. *Am. J. Physiol. Heart Circ. Physiol.* **313**, H1063–H1073 (2017).
141. Sattar, A., Kumar, P. & Kumar, S. Rheumatoid-and osteo-arthritis: quantitation of ultrastructural features of capillary endothelial cells. *J. Pathol.* **148**, 45–53 (1986).
142. Rondaij, M. G., Bierings, R., Kragt, A., van Mourik, J. A. & Voorberg, J. Dynamics and plasticity of Weibel-Palade bodies in endothelial cells. *Arterioscler. Thromb. Vasc. Biol.* **26**, 1002–1007 (2006).
143. Schillemans, M. et al. Weibel-Palade body localized syntaxin-3 modulates Von Willebrand factor secretion from endothelial cells. *Arterioscler. Thromb. Vasc. Biol.* **38**, 1549–1561 (2018).
144. Ozaka, T., Doi, Y., Kayashima, K. & Fujimoto, S. Weibel-Palade bodies as a storage site of calcitonin gene-related peptide and endothelin-1 in blood vessels of the rat carotid body. *Anat. Record* **247**, 388–394 (1997).
145. Xiong, Y. et al. Hypertensive stretch regulates endothelial exocytosis of Weibel-Palade bodies through VEGF receptor 2 signaling pathways. *Cell Res.* **23**, 820–834 (2013).
146. Pinsky, D. J. et al. Hypoxia-induced exocytosis of endothelial cell Weibel-Palade bodies. A mechanism for rapid neutrophil recruitment after cardiac preservation. *J. Clin. Invest.* **97**, 493–500 (1996).
147. Kudo, H. et al. Enhanced expression of endothelin-1 and endothelin-converting enzyme-1 in acute hypoxic rat aorta. *Histol. Histopathol.* **17**, 97–105 (2002).
148. Doi, Y. et al. Histamine release from Weibel-Palade bodies of toad aortas induced by endothelin-1 and sarafotoxin-S6b. *Anat. Rec.* **242**, 374–382 (1995).
149. Nahir, A., Hoffman, A., Lorber, M. & Keiser, H. Presence of immunoreactive endothelin in synovial fluid: analysis of 22 cases. *J. Rheumatol.* **18**, 678–680 (1991).
150. Wharton, J. et al. Autoradiographic localization and analysis of endothelin-1 binding sites in human synovial tissue. *Arthritis Rheum.* **35**, 894–899 (1992).
151. Olmos, G. et al. Hyperphosphatemia induces senescence in human endothelial cells by increasing endothelin-1 production. *Aging Cell* **16**, 1300–1312 (2017).
152. Chopra, S., Baby, C. & Jacob, J. J. Neuro-endocrine regulation of blood pressure. *Indian J. Endocrinol. Metab.* **15** (Suppl. 4), S281–S288 (2011).
153. Schiffrin, E. L. Vascular endothelin in hypertension. *Vasc. Pharmacol.* **43**, 19–29 (2005).

154. Ng, L. F. et al. WNT signaling in disease. *Cells* **8**, 826 (2019).
155. Catt, K. et al. Angiotensin II blood-levels in human hypertension. *Lancet* **297**, 459–464 (1971).
156. Paul, M., Poyan Mehr, A. & Kreutz, R. Physiology of local renin-angiotensin systems. *Physiol. Rev.* **86**, 747–803 (2006).
157. Kawakami, Y. et al. Expression of angiotensin II receptor-1 in human articular chondrocytes. *Arthritis* **2012**, 648537 (2012).
158. Tsukamoto, I. et al. Expressions of local renin-angiotensin system components in chondrocytes. *Eur. J. Histochem.* **58**, 2387 (2014).
159. Wu, Y. et al. Differential expression of renin-angiotensin system-related components in patients with rheumatoid arthritis and osteoarthritis. *Am. J. Med. Sci.* **359**, 17–26 (2020).
160. Tang, Y., Hu, X. & Lu, X. Captopril, an angiotensin-converting enzyme inhibitor, possesses chondroprotective efficacy in a rat model of osteoarthritis through suppression local renin-angiotensin system. *Int. J. Clin. Exp. Med.* **8**, 12584 (2015).
161. Tsukamoto, I. et al. Activating types 1 and 2 angiotensin II receptors modulate the hypertrophic differentiation of chondrocytes. *FEBS Open Bio.* **3**, 279–284 (2013).
162. Kawahata, H. et al. Continuous infusion of angiotensin II modulates hypertrophic differentiation and apoptosis of chondrocytes in cartilage formation in a fracture model mouse. *Hypertens. Res.* **38**, 382–393 (2015).
163. Osako, M. K. et al. Cross-talk of receptor activator of nuclear factor-κB ligand signaling with renin–angiotensin system in vascular calcification. *Arterioscler. Thromb. Vasc. Biol.* **33**, 1287–1296 (2013).
164. Rattazzi, M., Bertacco, E., Puato, M., Faggin, E. & Pauletto, P. Hypertension and vascular calcification: a vicious cycle? *J. Hypertens.* **30**, 1885–1893 (2012).
165. Shimizu, H. et al. Angiotensin II accelerates osteoporosis by activating osteoclasts. *FASEB J.* **22**, 2465–2475 (2008).
166. Asaba, Y. et al. Activation of renin-angiotensin system induces osteoporosis independently of hypertension. *J. Bone Miner. Res.* **24**, 241–250 (2009).
167. Touyz, R. M. & Schiffrin, E. L. Role of endothelin in human hypertension. *Can. J. Physiol. Pharmacol.* **81**, 533–541 (2003).
168. Barton, M., Shaw, S., Moreau, P. & Lüscher, T. F. Angiotensin II increases vascular and renal endothelin-1 and functional endothelin converting enzyme activityin vivo: role of ETA receptors for endothelin regulation. *Biochem. Biophys. Res. Commun.* **238**, 861–865 (1997).
169. Böhm, F. & Pernow, J. The importance of endothelin-1 for vascular dysfunction in cardiovascular disease. *Cardiovasc. Res.* **76**, 8–18 (2007).
170. Zhao, Z., Li, E., Cao, Q., Sun, J. & Ma, B. Endothelin-1 concentrations are correlated with the severity of knee osteoarthritis. *J. Invest. Med.* **64**, 872–874 (2016).
171. Roy-Beaudry, M. et al. Endothelin 1 promotes osteoarthritic cartilage degradation via matrix metalloprotease 1 and matrix metalloprotease 13 induction. *Arthritis Rheum.* **48**, 2855–2864 (2003).
172. Manacu, C. A. et al. Endothelin-1 in osteoarthritic chondrocytes triggers nitric oxide production and upregulates collagenase production. *Arthritis Res. Ther.* **7**, R324 (2005).
173. Kaufman, G. N., Zaouter, C., Valteau, B., Sirois, P. & Moldovan, F. Nociceptive tolerance is improved by bradykinin receptor B1 antagonism and joint morphology is protected by both endothelin type A and bradykinin receptor B1 antagonism in a surgical model of osteoarthritis. *Arthritis Res. Ther.* **13**, R76 (2011).
174. Vallee, A., Levy, B. L. & Blacher, J. Interplay between the renin-angiotensin system, the canonical WNT/β-catenin pathway and PPARγ in hypertension. *Curr. Hypertens. Rep.* **20**, 62 (2018).
175. Kim, S.-J. et al. β-Catenin regulates expression of cyclooxygenase-2 in articular chondrocytes. *Biochem. Biophys. Res. Commun.* **296**, 221–226 (2002).
176. Wain, L. V. et al. Genome-wide association study identifies six new loci influencing pulse pressure and mean arterial pressure. *Nat. Genet.* **43**, 1005–1011 (2011).
177. Kuipers, A. L. et al. Wnt pathway gene expression is associated with arterial stiffness. *J. Am. Heart Assoc.* **9**, e014170 (2020).
178. Sarzani, R. et al. Carotid artery atherosclerosis in hypertensive patients with a functional LDL receptor-related protein 6 gene variant. *Nutr. Metab. Cardiovasc. Dis.* **21**, 150–156 (2011).
179. Zhou, L. et al. Multiple genes of the renin-angiotensin system are novel targets of Wnt/β-catenin signaling. *J. Am. Soc. Nephrol.* **26**, 107–120 (2015).
180. Sumida, T. et al. Complement C1q-induced activation of β-catenin signalling causes hypertensive arterial remodelling. *Nat. Commun.* **6**, 6241 (2015).
181. Cuevas, C. A., Gonzalez, A. A., Inestrosa, N. C., Vio, C. P. & Prieto, M. C. Angiotensin II increases fibronectin and collagen I through the β-catenin-dependent signaling in mouse collecting duct cells. *Am. J. Physiol. Renal Physiol.* **308**, F358–F365 (2015).
182. Corr, M. Wnt–β-catenin signaling in the pathogenesis of osteoarthritis. *Nat. Clin. Pract. Rheumatol.* **4**, 550–556 (2008).
183. Day, T. F., Guo, X., Garrett-Beal, L. & Yang, Y. Wnt/β-catenin signaling in mesenchymal progenitors controls osteoblast and chondrocyte differentiation during vertebrate skeletogenesis. *Dev. Cell* **8**, 739–750 (2005).
184. Hopwood, B., Tsykin, A., Findlay, D. M. & Fazzalari, N. L. Microarray gene expression profiling of osteoarthritic bone suggests altered bone remodelling, WNT and transforming growth factor-β/bone morphogenic protein signalling. *Arthritis Res. Ther.* **9**, R100 (2007).
185. Dell'Accio, F., De Bari, C., Eltawil, N. M., Vanhummelen, P. & Pitzalis, C. Identification of the molecular response of articular cartilage to injury, by microarray screening: Wnt-16 expression and signaling after injury and in osteoarthritis. *Arthritis Rheum.* **58**, 1410–1421 (2008).
186. Barker, N. in Wnt Signaling Volume 1: Pathway Methods and Mammalian Models (ed Vincan, E.) 5-15 (Springer, 2008).
187. Lane, N. E., Nevitt, M. C., Lui, L. Y., De Leon, P. & Corr, M. Wnt signaling antagonists are potential prognostic biomarkers for the progression of radiographic hip osteoarthritis in elderly Caucasian women. *Arthritis Rheum.* **56**, 3319–3325 (2007).
188. Min, J. et al. Association of the Frizzled-related protein gene with symptomatic osteoarthritis at multiple sites. *Arthritis Rheum.* **52**, 1077–1080 (2005).
189. Valdes, A. M. et al. Sex and ethnic differences in the association of ASPN, CALM1, COL2A1, COMP, and FRZB with genetic susceptibility to osteoarthritis of the knee. *Arthritis Rheum.* **56**, 137–146 (2007).
190. Clines, G. A. et al. Dickkopf homolog 1 mediates endothelin-1-stimulated new bone formation. *Mol. Endocrinol.* **21**, 486–498 (2007).
191. Zhang, Y. et al. Renin inhibitor aliskiren exerts beneficial effect on trabecular bone by regulating skeletal renin-angiotensin system and kallikrein-kinin system in ovariectomized mice. *Osteoporos. Int.* **27**, 1083–1092 (2016).
192. Gu, S.-S. et al. Involvement of the skeletal renin-angiotensin system in age-related osteoporosis of ageing mice. *Biosci. Biotechnol. Biochem.* **76**, 1367–1371 (2012).
193. Price, A. et al. Angiotensin II type 1 receptor as a novel therapeutic target in rheumatoid arthritis: in vivo analyses in rodent models of arthritis and ex vivo analyses in human inflammatory synovitis. *Arthritis Rheum.* **56**, 441–447 (2007).
194. Cobankara, V. et al. Renin and angiotensin-converting enzyme (ACE) as active components of the local synovial renin-angiotensin system in rheumatoid arthritis. *Rheumatol. Int.* **25**, 285–291 (2005).
195. Yan, K. & Shen, Y. Aliskiren has chondroprotective efficacy in a rat model of osteoarthritis through suppression of the local renin-angiotensin system. *Mol. Med. Rep.* **16**, 3965–3973 (2017).
196. Chan, P. et al. Role of systemic hypertension in cell senescence and subchondral bone disturbance of knee joint [abstract]. *Osteoarthr. Cartil.* **26**, S118 (2018).
197. Silveira, K. D. et al. Mechanisms of the anti-inflammatory actions of the angiotensin type 1 receptor antagonist losartan in experimental models of arthritis. *Peptides* **46**, 53–63 (2013).
198. Kwok, T. et al. Does the use of ACE inhibitors or angiotensin receptor blockers affect bone loss in older men? *Osteoporos. Int.* **23**, 2159–2167 (2012).
199. Wen, C., Yan, C. & Chiu, K. Development of osteoarthritis-like changes in transgenic endothelin-1 overexpressed mice [abstract]. *Osteoarthr. Cartil.* **22**, S363 (2014).
200. Zhao, W., Leung, V., Chiu, K., Chung, S. & Lu, W. Role of endothelin-1 in endochondral ossification and osteoarthritis [abstract]. *Osteoarthr. Cartil.* **24**, S51–S52 (2016).
201. Au, M., Liu, Z., Rong, L., Zheng, Y. & Wen, C. Endothelin-1 induces chondrocyte senescence and cartilage damage via endothelin receptor type B in a post-traumatic osteoarthritis mouse model. *Osteoarthr. Cartil.* **28**, 1559–1571 (2020).
202. Hoeppner, L. H., Secreto, F. J. & Westendorf, J. J. Wnt signaling as a therapeutic target for bone diseases. *Expert Opin. Therap. Targets* **13**, 485–496 (2009).
203. Wang, Y., Fan, X., Xing, L. & Tian, F. Wnt signaling: a promising target for osteoarthritis therapy. *Cell Commun. Signal.* **17**, 97 (2019).
204. Deshmukh, V. et al. A small-molecule inhibitor of the Wnt pathway (SM04690) as a potential disease modifying agent for the treatment of osteoarthritis of the knee. *Osteoarthr. Cartil.* **26**, 18–27 (2018).
205. Takamatsu, A. et al. Verapamil protects against cartilage degradation in osteoarthritis by inhibiting Wnt/β-catenin signaling. *PLoS One* **9**, e92699 (2014).
206. Ramsay, L. E., Silas, J. H. & Freestone, S. Diuretic treatment of resistant hypertension. *Br. Med. J.* **281**, 1101–1103 (1980).
207. Elsaman, A. M., Radwan, A. R., Mohammed, W. I. & Ohrndorf, S. Low-dose spironolactone: treatment for osteoarthritis-related knee effusion. A prospective clinical and sonographic-based study. *J. Rheumatol.* **43**, 1114–1120 (2016).
208. Youcef, G. et al. Preventive and chronic mineralocorticoid receptor antagonism is highly beneficial in obese SHHF rats. *Br. J. Pharmacol.* **173**, 1805–1819 (2016).
209. Deng, C. et al. Eplerenone treatment alleviates the development of joint lesions in a new rat model of spontaneous metabolic-associated osteoarthritis. *Ann. Rheum. Dis.* **77**, 315–316 (2018).
210. Yuan, F.-L. et al. Inhibition of acid-sensing ion channels in articular chondrocytes by amiloride attenuates articular cartilage destruction in rats with adjuvant arthritis. *Inflamm. Res.* **59**, 939–947 (2010).
211. Izumi, M., Ikeuchi, M., Ji, Q. & Tani, T. Local ASIC3 modulates pain and disease progression in a rat model of osteoarthritis. *J. Biomed. Sci.* **19**, 77 (2012).
212. TenBroek, E. M., Yunker, L., Nies, M. F. & Bendele, A. M. Randomized controlled studies on the efficacy of antiarthritic agents in inhibiting cartilage degeneration and pain associated with progression of osteoarthritis in the rat. *Arthritis Res. Ther.* **18**, 24 (2016).
213. Reuben, S. S. & Sklar, J. Intravenous regional anesthesia with clonidine in the management of complex regional pain syndrome of the knee. *J. Clin. Anesth.* **14**, 87–91 (2002).
214. Valdes, A. M. et al. Association of beta-blocker use with less prevalent joint pain and lower opioid requirement in people with osteoarthritis. *Arthritis Care Res.* **69**, 1076–1081 (2017).
215. Zhou, L., Kwoh, C., Ran, D., Ashbeck, E. & Lo-Ciganic, W.-H. Lack of evidence that beta blocker use reduces knee pain, areas of joint pain, or analgesic use among individuals with symptomatic knee osteoarthritis. *Osteoarthr. Cartil.* **28**, 53–61 (2020).
216. Garlichs, C., Zhang, H., Mügge, A. & Daniel, W. Beta-blockers reduce the release and synthesis of endothelin-1 in human endothelial cells. *Eur. J. Clin. Invest.* **29**, 12–16 (1999).
217. Uzieliene, I. et al. The antihypertensive drug nifedipine modulates the metabolism of chondrocytes and human bone marrow-derived mesenchymal stem cells. *Front. Endocrinol.* **10**, 756 (2019).
218. Abramson, S. B. Osteoarthritis and nitric oxide. *Osteoarthr. Cartil.* **16** (Suppl. 2), S15–S20 (2008).
219. Raisi-Estabragh, Z. et al. Poor bone quality is associated with greater arterial stiffness: insights from the UK Biobank. *J. Bone Miner. Res.* **36**, 90–99 (2021).
220. Saavedra, J. M. Naloxone reversible decrease in pain sensitivity in young and adult spontaneously hypertensive rats. *Brain Res.* **209**, 245–249 (1981).
221. Lewis, S. J., Meller, S. T., Brody, M. J. & Gebhart, G. Reduced nociceptive effects of intravenous serotonin (5-HT) in the spontaneously hypertensive rat. *Clin. Exp. Hypertens. A* **13**, 849–857 (1991).
222. Ring, C. et al. Effects of naltrexone on electrocutaneous pain in patients with hypertension compared to normotensive individuals. *Biol. Psychol.* **77**, 191–196 (2008).
223. Sheps, D. S. et al. Relation between systemic hypertension and pain perception. *Am. J. Cardiol.* **70**, F3–F5 (1992).

224. Bruehl, S., Chung, O. Y., Ward, P., Johnson, B. & McCubbin, J. A. The relationship between resting blood pressure and acute pain sensitivity in healthy normotensives and chronic back pain sufferers: the effects of opioid blockade. *Pain* **100**, 191–201 (2002).
225. Bruehl, S., Burns, J. W. & McCubbin, J. A. Altered cardiovascular/pain regulatory relationships in chronic pain. *Int. J. Behav. Med.* **5**, 63–75 (1998).
226. Bagge, E., Bjelle, A., Eden, S. & Svanborg, A. Factors associated with radiographic osteoarthritis: results from the population study 70-year-old people in Göteborg. *J. Rheumatol.* **18**, 1218–1222 (1991).
227. Hart, D. J., Doyle, D. V. & Spector, T. D. Association between metabolic factors and knee osteoarthritis in women: The Chingford study. *J. Rheumatol.* **22**, 1118–1123 (1995).
228. Sowers, M. et al. Association of bone mineral density and sex hormone levels with osteoarthritis of the hand and knee in premenopausal women. *Am. J. Epidemiol.* **143**, 38–47 (1996).
229. Kim, I. et al. The prevalence of knee osteoarthritis in elderly community residents in Korea. *J. Korean Med. Sci.* **25**, 293 (2010).
230. Reid, J. L. et al. Obesity and other cardiovascular disease risk factors and their association with osteoarthritis in Southern California American Indians, 2002-2006. *Ethn. Dis.* **20**, 416 (2010).
231. Inoue, R. et al. Medical problems and risk factors of metabolic syndrome among radiographic knee osteoarthritis patients in the Japanese general population. *J. Orthop. Sci.* **16**, 704–709 (2011).
232. Yoshimura, N. et al. Accumulation of metabolic risk factors such as overweight, hypertension, dyslipidaemia, and impaired glucose tolerance raises the risk of occurrence and progression of knee osteoarthritis: a 3-year follow-up of the ROAD study. *Osteoarthr. Cartil.* **20**, 1217–1226 (2012).
233. Han, C. D., Yang, I. H., Lee, W. S., Park, Y. J. & Park, K. K. Correlation between metabolic syndrome and knee osteoarthritis: data from the Korean National Health and Nutrition Examination Survey (KNHANES). *BMC Public. Health* **13**, 603 (2013).
234. Shin, D. Association between metabolic syndrome, radiographic knee osteoarthritis, and intensity of knee pain: results of a national survey. *J. Clin. Endocrinol. Metab.* **99**, 3177–3183 (2014).
235. Liu, Y. et al. Prevalence and associated factors of knee osteoarthritis in a rural Chinese adult population: an epidemiological survey. *BMC Public. Health* **16**, 94 (2015).
236. Li, H., George, D. M., Jaarsma, R. L. & Mao, X. Metabolic syndrome and components exacerbate osteoarthritis symptoms of pain, depression and reduced knee function. *Ann. Transl. Med.* **4**, 133 (2016).
237. Kim, H. S. et al. Association between knee osteoarthritis, cardiovascular risk factors, and the Framingham Risk Score in South Koreans: a cross-sectional study. *PLoS One* **11**, e0165325 (2016).
238. Xie, D.-x et al. Association between metabolic syndrome and knee osteoarthritis: a cross-sectional study. *BMC Musculoskelet. Disord.* **18**, 533 (2017).
239. Yasuda, E. et al. Association between the severity of symptomatic knee osteoarthritis and cumulative metabolic factors. *Aging Clin. Exp. Res.* **30**, 481–488 (2018).
240. Sanchez-Santos, M. T. et al. Association of metabolic syndrome with knee and hand osteoarthritis: a community-based study of women. *Semin. Arthritis Rheum.* **48**, 791–798 (2019).

Acknowledgements
The work of the authors is supported by the Research Grants Council of Hong Kong Early Career Scheme (PolyU 251008/18M) and General Research Fund (15106120), the PROCORE-France/Hong Kong Joint Research Scheme (F-PolyU504/18), the Health and Medical Research Fund Scheme (#01150087, #15161391 and #16172691), and the Project of Strategic Importance at The Hong Kong Polytechnic University (all grants awarded to C.W.).

Author contributions
The authors contributed equally to all aspects of the article.

Competing interests
The authors declare no competing interests.

Peer review information
Nature Reviews Rheumatology thanks R. Okamoto, A. Mobasheri and J.-Y. Reginster for their contribution to the peer review of this work.

QUERY FORM

Nature Reviews Rheumatology	
Manuscript ID	**650**
Author	**Karen Ching**

AUTHOR:

The following queries have arisen during the editing of your manuscript. Please answer by making the requisite corrections directly in the e.proofing tool rather than marking them up on the PDF. This will ensure that your corrections are incorporated accurately and that your paper is published as quickly as possible.

Query No.	*Nature of Query*
Q1:	References [15 and 117] are a duplicate of [6 and 29] and hence the repeated version have been deleted. Please check.
Q2:	Please check your article carefully, coordinate with any co-authors and enter all final edits clearly in the eproof, remembering to save frequently. Once corrections are submitted, we cannot routinely make further changes to the article.
Q3:	Note that the eproof should be amended in only one browser window at any one time; otherwise changes will be overwritten.
Q4:	Author surnames have been highlighted. Please check these carefully and adjust if the first name or surname is marked up incorrectly. Note that changes here will affect indexing of your article in public repositories such as PubMed. Also, carefully check the spelling and numbering of all author names and affiliations, and the corresponding email address(es).
Q5:	AU: Pease check if edits to the sentences starting 'Analytical techniques such as Mendelian randomization…' and 'Mendelian randomization deploys…' are correct.
Q6:	AU: Please check if edits to sentence starting 'Despite the strong conclusions of this study…' are correct.
Q7:	AU: Please check the part sentence '…ratio of proteins in the synovial fluid over the serum…' as this is unclear.