Caspian Journal of Internal Medicine 2025 (Autumn); 16(4): 599-620
DOI: 10.22088/cjim.16.4.599

Review Article

Bridging the gap: Exploring the intercurrent relationship between knee osteoarthritis and cerebral small vessel disease

Mazira Mohamad Ghazali (PhD) [1, 2]
Nor Farid Mohd Noor (MD, PhD) [2]
Muhamad Afiq Mahayidin (MD, PhD) [2]
Mohd Nasir Mat Nor (PhD) [2]
Che Mohd Nasril Che Mohd Nassir (PhD) [2*]

1. Department of Neurosciences, School of Medical Sciences, Universiti Sains Malaysia, 15160 Kubang Kerian, Kelantan, Malaysia
2. Department of Anatomy and Physiology, School of Basic Medical Sciences, Universiti Sultan Zainal Abidin, Medical Campus, 20400 Kuala Terengganu, Terengganu, Malaysia

*** Correspondence:**
Che Mohd Nasril Che Mohd Nassir, Department of Anatomy and Physiology, School of Basic Medical Sciences, Universiti Sultan Zainal Abidin, Medical Campus, 20400 Kuala Terengganu, Terengganu, Malaysia

E-mail:
nasrilnassir@unisza.edu.my
Tel: +60 179453568

Received: 19 June 2024
Revised: 4 Oct 2024
Accepted: 27 Nov 2024
Published: 14 Oct 2025

Abstract

Knee osteoarthritis (KOA) and cerebral small vessel disease (CSVD) are two prevalent and debilitating conditions that have traditionally been studied within distinct medical disciplines – rheumatology and neurology, respectively. However, emerging evidence suggests a deeper connection between these seemingly disparate diseases, transcending conventional boundaries and prompting a paradigm shift in our understanding of their pathophysiology and clinical implications. This narrative review explores the multifaceted crosstalk between KOA and CSVD, delving into shared risk factors, inflammatory cascades, and vascular mechanisms underpinning their co-occurrence. Beyond conventional etiological factors, we illuminate the role of systemic inflammation, aberrant biomechanics, and neuro-gliovascular interactions in shaping the complex interplay between KOA and CSVD. Furthermore, we scrutinize the bidirectional impact of these conditions on cognitive function, emphasizing the shared burden of neurocognitive impairment in affected individuals. Through a synthesis of cutting-edge research and theoretical frameworks, we propose a novel conceptual model that integrates musculoskeletal and cerebrovascular pathways, shedding light on previously unexplored avenues for therapeutic intervention and personalized management strategies. This comprehensive analysis not only advances our understanding of the interconnected nature of KOA and CSVD but also underscores the imperative for interdisciplinary collaboration and holistic approaches to patient care in the era of precision medicine.

Keywords: Knee osteoarthritis, Cerebral small vessel disease, Mechanistic crosstalk, Risk factors, Microvascular dysfunction.

Citation:
Mohamad Ghazali M, Mohd Noor NF, Mahayidin MA, Mat Nor MN, Che Mohd Nassir CMN. Bridging the gap: Exploring the intercurrent relationship between knee osteoarthritis and cerebral small vessel disease. Caspian J Intern Med 2025; 16(4): 599-620.

Knee osteoarthritis (KOA) and cerebral small vessel disease (CSVD) have long been considered independent entities in medicine, each falling within the purview of a different speciality rheumatology and neurology, respectively. However, as our awareness of these situations grows, compelling evidence emerges, crossing disciplinary borders and challenging traditional thinking. Emerging evidence reveals a fundamental link between KOA and CSVD, revealing a complex web of similar pathophysiological mechanisms and clinical implications that require our attention and investigation (1, 2). Conventionally, osteoarthritis (OA) i.e., KOA and CSVD, were thought to be musculoskeletal and cerebrovascular system illnesses, however, they are now regarded as nodes in a network of linked processes (3). Hence, this narrative review seeks to explain the complex interplay between these seemingly distinct illnesses, providing a thorough examination of their common risk factors, inflammatory cascades, and vascular complexities. As we dive deeper, it becomes clear that the junction of KOA and CSVD is more than just a coincidence, indicating a convergence of pathogenic pathways that influence their co-occurrence and clinical outcomes (2, 4). At the centre of this narrative review, is a confluence of cutting-edge research and theoretical frameworks, which may shed new light on the etiological landscape of KOA and CSVD.

While classic etiological factors have long been investigated (1) , our focus goes beyond the apparent, giving light to the critical role of systemic inflammation, abnormal biomechanics, and complex neuro-gliovascular connections. By combining these varied perspectives, we can gain a better understanding of the intricate interplay between KOA and CSVD, paving the way for novel therapeutic methods and tailored management techniques. Furthermore, as we move through this terrain, it becomes clear that KOA and CSVD do not exist in isolation. Rather, they have a bidirectional influence on one another, having ramifications that go beyond the boundaries of their respective areas. Our review will focus on the influence of these disorders on cognitive performance, emphasizing the shared burden of neurocognitive impairment among affected individuals (5). This realization emphasizes the importance of a comprehensive strategy for patient care one that acknowledges the linked nature of KOA and CSVD and encourages interdisciplinary teamwork in the quest for optimal results. Therefore, in this narrative review, we seek to not only solve the mystery of KOA and CSVD but also to advocate for a paradigm shift in our approach to these disorders. We hope to increase our understanding of the interconnectedness of musculoskeletal and cerebrovascular pathways by integrating diverse strands of information and envisioning a unique paradigm that unifies them, paving the door for more successful therapeutic options. As we approach a new era in medicine, marked by the promise of precision and customized care, the insights gained from this narrative review serve as a siren cry for interdisciplinary collaboration and a reworking of traditional paradigms.

KOA: Definition, Risk factors, and classification

Osteoarthritis (OA) is the most common chronic inflammatory joint disease, which causes chronic diseases and disabilities because of pathological changes such as synovial inflammation, cartilage degradation, subchondral bone modifications, and musculoskeletal disability (6). Although OA can affect numerous joints, including the shoulder, elbow, wrist, spine, hip, knee, and ankle, the knee joint is one of the most prevalent and vulnerable (7). OA, particularly KOA, is a significant health concern, impacting millions globally (8). Whereby it is characterized by progressive joint degeneration that affects the cartilage in the knee. Cartilage is a smooth elastic tissue that cushions the bones where they meet in the joint. In KOA, this cartilage wears down over time leading to pain, stiffness, and functional limitations. Currently, there are two main types of KOA i.e., primary, and secondary. Primary KOA refers to joint degeneration that occurs without a known cause, whereas secondary KOA develops due to abnormal forces on the joint, like those from past injuries, or because of an unhealthy cartilage structure, as seen in rheumatoid arthritis. Established risk factors that contribute to the development of KOA, include ageing, obesity, or body mass index (BMI) status, female gender, high physical job demands, and previous injury (9–11). However, age is the biggest risk factor, as we get older, cartilage naturally breaks down. Besides, cartilage damage is accelerated due to being overweight or obese which puts pressure on the knee joint. Gender-wise, women are generally more affected by KOA than men (12) which can lead to functional limitations and decreased health-related quality of life (13). Additionally, occupations that put a lot of stress on the knee can increase the risk of KOA. However, inactivity is also a risk factor because the cartilage needs less stress to stay healthy. A knee injury, such as a torn anterior cruciate ligament or torn meniscus, can increase the risk of developing KOA later in life (14).

Although not all individuals with these risk factors will always develop KOA, reducing the probability of this condition includes keeping a healthy weight, exercising to strengthen muscles that support the knee, and avoiding activities that put strain on the knee. Moreover, vitamin D deficiency has been linked to KOA, indicating that low serum levels of vitamin D may serve as a risk factor for the progression of KOA (15).

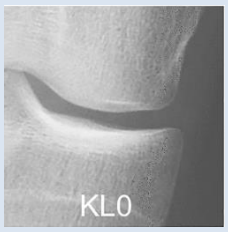
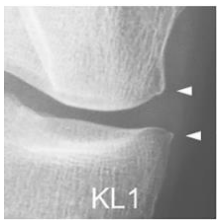
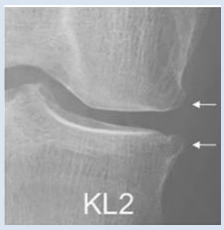
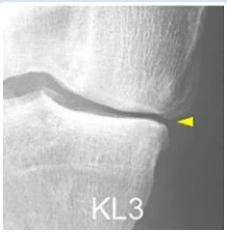
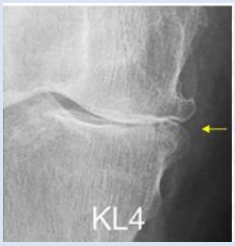
The diagnosis of KOA needs to be confirmed based on clinical and/or radiological features. Whereby, plain radiography is still the gold standard for diagnosing KOA. Kellgren and Lawrence described the first formalized attempts to establish a radiographic classification scheme for OA in 1957 (16). The Kellgren and Lawrence (KL) system is a common method of classifying the severity of OA using five grades from 0 to 4 (table 1). The classification was originally described using anterior-posterior knee radiographs.

Current epidemiology of KOA

KOA is a common chronic condition that becomes more prevalent due to population ageing and an increase in related factors such as obesity. Its incidence is reported to vary across different geographical locations (18). KOA is common among the elderly in the United States, Europe, the Middle East, and Asia, with prevalence rates ranging from 13-20 % (19), 9–17 % (20), 22- 25 % (21), and 10- 38 % (22) respectively. Due to a combination of risk factors, Southeast Asia such as Malaysia is also seeing an increase in the prevalence of OA. Obesity and age are two main factors that increase the risk of OA, and both are becoming more common in Malaysia. In 2019, the percentage of the Malaysian population aged ≥65 years was estimated at 6.7%

out of 32.6 million people; by 2040, that number is expected to rise to 14.5 % (23). Knee pain was reported by 33.2% of 1212 study participants in a cross-sectional survey from the Malaysian Elders Longitudinal Research (MELoR) research (24). The prevalence of overweight and obesity in Malaysia was 30.4 % and 19.7 %, respectively, according to the 2019 Malaysian National Health and Morbidity Survey (25). Moreover, recent studies have shown that the frequency of KOA in Asian people ranges from 13.1-71.1% in various Asian nations, where OA is mostly associated with risk factors such as obesity, female gender, and advanced age (26, 27).

Table 1. Numerous variations of the Kellgren and Lawrence (KL) classification system described using anterior-posterior knee radiographs (16, 17)

Grade	Figure	Description
Grade 0 (None)		• Definite absence of X-ray changes of OA
Grade 1 (Doubtful)		• Doubtful joint space narrowing and possible osteophytic lipping
Grade 2 (Minimal)		• Definite osteophytes and possible joint space narrowing
Grade 3 (Moderate)		• Moderate multiple osteophytes, definite narrowing of joint space and some sclerosis, and possible deformity of bone ends
Grade 4 (Severe)		• Large osteophytes marked narrowing of joint space, severe sclerosis, and definite deformity of bone ends.

Current knowledge of the pathomechanism of KOA

KOA is a complex disorder characterized by articular cartilage degeneration, synovial inflammation, and underlying bone remodelling (28). Although traditionally viewed as "wear and tear", the understanding of the pathological mechanisms of KOA has advanced significantly (29). KOA can be initiated by a combination of mechanical and biological factors. The abnormal joint loading due to age, obesity, misalignment (e.g. varus or valgus knee), or past injury can put pressure or stress on the

cartilage, potentially triggering its degeneration (30). Low-grade synovial inflammation is now recognized as a hallmark of KOA (31). Pro-inflammatory mediators such as cytokines and chemokines are released, actively contributing to cartilage damage and pain sensation (32). This understanding has led to the exploration of anti-inflammatory drugs as a potential therapeutic approach for the management of KOA. It is important to distinguish this from an acute event that occurs after injury, as KOA injuries are chronic and low-grade processes. Moreover, the involvement of the subchondral bone below the cartilage plays an important role in KOA. Microfractures, increased bone density, and altered blood flow in this region can cause pain and further cartilage degeneration (33). The overall health of the joint environment is very crucial. The synovial fluid, ligaments, and meniscus all work together to maintain joint stability and lubrication. Meniscus and ligaments can become damaged due to mechanical stress or instability, leading to abnormal joint mechanics and accelerated cartilage wear. Dysfunction in any of these tissues can contribute to the development and progression of KOA (34). There is significant individual variability in how KOA develops. Genetic predisposition, metabolic factors, and even the composition of the gut microbiome can influence the causes of this disease (35–37). Therefore, KOA is a multifaceted disease with a complex interplay between mechanical stress, inflammation, and even biological processes (figure 1). Although important steps have been made in understanding its pathomechanisms, further studies are needed to develop more targeted and effective treatments.

Cerebral small vessel disease (CSVD)

CSVD is responsible for approximately 25% of ischemic strokes, most intracerebral hemorrhage in individuals over the age of 65, as well as the primary cause of vascular dementia and Alzheimer's disease (38, 39). Recent study also has linked CSVD with vascular Parkinsonism (40). Additionally, it is linked to issues with mobility, gait, neurocognitive functions, and mood disorders (39). The pathophysiological foundation of CSVD encompasses alterations in the structure and function of the microvasculature within the deep subcortical regions. These alterations primarily affect arteries, including tributaries of the middle cerebral artery, and arterioles, resulting in phenomena such as fibrinolysis, lipohyalinosis, necrosis, and microthrombosis leading to cerebral white matter disease and brain infarcts (41, 42). Various etiopathogenic classifications exist for CSVD. Nevertheless, the most widely acknowledged categories of CSVD include amyloidal CSVD (e.g., sporadic, and hereditary cerebral amyloid angiopathy) and non-amyloidal CSVD, which encompasses age-related and small vessel disease related to vascular risk factors (such as arteriolosclerosis and ageing) (38). Meanwhile, the less prevalent categories of CSVD encompass inherited or genetic (monogenic) CSVD, which exhibits distinct characteristics separate from cerebral amyloid angiopathy for example, Fabry's disease and cerebral autosomal dominant arteriopathy with subcortical ischemic strokes and leukoencephalopathy (CADASIL), as well as inflammatory and immunologically-mediated CSVD, venous collagenases, and other forms of CSVD, including non-amyloid micro-vessel degeneration in Alzheimer disease and post-radiation angiopathy (43). Various pathomechanism and molecular cascades have been proposed for the onset and progression of CSVD, and most of them are intercurrent in the majority if not all categories of CSVD.

Risk factors and current epidemiology

White matter disease in CSVD is more common with ageing, i.e., rising from 5% at age 50 to over 100% at age 90 (44). Moreover, a 1999 study found that Black Americans had a greater incidence of lacunar infarcts; however, this finding has not been replicated (45). Alarmingly, it is reported that, for every symptomatic stroke, there are approximately ten silent (asymptomatic) brain infarctions (46). The incidence of silent cerebral ischemia ranges from 8 to 31% and rises with age (41). On the other hand, in individuals with silent cerebral infarctions, the risk of future symptomatic stroke increases threefold, regardless of other risk factors (47). Cerebral microbleeds (CMBs) are similarly substantially related to increasing age, with varying prevalence rates ranging from 4.7 to 24.4%, primarily due to disparities in the sensitivity of imaging modalities and CMB classifications (47).

According to a systematic review and meta-analysis, the incidence of intracerebral hemorrhage (ICH) in people born between 1980 and 2008 was estimated to be 24.6 in White people, 22.9 in Black people, 19.6 in Hispanic people, and 51.8 in Asian people per 100,000 people (48). At one month, case fatality was almost 40%; this result remained relatively constant throughout the twenty-eight-year assessment. The relative risk for spontaneous ICH doubles with every ten years increase in age, making age one of the main risk factors (49). Given that men are regularly found to have a higher risk of ICH than women, gender is another important risk factor for ICH. There is a large overlap between the modifiable risk factors for ischemic stroke and ICH resulting from CSVD. Modifying these risk factors is more effective in lowering the risk of ICH than it is for other ICH etiologies, such as cerebral amyloid angiopathy (50).

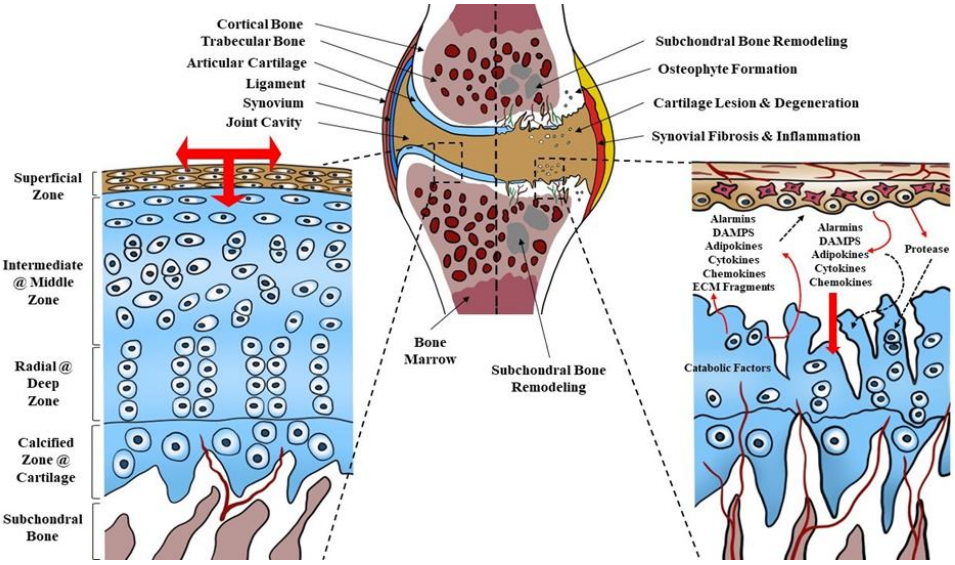


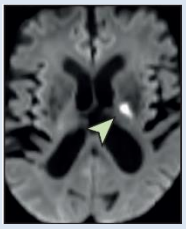
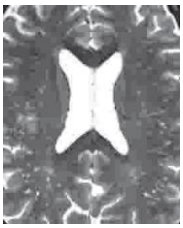
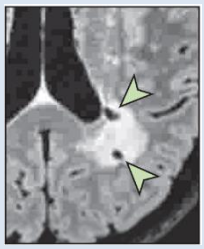
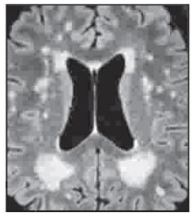
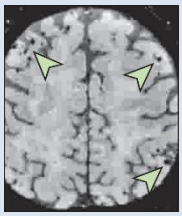
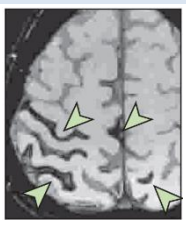
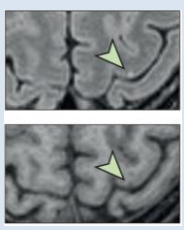
Figure 1. Pathophysiology of knee osteoarthritis (KOA). Comparison between a normal and diseased joint. Healthy articular cartilage (Left): Chondrocytes can survive in a hypoxic environment due to the absence of capillaries in cartilage. The survival and function of chondrocytes depend on hypoxia. To maintain cartilage homeostasis, cartilage's primary job is the absorption and removal of mechanical load. Osteoarthritis articular cartilage (right): The formation of arteries, also known as vascular channels, is thought to help the cartilage and bone communicate biochemically (e.g., by producing cytokines, chemokines, and alarmins). It starts a destructive cycle of cartilage deterioration. (DAMPs) damage-associated molecular pattern molecules; ECM, extracellular matrix.

Additionally, the risk factor most traditionally linked to CSVD is hypertension. However, other common vascular risk factors, such as diabetes mellitus, high cholesterol, and tobacco use, probably also play a role. However, in recent decades, there has been a drop in CSVD among populations along with advancements in vascular risk factor control (51). Additionally, roughly 20% of CSVD cases are thought to be caused by genetic or hereditary risk factors (52). Moreover, vascular cognitive impairment and dementia can result from the burden of CSVD when modifiable risk factors are left unchecked and cause chronic vascular brain injury. Finally, frequent cardio-cerebrovascular risk factors for sporadic CSVD, including ageing, type 2 diabetes (T2DM), hypertension, smoking, and dyslipidaemia, elevate the risk of pathological alterations in arteries and arterioles, potentially resulting in vessel blockage, which in turn leads to the development of arteriosclerosis and arteriolosclerosis (42), hence CSVD. To date, dementia resulting from CSVD, commonly known as "vascular dementia," is more common with ageing and accounts for 15% to 20% of all dementia (53). After Alzheimer's disease, vascular dementia is the second most frequent cause of dementia. Although the incidence of vascular dementia is not directly influenced by race or ethnicity, racial differences in cardiovascular and cerebrovascular risk factors have been shown to exist (54) . In a cohort study that sought to trace an association between the prevalence of vascular risk factors in midlife and the incidence of dementia 25 years later (55), the prevalence of hypertension (56% versus 27%) and T2DM (18% versus 7%) was found to be twice as high among Black individuals compared to White individuals. Risk factors linked to dementia include Black race, older age, low educational attainment, APOE ε4 genotype, midlife smoking, diabetes, prehypertension, and hypertension (55). Therefore, the strength of the connection between CSVD risk factor presence and dementia incidence was equal across ethnic groups, indicating that the frequency of modifiable risk factors may have a greater influence on incident CSVD-mediated dementia than race.

Neuroimaging manifestation of CSVD

CSVD is a condition that becomes increasingly prevalent with age and is frequently encountered as an incidental discovery during neuroimaging. This condition is frequently underestimated by healthcare professionals because of its covert (silent) nature, as it often presents without symptoms. Current neuroimaging indicators (or manifestation) of CSVD based on Standards for Reporting Vascular Changes on Neuroimaging 2 (STRIVE-2) have encompassed recent small subcortical infarcts, white matter hyperintensities (WMHs) of presumed vascular origin, lacune infarcts (of presumed vascular origin), enlarged perivascular spaces (ePVS), cerebral microbleed, cortical superficial siderosis, brain atrophy, and cortical cerebral microinfarct (56) (table 2).

Table 2. Neuroimaging (i.e., magnetic resonance imaging, MRI) manifestations for cerebral small vessel disease based on Standards for Reporting Vascular Changes on Neuroimaging 2 (STRIVE-2) (56)

Manifestation	MRI	Description
Recent small subcortical infarct		• Typical diameter: ≤ 20 mm • Increased signal intensity on DWI, FLAIR, and T2-weighted images. • Decrease signal intensity on T1-weighted image. • Iso-intense on T2*-weighted image. • Best seen on DWI.
Enlarged Perivascular Space (EPVS)		• Typical diameter: ≤ 2 mm • Iso-intense on DWI, and T2*-weighted image. Sometimes iso-intense is seen in FLAIR. • Increase signal intensity on T2-weighted image. • Decrease signal intensity on T1-weighted, sometimes in FLAIR. • Best seen on T2-weighted image.
Lacune		• Typical diameter: 3 – 15 mm • Iso-intense on DWI and T2*-weighted image. • Decrease intensity on FLAIR and T1-weighted image, sometimes on DWI. • Increase intensity on T2-weighted image. • Best seen on FLAIR
White matter hyperintensity (WMHs)		• Typical diameter: variable • Iso-intense on DWI and T1-weighted image. • Decrease intensity on T1-weighted image. • Increase intensity on FLAIR, T2-weighted and T2*-weighted image. • Best seen on FLAIR
Cerebral microbleed (CMBs)		• Typical diameter: ≤ 10 mm • Iso-intense on DWI, FLAIR, T2- and T1-weighted image. • Decrease intensity on T2*-weighted image. • Best seen on T2*-weighted image and SWI.
Cortical superficial siderosis		• Typical diameter: variable • Iso-intense on DWI, FLAIR, T2- and T1-weighted image. • Decrease intensity on T2*-weighted image. • Best seen on T2*-weighted image and SWI.
Cortical cerebral microinfarcts		• Typical diameter: < 4 mm • Iso-intense on DWI and T2*-weighted image. • Increase intensity on FLAIR, T2-weighted image. • Decrease intensity on T1-weighted image, sometimes on FLAIR (referred to as acute) • Best seen on T1- and T2-weighted images.

Recent knowledge of pathomechanism of CSVD

Although there has been an increasing understanding gained from histopathological, epidemiological, physiological, and neuroimaging research, the exact underlying mechanisms of CSVD still require further investigation. In general, it is widely recognized that the pathomechanism of cerebrovascular disease linked to hypertensive alterations in the vasculature leads to the formation of arteriosclerosis or lipohyalinosis (thickening and/or damage to the walls of arterioles), fibrohyalinosis, and the subsequent blockage of cerebral penetrating arteries (47). These pathologies are believed to relate to the CSVD manifestation and the increased growth of connective tissue fibres. This, in turn, leads to a decline in vascular contractility before advancing into vascular and/or microvascular sclerosis. Apart from that, pathological alterations associated with CSVD may occur when a small cerebral vessel becomes blocked due to age-related arteriolar contortion, venous collagenases, demyelination, and glial cell loss (57). These changes can be exacerbated by inflammaging, a concept that has been introduced recently to characterize age-related, persistent, low-grade inflammation that arises because of extended immune system activity (58). These enduring effects encompass a range of molecular and cellular mechanisms, including dysfunction in mitochondria, imbalance in gut microbiota, meta-inflammation, immunosenescence, and cellular senescence. Therefore, it can be argued that inflammaging may potentially encompass various other factors tied to DNA repair, the release of pro-inflammatory cytokines, and stem cell senescence (58). Regarding cerebral blood flow, a recent study utilizing arterial spin labelling-based imaging has made it possible to establish a correlation between cerebral blood flow values and the extent of CSVD manifestations such as WMHs. This correlation can potentially serve as a biomarker for assessing vascular cognitive impairment in cases of CSVD (59).

Additionally, the breakdown of the blood-brain barrier (BBB) can be exacerbated by an accompanying hypercoagulation i.e., an increase in the deposition of blood components, notably platelets, whose activation also plays a role in the formation of microthrombi associated with arteriosclerosis and/or arteriolosclerosis (60). Furthermore, upon receiving an inflammatory signal, damaged endothelial cells release von Willebrand factors (vWF), thereby enhancing the platelets' ability to activate and adhere to vWF. Activated platelets also increase the production of soluble vasoconstrictive compounds like thromboxane A_2 or B_2 and adenosine diphosphate. This synthesis occurs after platelet binding to plasma fibrinogen (61). These substances trigger platelet activation and the aggregation of platelets and monocytes. Thus, these events have been employed as indicators for the initiation and progression of arteriosclerosis and/or arteriolosclerosis, contributing to the formation of microthrombi, which in turn lead to the manifestation of CSVD (61). These pathophysiological reactions result in additional insult to the cerebral tissue, leading to various issues such as axonal injury, neuronal apoptosis, demyelination, and damage to oligodendrocytes. This damage gives rise to clinical symptoms and a range of complex neuroimaging manifestations, including silent or occult CSVD (62). However, it is worth noting that a significant portion of current therapeutic understandings appears to be derived from the pathomechanisms of sporadic CSVD. These mechanisms involve molecular and cellular outcomes related to several systemic dysregulations, including coagulopathy, heightened microthrombosis, increased cellular activation, inflammation, and oxidative stress. Some or all of these processes can lead to microstructural changes in cerebral parenchyma, which are well-known characteristics of CSVD. These changes encompass endothelial dysfunction, alterations in cerebral blood flow, and the impairment of the BBB (62).

KOA and CSVD – Emerging links and risk factors

Interesting similarities can be seen from two different conditions which are anatomically location distance away: CSVD in the brain and KOA in the knee. As discussed CSVD is a spectrum affecting the small vessels of the brain cerebrum which is commonly associated with multi-factors such as ageing, hypertension, T2DM, obesity, smoking and inflammatory processes. On the other hand, KOA is an alteration of joint tissue anatomy and physiologically which includes degradation of the cartilage of the joint and osteophyte formation (63). Both KOA and CSVD share several common shared risk factors (figure 2) as mentioned above and contribute to the development and progression of both conditions.

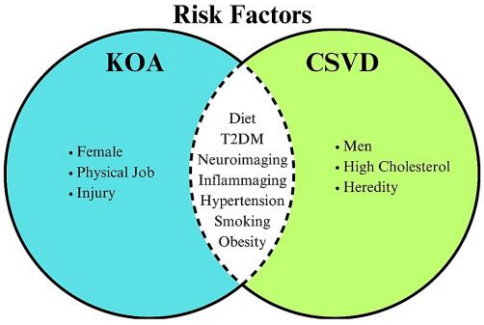


Figure 2. Shared Risk Factors between knee osteoarthritis (KOA) and cerebral small vessel disease (CSVD). T2DM, type 2 diabetes mellitus

Ageing

In addition to diagnosis, neuroimaging parameters are critical for monitoring the progression of CSVD over time. They not only aid in assessing disease advancement but also help evaluate the effectiveness of treatment and the potential for preventing further deterioration. Age is a significant factor influencing CSVD, particularly its impact on the brain. A study in adults over 60 years old (mean age 71.2 years) with a follow-up of 3 to 6 years demonstrated that men in the middle-to-older age group experienced faster progression of CSVD, as evidenced by increased WMHs and reduced grey matter and ventricular volumes (64). Additional risk factors, such as smoking and alcohol consumption, may also contribute to the rapid progression observed in men, though these require further investigation. The deterioration in CSVD can significantly worsen the patient's condition, potentially leading to mortality. A 5-year follow-up study of patients over 50 found an 8.4% mortality rate in those with advanced, untreated CSVD (65), with neuron degeneration and circulatory disorders like hemorrhagic stroke likely contributing to these outcomes. The accelerated progression of CSVD in older adults may also be linked to neurodegenerative processes, such as brain atrophy (64). Similarly, ageing plays a crucial role in the progression of KOA. Lysosomal dysfunction and mitochondrial degradation are primary drivers of age-related cartilage damage, which leads to joint degeneration. Although cartilage and neurons originate from different tissue types, both are highly susceptible to age-related cellular damage, including oxidative stress and impaired autophagy (66).

This common vulnerability opens the door to further exploration of how cellular mechanisms, like mitochondrial dysfunction, affect both KOA and CSVD. Ageing thus plays a central role in both KOA and CSVD, driving degenerative changes in distinct but interconnected tissues, cartilage in KOA and small cerebral vessels in CSVD. Neuroimaging is essential for tracking CSVD progression, particularly as WMHs and grey matter atrophy become more pronounced in older adults. Similarly, KOA progression is marked by cartilage deterioration due to lysosomal and mitochondrial dysfunction. Although these tissues are histologically different, both conditions share similar age-related processes, such as oxidative stress and autophagy impairment, which exacerbate degeneration. This shared vulnerability to ageing suggests a common pathway in both conditions, with mitochondrial dysfunction emerging as a key contributor. Future research is needed to identify the specific enzymes and inflammatory mediators that drive these degenerative processes, offering potential therapeutic targets to slow the progression of both KOA and CSVD.

Hypertension and type 2 diabetes mellitus (T2DM)

Diabetes mellitus is primarily a disorder related to pancreatic dysfunction and glucose regulation, while hypertension affects the cardiovascular system, specifically the heart and blood vessels. Although these conditions have distinct pathological pathways, they frequently coexist in patients. Research has found that primary hypertension, which has no identifiable cause, is more strongly associated with CSVD than secondary hypertension, which is typically linked to other organ dysfunctions, such as the kidneys (58, 67). This suggests that primary hypertension may share a common underlying etiology with CSVD, whereas secondary hypertension may follow a different pathological mechanism concerning CSVD.

Exploring the root causes of primary hypertension could therefore provide valuable insights into the origins of CSVD. The pathogenesis of hypertension-related circulatory disorders is closely tied to vascular damage, particularly the disruption of the inner lining of blood vessels. This endothelial damage, which contributes to CSVD, may lead to the breakdown of the BBB (58). Interestingly, a similar mechanism might be at play in KOA. Studies suggest a stronger correlation between hypertension and radiographic KOA, likely due to reduced blood flow to the bones, which mirrors the vascular dysfunction seen in CSVD (68, 69). This suggests impaired circulation could be a common factor linking CSVD and KOA. Another significant factor to consider is T2DM, which is believed to influence KOA through abnormal cellular metabolism and insulin resistance (69). Additionally, research shows that hemoglobin A1C (HbA1c) levels, a marker of long-term glucose regulation, are significantly elevated in CSVD patients (mean 5.99%), with 22% of CSVD patients showing elevated fasting blood glucose levels compared to 12% of those without CSVD (70). This further highlights the intersection of metabolic and vascular disorders in both conditions. In conclusion, while diabetes mellitus and hypertension follow different pathophysiological pathways, they often coexist in patients and contribute to both CSVD and KOA. Primary hypertension, in particular, has a notable correlation with CSVD, suggesting a shared etiology. The vascular damage caused by hypertension, including endothelial dysfunction and BBB disruption, may have parallels in the development of KOA. Additionally, the influence of T2DM and elevated HbA1c levels in CSVD patients underscores the connection between metabolic and vascular disorders, presenting avenues for further research into shared mechanisms driving these conditions.

Obesity and smoking

Obesity is strongly associated with lipid profile disorders, which contribute to numerous health problems, including cardiovascular disease. According to the World Health Organization (WHO), one in eight people worldwide suffered from obesity in 2022. Since 1990, the global rate of adult obesity has more than doubled, while teenage obesity has quadrupled. In 2022, 2.5 billion adults (aged 18 and above) were overweight, with 890 million classified as obese. Of all adults, 16% were obese, and 43% of overweight individuals. Additionally, 37 million children under the age of five and 390 million children and teenagers (aged 5 to 19) were overweight, with 160 million of them considered obese (71). Obesity in the modern world is closely linked to abnormal BMI and poor glucose management, such as in diabetes mellitus. A study of Chinese patients over the age of 45 found that those with CSVD had higher low-density lipoprotein levels and BMI (26.82 kg/m²) than those without CSVD (70). The pathogenesis of CSVD related to lipids may involve the penetration of lipid molecules into the arterial walls, contributing to vascular damage (70).

Obesity also has a direct impact on the knees due to increased weight-bearing activity, which can accelerate the development of KOA. Approximately 79.6% of stage II/III obese patients undergo treatment for KOA-related pain, compared to a much lower rate in non-obese patients (72). This suggests that circulatory disturbances due to lipid disorders may contribute similarly to both KOA and CSVD. Additionally, smoking remains a global issue, with substantial research linking it to the development of CSVD (73–75). Smokers have a 2.089 times higher incidence of KOA compared to non-smokers (76). Smoking behaviour is typically categorized into two groups: current smokers, who tend to have lower BMI, and those who have quit smoking, who often experience weight gain and a higher likelihood of developing KOA (76). Both CSVD and KOA have a significant association with smoking, highlighting the importance of addressing this risk factor in the management of both conditions.

Inflammatory pathway

The intricate interplay among various inflammatory mediators and cellular mechanisms characterizes the concurrent inflammatory pathways of CSVD and KOA, highlighting their significant interconnection. Inflammation is a crucial factor in the development of KOA, where pro-inflammatory cytokines, including interleukins (IL)-1 and IL-6, as well as tumour necrosis factor-alpha (TNF-α), are released by chondrocytes, synoviocytes, and infiltrating immune cells in response to mechanical stress or joint injury (28). These cytokines drive the destruction of cartilage and extracellular matrix components in the joint, stimulating the production of matrix metalloproteinases and other catabolic enzymes. They also promote the expression of inflammatory mediators, such as nitric oxide (NO) and prostaglandins, which exacerbate pain and lead to further tissue damage. This inflammatory cascade perpetuates the cycle of osteophyte formation, synovitis, and cartilage degradation characteristic of osteoarthritis (28, 30, 32). Interestingly, the mechanisms of inflammation and tissue damage in KOA are mirrored in CSVD. Prolonged inflammation in the cerebral vasculature results in microvascular damage and vascular dysfunction, highlighting a shared pathological landscape. Key features of endothelial dysfunction, including increased expression of adhesion molecules and decreased NO production, trigger the recruitment and activation of inflammatory cells, such as macrophages and leukocytes (77, 78). These immune cells further exacerbate endothelial damage and promote atherosclerosis and arteriolosclerosis through the release of additional pro-inflammatory cytokines and reactive oxygen species (79).

The resultant narrowing and stiffening of small cerebral vessels impair cerebral blood flow regulation and elevate the risk of microinfarcts, white matter lesions, and ischemic injury (80). Collectively, these factors contribute to cognitive decline and vascular dementia (81). Vitamin D deficiency has been implicated in both KOA and CSVD. Low serum levels of vitamin D are associated with increased inflammatory markers and may exacerbate joint pain and cartilage degeneration in KOA (15, 82). In CSVD, vitamin D deficiency is linked to endothelial dysfunction and an increased risk of vascular complications (83). Moreover, vitamin D is known to regulate the expression of several cytokines, including IL-10 (anti-inflammatory) and TNF-α (pro-inflammatory), suggesting that maintaining adequate vitamin D levels may mitigate some of the inflammatory processes common to both KOA and CSVD.

Moreover, the relationship between KOA and CSVD is further underscored by their shared risk factors, such as obesity, diabetes, and hypertension, which exacerbate inflammation in both conditions. The systemic inflammation arising from KOA may potentially affect cerebral circulation, leading to the development or worsening of CSVD. Conversely, the vascular dysfunction associated with CSVD may impair blood flow to the knee joint, aggravating KOA symptoms. This interconnectedness emphasizes that the two conditions should not be viewed in isolation; rather, they are part of a broader spectrum of degenerative diseases that may impact patient outcomes.

Overall, the interactions among cytokines, inflammatory cells, and vascular dysfunction highlight the complex inflammatory pathways shared by both CSVD and KOA. This emphasizes inflammation as a major pathological factor in both conditions and points to potential targets for future therapeutic interventions aimed at restoring tissue homeostasis and modulating inflammatory signalling. Addressing these interconnected pathways may lead to improved management strategies for patients suffering from both KOA and CSVD.

Shared imaging findings

WMHs are frequently seen on brain MRI images in patients with CSVD and are a sign of demyelination and tiny vessel damage in the brain. A recent study using multimodal MRI has indicated KOA patients have brain structural and functional abnormalities i.e., reduced grey matter volume compared to healthy control (84). This was later supported by another research that indicated a possible connection between brain microvascular dysfunction and OA-related joint pathology by linking KOA to the higher prevalence and severity of WMHs (85). Hence, patients with CSVD and KOA who also have WMHs may have a common underlying vascular pathology that plays a role in the onset and course of their respective illnesses.

Besides, lacunar infarcts i.e., a hallmark of CSVD, are tiny, deep brain lesions brought on by the blockage of tiny perforating arteries. According to previous study research, those with KOA had a higher frequency of lacunar infarcts than people without the condition (86). Although lacunar infarcts are mainly linked to CSVD, there is mounting evidence that supports the link to OA (87, 88) for example KOA. Hence, patients with KOA who also have lacunar infarcts may have similar risk factors or vascular anomalies that contribute to both disorders. Furthermore, small patches of hemosiderin deposition brought on by blood extravasation are known as CMBs, and they are frequently linked to CSVD. According to recent studies, there may have been a link between CMBs and KOA (87), especially in those with more advanced OA and extensive joint disease. Thus, CMBs observed in patients with both CSVD and KOA may indicate a possible involvement of vascular dysfunction and disruption of the BBB in the pathophysiology of these disorders. Moreover, although MRIs are the main diagnostic tool for KOA, alterations in bone and cartilage may also have effects outside of the joint. Studies have shown correlations between the severity of KOA, as measured by osteophyte production and cartilage degradation, and WMH volume or cognitive decline in the elderly, pointing to possible systemic implications of OA-related joint pathology (89). Besides, multiple studies have linked KOA and brain structure and function, utilizing advanced MRI techniques such as diffusion tensor imaging and functional MRI (fMRI) (85, 90). These results may emphasize the need for additional research into the processes behind the correlation between structural alterations associated with KOA and findings from brain imaging. Therefore, the imaging similarities between CSVD and KOA point to a possible interaction between joint degeneration, neurocognitive outcomes, and vascular pathology. To clarify the exact mechanisms behind these relationships and their significance for therapeutic care, more research is required.

Role of inflammaging in KOA and CSVD

Another concept that may help explain the relationship between CSVD and KOA is inflammaging. Inflammaging is a concept where during the ageing process, there is a chronic, sterile, low-grade inflammation developed that is greatly involved in age-related diseases (91). It is a result of long-term chronic physiological stimulation of the innate immune system that can potentially cause damage during ageing. The ageing process has been shown to cause a constant increase in pro-inflammatory status based on innate and adaptive immune systems (92). Inflammaging at its initial stage is thought to be neither harmful nor beneficial, but it can be harmful if it progresses in a maladaptive manner. Inflammaging seems to be closely related to the metabolic inflammation that occurs in metabolic diseases. It also has been suggested that chronic diseases that are the result of ageing and inflammaging are also manifestations of accelerated ageing problems (91) .

There is increasing evidence that inflammaging is a risk factor for CSVD (93). Its role in CSVD is through the ageing of the immune system and by increasing the harmful effects of other traditional cerebrovascular risk factors such as obesity, hypertension, and diabetes mellitus. There is a close relationship between inflammaging and age-related CSVD where vascular inflammation is related to deep perforator arteriopathy and systemic inflammation is related to cerebral amyloid angiopathy (64). Inflammaging and immunosenescence have a dynamic interaction that is related to cellular ageing and loss of BBB which leads to continuous activation of the immune system (94). Identifying therapeutic targets to mitigate the effect of immunosenescence has been suggested as a potential treatment for CSVD.

Mechanical stress and inflammaging in KOA

While OA is considered as a degenerative disease from mechanical events leading to wear and tear and eventually loss of cartilage, it also involves inflammation processes (95). The inflammation that occurs in osteoarthritis can be

local such as synovitis and also systemic inflammation (96). For KOA, there is a correlation between local synovitis and systemic inflammation. In a study of inflammatory biomarkers, the levels of highly sensitive C-reactive protein (hs-CRP) obtained from knee synovial fluids (SF) are positively correlated with the ones obtained from the serum (97). Another study involving symptomatic KOA patients found that inflammatory plasma lipid biomarkers such as prostaglandin E2 and 15-hydroxyeicosatetraenoic acid to be significantly elevated in symptomatic KOA patients when compared to non-OA controls (98).

The same study also suggested that peripheral blood leukocytes inflammatory transcriptome can help identify symptomatic KOA patients that are more likely to develop radiographic progression such as joint space narrowing. Low-grade systemic inflammation is present in KOA (95) and it has been suggested as one link between KOA and atherosclerosis (99). Since OA is an age-related disease with the involvement of inflammation, it is acceptable to suggest that inflammaging plays a significant role in many aspects of the disease. OA is associated with low-grade systemic inflammation and local inflammation that involve innate and adaptive immune systems (100). One aspect that may suggest this is the health of the articular cartilage. Aging plays more role in the senescence of chondrocytes. Chondrosenescence is the age-dependent deterioration of chondrocytes because of replicative (intrinsic) and stress-induced (extrinsic) factors (101). Pro-inflammatory mediators such as IL-6 and IL-7 are released more in the elderly population, and both are also released more in patients with OA when compared with age-matched non-OA participants (102). Increased levels of pro-inflammatory cytokines and ROS leads to vascular impairment. This is followed by a fluctuating supply of nutrients and oxygen, leading to reduced cartilage elasticity and water content (103). Inflammaging and OA are also linked by damage-associated molecular patterns (DAMPs). DAMPs are produced by synovial cells along with other inflammatory mediators into the synovial fluid during the progress of OA (104). DAMPs trigger the immune system and contribute to the association between ageing and OA (105). The release of DAMPs increases and sustains inflammation, producing the chronic low-grade inflammation associated with OA (104). However, it is not clear whether the release is due to OA or ageing.

Endothelial dysfunction and inflammaging in KOA-CSVD crosstalk

One mechanism that can present in KOA and cerebrovascular disease as a result of inflammaging is endothelial dysfunction. Endothelial cells play a role in regulating the vascular tone through the substances affecting vasoconstriction and vasodilation (106). Examples of substances that contribute to the vasodilation effect are prostacyclin, NO, and bradykinin. Under normal physiology, these effects are balanced by vasoconstrictor substances such as endothelin which are also produced by the endothelium (107). One of the features of endothelial dysfunction is increased vascular smooth muscle tone secondary to impaired processing of vasodilator substances and increased production of vasoconstrictor substances (106,108). Endothelial dysfunction is thought to play a significant role in atherosclerosis and other vascular diseases (109). Regarding cerebral blood vessels, the endothelium is essential for the control of blood circulation through influencing the vascular smooth muscle. Examples of vasodilator substances involved are NO and endothelium-derived hyperpolarization factor while an example of a vasoconstrictor substance is endothelin-1 (110). Conditions such as stroke or trauma can significantly affect the endothelial control over the vascular tone such as shifting from a predominantly vasodilatory state to vasoconstricting.

Because of increasing evidence of a relationship between KOA, systemic inflammation, and endothelial dysfunction, it is not surprising that there has been more focus on establishing a connection between KOA and cerebrovascular problems. A review by Al-Khazraji et al. (2018) (1) discussed a few inflammatory markers regarding their local and systemic role, and how they may contribute to cerebrovascular dysfunction. Among the substances discussed are hs-CRP, lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) and IL-6 and ROS. ROS is the one inflammatory substance that may show a link with CSVD. ROS can be produced by chondrocytes and cerebral vascular cells. For local KOA inflammation, the level of ROS production is elevated through increased nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activities (111, 112) and accumulation of nitro-tyrosine (102). An increase in local ROS production in CSVD also occurs primarily through NADPH oxidase activity (113). Additionally, ROS may affect BBB integrity, leading to the accumulation of ROS in cerebral vessels (1) In a study evaluating the cerebrovascular function of KOA patients, it was found that those with KOA showed impaired peripheral vascular health, dysfunctional cerebrovascular activity, autoregulatory capacity, and greater white matter lesions when compared to healthy control without KOA or cardiovascular complications (1). The data from the study suggested that the association between KOA and cerebrovascular dysfunction is subclinical where the

participants did not report symptoms of established cerebrovascular dysfunction such as pre-syncope or stroke. In a systemic review regarding vascular pathology and KOA (114), it is found that vascular pathologies in KOA include the narrowing of small arteries which may also suggest a relationship with CSVD. Interestingly though, vascular pathologies are also found in hand OA but not hip OA.

Immune system and inflammaging in KOA-CSVD crosstalk

Apart from inflammatory substances, there is also a possible link between KOA and CSVD based on changes in the immune cells and their functions. This has been discussed a lot due to the interaction between inflammaging and immunosenescence. Aging can lead to the alteration of B cell receptors and functions causing increased production of cytokines (115). Chronic stimulation of B cells due to inflammation also causes B cells to produce more proinflammatory cytokines (116). Senescent T cell functions can be increased or suppressed depending on the stage of inflammaging (117) . As age increases, the production of inflammatory factors such as interferon-inducible protein-10, IL-6, and IL-8 increases due to the imbalance of T-cell subtypes (118). This exacerbates the inflammaging state. In age-related CSVD, immune cell senescence initially suppresses the normal immune response. However, at the latter stage, pro-inflammatory cytokines such as IL-6 and IL-8 will be produced causing accelerated and aggravated BBB leakage and injury to the endothelial cells (117). Microglia, which is an important phagocyte for the central nervous system has been shown to undergo senescent and loss of function. Senescent microglia have decreased responsiveness. It also suffers from migration and phagocytosis. This leads to the accumulation of senescent cells and debris that become a source of chronic inflammation causing damage to cerebrovascular structures and neurons (119). Senescent microglia seem to be one of the factors in activating inflammaging by producing a pro-inflammatory state. This leads to neuron degeneration and BBB leakage (120). CSVD patients have been shown to have anti-endothelial antibodies, suggesting a relationship between B cell activation and endothelial dysfunction (121). As a whole, the senescence of immune cells that occurs with inflammaging contributes greatly to microglia dysfunction, BBB leakage and endothelial dysfunction therefore essential in the development and progress of CSVD. Moreover, changes in the adaptive immune system also may connect KOA and inflammaging. Blood lymphocyte composition of KOA patients has been shown to have compromised T and B cell functions. Compared to the control, KOA showed increased CD8 while a decrease in CD4 and T regulatory cells (122). A study of 30 symptomatic KOA patients revealed altered T cell profiles where some types of T cells increased and others decreased when adjusted for age (123) . A review study found that the alteration of T cells in KOA occurs in various subtypes of T cells. However, the exact relationship between the alteration of T cells and with development and progression of KOA is still unclear (124). The profile of B cells also changed in KOA patients where the levels of many B cell subtypes decreased (123). Interestingly, the alteration that occurred in KOA also affects B cell proliferation, maturation, and differentiation. The altered function may explain the presence of autoantibodies in the synovial fluid of KOA (125). These alterations suggest that impairment of the adaptive immune system does occur in KOA and may play a relevant role in the pathogenesis of OA (100). Alterations in the adaptive immune system occur in both CSVD and KOA. The changes involved an increase in certain functions while a decrease in some others. Senescence in immune cells that accompanies ageing and inflammaging seems to be more established in CSVD when compared to KOA. However, there are enough suggestions that KOA may share the same problem of immunosenescence. Immunosensence are a key factor in rheumatoid arthritis (126), therefore it is not unlikely that KOA is also the same. It is an aspect that may show further relationship between CSVD and KOA. Even though CSVD is a vascular disease while KOA is a degenerative disease, it has been shown that they potentially share some mechanisms for the disease development and progression. Both are affected by inflammation and since age is a major factor for them, the process of inflammaging is a reasonable point to find a common link between the two. The senescence of immune cells and their altered profile is related to the systemic and local inflammation that occurred in CSVD and KOA. This causes increased release of various proinflammatory substances resulting in endothelial dysfunction, damaged small vessels, BBB leakage, synovitis, and damaged cartilages. However, further studies are required to understand the nature of the association between CSVD and KOA because as stated by Al-Khazraji et al. (2018) (1), while the mechanisms seem to be overlapping, the direction of the relationship between the two diseases and how the presence of one affects the progress of the other is far from clear.

Impact on cognitive function

There is vast evidence showing a close association between OA and CSVD which plays a pivotal role in cognitive function. The literature on OA and CSVD has

highlighted several factors contributing to their progression and ultimately interrupting cognitive capabilities (1, 4, 127). In comparison between males and females, the previous study indicated that several vascular risks including CSVD have higher risk in females rather than males resulting in cognitive decline in both genders (31). Inflammation (i.e., inflammaging) and oxidative stress were discussed linking OA (i.e., KOA) and CSVD. There is a large volume of published studies describing the role of inflammatory and oxidative and their role in the onset and progression of both KOA and CSVD (4, 127-129). For instance, through mechanisms of C-reactive protein (CRP) (1). Initially, CRP is an acute-phase reactant produced by the liver in response to inflammation and inflammation mediated by CRP can contribute to oxidative stress in the vascular. Data from several studies suggest that increased CRP is correlated with verbal fluency performance. It seems that the results are due to loss in brain white matter integrity and changes in the anatomy resulting in a huge impact on the performance of cognitive outcomes. Moreover, an increase in pro-inflammatory IL-6 and CRP have decreased cognitive performance. It is believed that the CRP with pro-inflammatory cytokines affects the endothelium and the BBB resulting in impairment of microvascular and leading to CVSD followed by changes in cognitive function (1). Moreover, serum pyruvate kinase M2 (PKM2) has been shown to play a major role in Toll-like receptors resulting in abnormal activation of the immune system leading to inflammation activation as seen in the CVSD. Moreover, the Toll-like receptors (TLRs) have been shown to play critical roles in regulating the abnormal activation of the immune cells resulting in the pathogenesis of inflammation and autoimmune diseases. TLR-mediated therefore induced inflammation and autoimmunity by promoting PKM2 activation. The observed increase in PKM2 could be attributed to an increase with suspected dementia, mild dementia, and mild to moderate dementia. These results are consistent with those of other studies and suggest the association between PKM2 and CSVD (130, 131).

Another study using fMRI in association with CVSD showed that brain lesions have been seen in the CSVD resulting in their impact on the cognitive reserve (132). At the beginning of the CVSD, the impairment of brain function outweighs the behavioural impairments since the presentation of compensatory and regulatory mechanisms takes place. However, in the late stage, dysfunction and dysregulation are associated with white matter damage and following the impact on cognitive function (133). A further study with more focus on CSVD is therefore suggested that the CMBs as hallmarks of underlying depression and cognitive dysfunction. These research findings indicate that individuals with CSVD exhibit diminished overall connectivity and specialized function within their white matter networks of the patient. Additionally, there is a notable reduction in nodal efficiency, particularly in areas associated with depression and cognitive impairment, such as those within the attention, default mode, and sensorimotor networks that ultimately impact cognitive function (134, 135).

In the triple-network model study, data patients diagnosed with CSVD displayed heightened connectivity within the central executive network and default mode network, alongside diminished connectivity between the default mode network and the salience network, as well as between the central executive network and the salience network. There were also observed imbalances within the salience and default mode networks. It is believed that these disruptions within the triple-network system affect brain regions responsible for motor execution, emotional processing, and cognitive control, ultimately resulting in inefficient cognitive control and reactions (136). In a separate study examining KOA and cognitive impairment, researchers found that both are primary contributors to functional decline and disability among older adults. The current findings suggest a link between cognitive performance, pain, and functionality in individuals with OA. These results enlighten the importance of investigating the intricate relationship between chronic pain severity and cognitive function (134). However, the findings of the current study do not support the previous research. In the animal model of KOA, there were no significant differences, particularly in cognitive function. Although rearing was diminished, locomotor activity remained normal, and no alterations were observed in startle response or pre-pulse inhibition in rats. Moreover, the rats were unaffected performance in the water maze delayed-matching-to-place task, indicating no significant disruption in hippocampal function. Furthermore, there were no impairments noted in novel object recognition memory or the operant task assessing behavioural flexibility. These findings suggest that OA-like pain does not affect hippocampal function (137).

However, more studies revealed that there were associations with KOA, CVSD and cognitive capabilities. Another study investigated the effects of vortioxetine in an animal model of monosodium iodoacetate-induced OA and its correlation with impaired cognitive function. The results showed that vortioxetine effectively reversed cognitive deficits in both male and female rats in a dose-dependent manner. One of the primary mechanisms believed to

contribute to the cognitive-enhancing properties of vortioxetine involves the blockade of serotonin receptors on γ-aminobutyric acid interneurons, leading to the disinhibition of pyramidal neuron activity in the hippocampus. Additionally, electrophysiological studies have revealed that vortioxetine enhances N-methyl-D-aspartate (NMDA)-mediated glutamatergic neurotransmission and long-term potentiation in the hippocampus, a neural process dependent on NMDA receptors that are implicated in memory formation (138).

In a separate study aimed at assessing cerebrovascular outcomes in individuals with KOA, it was found that KOA may predispose individuals to neurological damage. Cerebral microvascular dysfunction is often identified as the primary cause of CSVD, leading to compromised brain perfusion and subsequent cognitive decline. Moreover, in a transgenic mouse model of Alzheimer's disease, mice induced with KOA (via viral injection into knees) exhibited increased amyloid β plaques and neuroinflammation compared to those without KOA, suggesting a potential link between peripheral inflammation and Alzheimer's pathology (127). Characteristic changes indicative of cerebrovascular impairment, such as WMHs, brain atrophy, cerebral cortical microinfarcts, and CMBs, are often observed in individuals with this condition. Additionally, individuals with KOA who undergo joint replacements may exhibit a higher volume of WMHs, despite lacking a history of cardiac or cerebrovascular events (1). Finally, individuals diagnosed with KOA and CSVD face a heightened risk of declining cognitive function. Understanding the causality behind this association could offer valuable insights for enhancing prevention and treatment strategies in clinical settings.

KOA-CSVD intercurrent relationship: Potential therapy and future directions

There are important clinical ramifications to the intricate interaction that exists between CSVD and KOA. Future research areas and possible treatment strategies may be guided by an understanding of this link. As discussed, the pathophysiological pathways of KOA and CSVD are similar in that they involve endothelial dysfunction, oxidative stress, and chronic inflammation. By focusing on these overlapping pathways, treatment advantages for both illnesses might be provided concurrently. A comprehensive strategy for treatment is necessary due to the complex nature of the intercurrent interaction between KOA and CSVD. A mix of pharmaceutical therapies, lifestyle changes, and rehabilitative techniques designed to address joint and cerebrovascular health may be used to achieve this. Chronic inflammation is a common thread in both KOA and CSVD. Inflammatory mediators such as cytokines and chemokines, which are produced in the knee joint during KOA, may enter the bloodstream and contribute to vascular dysfunction and affect the brain, potentially accelerating the development of CSVD (139). Traditional vascular risk factors such as hypertension, diabetes, and dyslipidaemia (abnormal cholesterol levels) are implicated in KOA as well as CSVD. These factors can damage blood vessels throughout the body, including those supplying the knee joints and the brain. Herewith in Figure 3, we proposed the novel conceptual model for intercurrent crosstalk between KOA and CSVD which may be aided in the prevention, management, and therapeutics strategies for both conditions.

Potential therapeutic strategies and future recommendations

Medications such as corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying osteoarthritis or disease-modifying anti-rheumatic medicines can help manage KOA symptoms and potentially reduce systemic inflammation (140) and may have a positive impact on CSVD as well. When prescribing these drugs, however, special consideration must be given to each patient's unique condition as well as any possible negative effects. To date, there is no gold standard for medication for CSVD. However, maintaining a healthy weight, engaging in regular physical activity appropriate for patients with KOA (e.g., low-impact exercises such as swimming or cycling), and eating a balanced diet such as fruits, vegetables, and whole grains (such as omega-3 fatty acids, antioxidants, and polyphenols), may have anti-inflammatory and neuroprotective effects, can improve cardiovascular health, and potentially slow the progression of both KOA and CSVD (141).

Enhancing joint function and mobility in KOA patients through exercise and physical therapies therapies can also have neuroprotective effects and improve cerebrovascular health (142, 143). Combining aerobic activity, strength training, and balancing exercises could help reduce symptoms associated with both KOA and CSVD synergistically. Besides, precision medicine techniques such as genetic profiling, biomarker identification, and imaging modalities have been used to identify patients who are more likely to develop KOA-CSVD intercurrent pathophysiology and modify treatment plans accordingly. Therapeutic outcomes may be improved by tailored therapies that target biological pathways implicated in both diseases. A recent study by Jiang et al. determined the best course of action for participants in an intensive exercise (E), diet weight loss (D), and D+E (IDEA) trial for KOA by

using a precision medicine approach using 24 machine learning models to create customized treatment guidelines. They found that there were indications that a subgroup of participants would probably benefit more from diet, which was consistent with the precision medicine models' support for the overall IDEA findings that the D+E intervention was best for most participants (131).

Apart from that, several of the most significant genetic indicators in KOA have been identified, for example, multiple genomic regions have been identified using a microRNAs approach for KOA i.e., miR-34a-5p for late KOA biomarker in obese patients (144), hsa-miR-335-3p, hsa-miR-199a-5p, hsa-miR-671-3p, has-miR-1260 b, hsa-miR-191-3p, and hsa-miR-335-5p for early symptomatic KOA biomarkers (Ali et al., 2020), miR-146a-5p and miR-186-5p for prevalent and incident KOA in women (145). Circular RNAs such as hsa_circ_101178 have been identified for early symptomatic KOA biomarkers (Chen, 2020). Moreover, mitochondria genetics such as Haplogroup J for prevalence and incidence KOA biomarker in Caucasian populations (146), mtDNA cluster JT for KOA progression biomarker in Caucasian populations (147), Haplogroup G for the prevalence of KOA biomarker in Chinese populations (148), and Haplogroup B for the incidence of KOA biomarker in Koreans populations (149) has been identified.

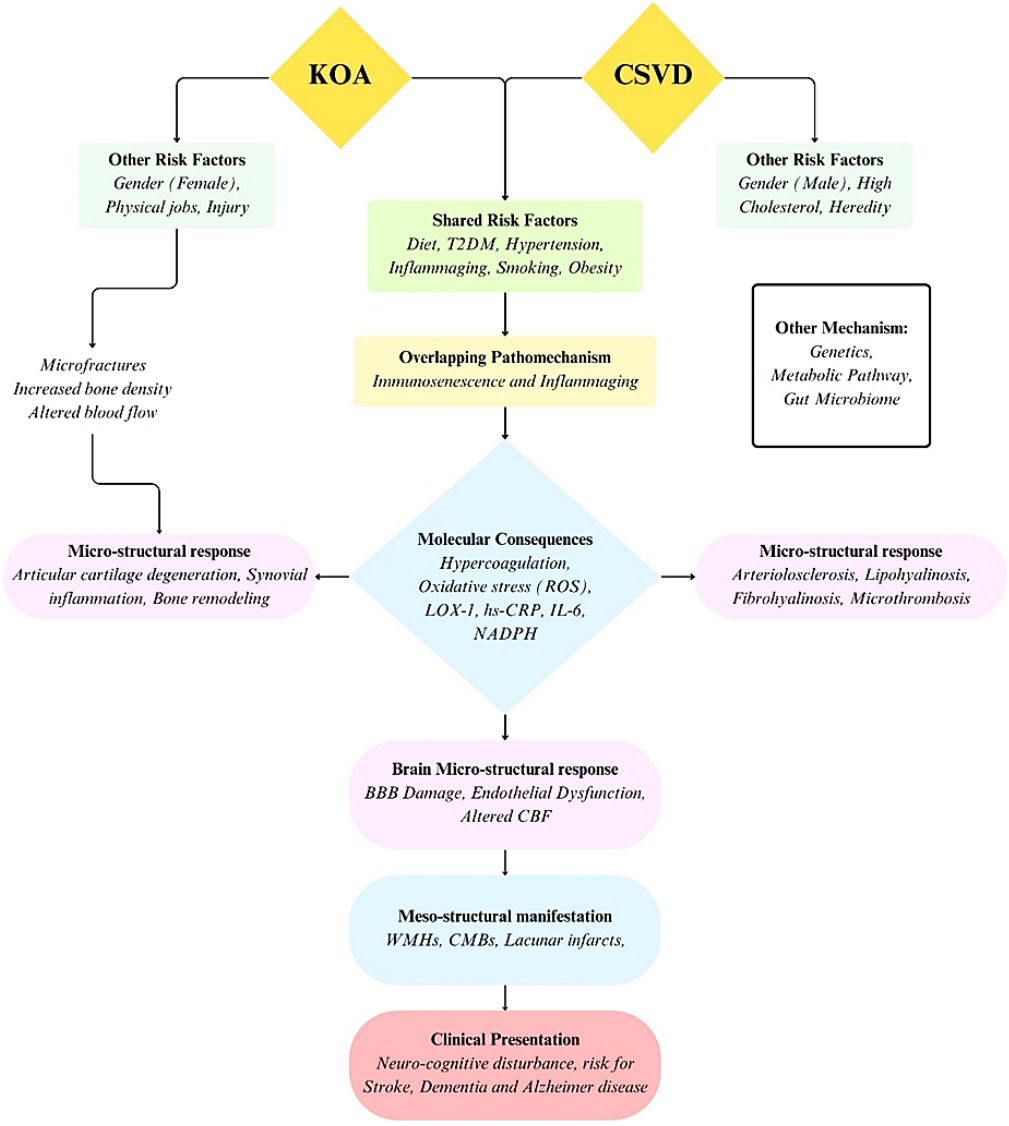


Figure 3. Proposed conceptual model for intercurrent crosstalk between knee osteoarthritis (KOA) and cerebral small vessel disease (CSVD). BBB, blood-brain barrier; CBF, cerebral blood flow; CMBs, cerebral microbleeds; IL, interleukins; hs-CRP, highly sensitive C-reactive protein; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1; NADPH, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species; T2DM, type 2 diabetes mellitus.

On the other hand, Mendelian forms only comprise 5% of CSVD patients (150), while most cases of CSVD are sporadic (151). Certain genetic mutations are the cause of monogenic CSVD, such as those found in CADASIL (152, 153), cerebral autosomal recessive arteriopathy (CARASIL) (153), Fabry's disease (Brady et al., 1967), *COL4A1/2*-related CSVD (154), retinal vasculopathy with cerebral leukodystrophy (RVCL) (152), and cathepsin A-related arteriopathy with strokes and leukoencephalopathy (CARASAL) (155). A recent genetic profiling study by Wang et al. found eight variants in total, with five novel variants, i.e., c.1774C>T (*NOTCH3*), c.3784C>T (*NOTCH3*), c. 1207C>T (*HTRA1*), c. 1274+1G> A (*HTRA1*), c.1937G>C (*COL4A1*), and three reported mutations were found in patients with CSVD in the Chinese Han population. They also reported that there were no variations in any of the 300 healthy controls. And conclude that there were no pathogenic mutations found in *TREX1*, *CTSA*, *GLA*, *COL4A2*, or *TREX1* genes (156, 157).

Therefore, the development of combination medicines that simultaneously address vascular health, inflammation, and other contributing factors may lead to a more successful management of CSVD and KOA. Potential interactions and adverse consequences must be carefully considered. Novel therapeutic approaches become possible when one comprehends the intricate connection between KOA and CSVD. Through the integration of orthopaedists, neurologists, and vascular experts' specialized knowledge, researchers can create a more comprehensive therapy strategy that efficiently targets both disorders.

Conclusion

In summary, a thorough and integrated approach to patient care is necessary due to the concurrent link between CSVD and KOA. Given their common pathophysiological mechanisms such as chronic inflammation (i.e., inflammaging) and endothelial dysfunction; managing both illnesses concurrently may be possible. Treatment strategies that emphasize reducing cardiovascular risk, reducing inflammation, encouraging physical activity, and applying precision medicine techniques have the potential to improve outcomes for those with KOA-CSVD intercurrent pathology. There is a need for a paradigm shift in understanding and treating KOA and CSVD as interconnected conditions rather than separate diseases. Future research should focus on identifying shared biomarkers, exploring precision medicine approaches, and testing anti-inflammatory and vascular-targeted interventions that benefit both conditions. Longitudinal studies are also critical to understanding how managing one condition impacts the other, thus advancing integrated treatment strategies. By focusing on underlying biological mechanisms, conducting rigorous clinical trials, and applying individualized therapy techniques, researchers and clinical professionals can work towards improving patient outcomes and quality of life. This interdisciplinary collaboration will be essential for effectively addressing the complex clinical junction between KOA and CSVD.

Acknowledgments

The authors would like to thank the Faculty of Medicine, Universiti Sultan Zainal Abidin (UniSZA), and the Affective Neuroscience research group members for their valuable support.

Funding: Funding was not received for this study.
Ethics approval: Not applicable to this article.
Conflict of interests: The authors declare no conflict of interest.
Authors' contribution: C.M.N.C.M.N., and M.M.G.: Conceptualization. All authors: Writing, Original draft, review, and editing.

References

1. Al-Khazraji BK, Appleton CT, Beier F, Birmingham TB, Shoemaker JK. Osteoarthritis, cerebrovascular dysfunction and the common denominator of inflammation: a narrative review. Osteoarthritis Cartilage 2018; 26 :462-70.
2. Mao CP, Bai ZL, Zhang XN, Zhang QJ, Zhang L. Abnormal subcortical brain morphology in patients with knee osteoarthritis: A cross-sectional study. Front Aging Neurosci 2016; 8: 3.
3. Hsu PS, Lin HH, Li CR, Chung WS. Increased risk of stroke in patients with osteoarthritis: a population-based cohort study. Osteoarthritis Cartilage 2017; 25: 1026–31.
4. Weber A, Mak S hung, Berenbaum F, et al. Association between osteoarthritis and increased risk of dementia. Medicine 2019; 98: e14355.
5. McKetton L, Cohn M, Tang-Wai DF, et al. Cerebrovascular resistance in healthy aging and mild cognitive impairment. Front Aging Neurosci 2019; 11: 79.
6. Yao Q, Wu X, Tao C, et al. Osteoarthritis: pathogenic signaling pathways and therapeutic targets. Signal Transduct Target Ther 2023; 8: 56.

7. Suri P, Morgenroth DC, Kwoh CK, et al. Low back pain and other musculoskeletal pain comorbidities in individuals with symptomatic osteoarthritis of the knee: Data from the osteoarthritis initiative. Arthritis Care Res (Hoboken) 2010; 62: 1715–23.
8. Cui A, Li H, Wang D, et al. Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. EClinicalMedicine 2020; 29–30: 100587.
9. Szilagyi IA, Waarsing JH, van Meurs JBJ, Bierma-Zeinstra SMA, Schiphof D. A systematic review of the sex differences in risk factors for knee osteoarthritis. Rheumatology (Oxford). 2023; 62: 2037-47.
10. Tudorachi NB, Totu T, Eva I, et al. Knee osteoarthritis in relation to the risk factors of the metabolic syndrome components and environment of origin. J Clin Med 2022; 11: 7302.
11. Silverwood V, Blagojevic-Bucknall M, Jinks C, et al. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage 2015; 23: 507–15.
12. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet 2019; 393: 1745–59.
13. Cho Y, Jeong S, Kim H, et al. Disease-modifying therapeutic strategies in osteoarthritis: current status and future directions. Exp Mol Med 2021; 53: 1689–96.
14. Jang S, Lee K, Ju JH. Recent updates of diagnosis, pathophysiology, and treatment on osteoarthritis of the knee. Int J Mol Sci 2021; 22: 2619.
15. Heidari B. Knee osteoarthritis diagnosis, treatment and associated factors of progression: Part II. Caspian J Intern Med 2011; 2: 249-55.
16. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957; 16: 494–502.
17. Kohn MD, Sassoon AA, Fernando ND. Classifications in brief: Kellgren-Lawrence classification of osteoarthritis. Clin Orthop Relat Res 2016; 474: 1886–93.
18. Kamsan SS, Singh DKA, Tan MP, Kumar S. Healthcare utilization and knee osteoarthritis symptoms among urban older Malaysian. Int J Environ Res Public Health 2021; 18: 3777.
19. Deshpande BR, Katz JN, Solomon DH, et al. Number of persons with symptomatic knee osteoarthritis in the US: Impact of race and ethnicity, age, sex, and obesity. Arthritis Care Res (Hoboken)2016; 68: 1743–50.
20. Postler A, Luque Ramos A, Goronzy J, et al. Prevalence and treatment of hip and knee osteoarthritis in people aged 60 years or older in Germany: an analysis based on health insurance claims data. Clin Interv Aging 2018; Volume 13: 2339–49.
21. AlKuwaity KW, Mohammad TN, Hussain MA, Alkhanani AJ, Ali AMB. Prevalence and determinant factors of osteoarthritis of the knee Jjoint among elderly in Arar, KSA. Egypt J Hosp Med 2018; 72: 5173–7.
22. Cho HJ, Morey V, Kang JY, Kim KW, Kim TK. Prevalence and risk factors of spine, shoulder, hand, hip, and knee osteoarthritis in community-dwelling Koreans older than age 65 years. Clin Orthop Relat Res 2015; 473: 3307–14.
23. Department of Statistics Malaysia. Population Projection (Revised), Malaysia, 2010–2040. 2016. Available from: https://www.statistics.gov.my/site/downloadrelease?id=population-projection-revised-malaysia-2010-2040&lang=English&admin_view=. Accessed Oct 13, 2025.
24. Mat S, Razack AH, Lim J, et al. Factors determining the increased risk of falls in individuals with knee pain in the Malaysian elders longitudinal research (MELoR) Study. Front Med (Lausanne) 2019;6: 277.
25. Ministry of Health. The 2019 Malaysia National Health and Morbidity Survey. NHMS 2015. Available from: https://iku.gov.my/nhms-2015. Accessed Oct 13, 2025.
26. Yeap SS, Tanavalee A, Perez EC, et al. 2019 revised algorithm for the management of knee osteoarthritis: the Southeast Asian viewpoint. Aging Clin Exp Res 2021; 33: 1149–56.
27. Aimi Asyrani Zamri N, Harith S, Mohd Yusoff NA, Mat Hassan N, Ong YQ. Prevalence, risk factors and primary prevention of osteoarthritis in Asia: A scoping review. Elderly Health J 2019; 5: 19-31.
28. Hsu H, Siwiec RM. Knee Osteoarthritis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507884/. Accessed Jun 23, 2023.
29. Primorac D, Molnar V, Rod E, et al. Knee osteoarthritis: A review of pathogenesis and state-of-the-art non-operative therapeutic considerations. Genes (Basel) 2020; 11: 854.
30. Robinson WH, Lepus CM, Wang Q, et al. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. Nat Rev Rheumatol 2016; 12: 580–92.
31. Jiménez-Sánchez L, Hamilton OKL, Clancy U, et al. Sex differences in cerebral small vessel disease: A systematic review and meta-analysis. Front Neurol 2021; 12: 756887.

32. Shayan S, Jinpu L, Shirin A, Mark AT. Arthritis. In: StatPearls. Treasure Island (FL): StatPearls Publishing 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/sites/books/NBK518992/. Accessed Jun 20, 2023.
33. Li G, Yin J, Gao J, et al. Subchondral bone in osteoarthritis: insight into risk factors and microstructural changes. Arthritis Res Ther 2013; 15: 223.
34. Mathiessen A, Conaghan PG. Synovitis in osteoarthritis: current understanding with therapeutic implications. Arthritis Res Ther 2017; 19: 18.
35. Levy M, Thaiss CA, Zeevi D, et al. Microbiota-modulated metabolites shape the intestinal microenvironment by regulating NLRP6 inflammasome signaling. Cell 2015; 163: 1428–43.
36. Fernandez-Moreno M, Rego I, Carreira-Garcia V, Blanco F. Genetics in osteoarthritis. Curr Genomics 2008; 9: 542–7.
37. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol 2010; 9: 689–701.
38. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. Lancet Neurol 2019; 18: 684–96.
39. Che Mohd Nassir CMN, Damodaran T, Yusof SR, et al. Aberrant neurogliovascular unit dynamics in cerebral small vessel disease: A rheological clue to vascular parkinsonism. Pharmaceutics 2021; 13: 1207.
40. Smith EE. Clinical presentations and epidemiology of vascular dementia. Clin Sci 2017; 131: 1059–68.
41. Prabhakaran S, Naidech AM. Ischemic brain injury after intracerebral hemorrhage. Stroke 2012; 43: 2258–63.
42. Mustapha M, Nassir CMNCM, Aminuddin N, Safri AA, Ghazali MM. Cerebral small vessel disease (CSVD) - Lessons from the animal models. Front Physiol 2019; 10: 1317.
43. de Leeuw FE. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. J Neurol Neurosurg Psychiatry 2001; 70: 9–14.
44. Woo D, Gebel J, Miller R, et al. Incidence rates of first-ever ischemic stroke subtypes among blacks. Stroke 1999; 30: 2517–22.
45. Leary MC, Saver JL. Annual incidence of first silent stroke in the United States: A preliminary estimate. Cerebrovasc Dis 2003; 16: 280–5.
46. Chojdak-Łukasiewicz J, Dziadkowiak E, Zimny A, Paradowski B. Cerebral small vessel disease: A review. Adv Clin Exp Med 2021; 30: 349–56.
47. van Asch CJ, Luitse MJ, Rinkel GJ, et al. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet Neurol 2010; 9: 167–76.
48. Giralt-Steinhauer E, Jiménez-Balado J, Fernández-Pérez I, et al. Genetics and epigenetics of spontaneous intracerebral hemorrhage. Int J Mol Sci 2022; 23: 6479.
49. Jolink WMT, Wiegertjes K, Rinkel GJE, ET AL. Location-specific risk factors for intracerebral hemorrhage. Neurology 2020; 95: e1807-18.
50. Lammie GA, Brannan F, Slattery J, Warlow C. Nonhypertensive cerebral small-vessel disease. Stroke 1997; 28: 2222–9.
51. Traylor M, Malik R, Nalls MA, et al. Genetic variation at 16q24.2 is associated with small vessel stroke. Ann Neurol 2017; 81: 383–94.
52. Gale SA, Acar D, Daffner KR. Dementia. Am J Med 2018; 131: 1161–9.
53. Chang Wong E, Chang Chui H. Vascular cognitive impairment and dementia. Continuum (Minneap Minn) 2022; 28: 750–80.
54. Gottesman RF, Albert MS, Alonso A, et al. Associations between midlife vascular risk factors and 25-year incident dementia in the atherosclerosis risk in communities (ARIC) cohort. JAMA Neurol 2017; 74: 1246.
55. Duering M, Biessels GJ, Brodtmann A, et al. Neuroimaging standards for research into small vessel disease—advances since 2013. Lancet Neurol 2023; 22: 602–18.
56. Zhuang FJ, Chen Y, He WB, Cai ZY. Prevalence of white matter hyperintensities increases with age. Neural Regen Res 2018; 13: 2141.
57. Li T, Huang Y, Cai W, Chen X, Men X, Lu T, et al. Age-related cerebral small vessel disease and inflammaging. Cell Death Dis 2020; 11: 932.
58. Jann K, Shao X, Ma SJ, et al. Evaluation of cerebral blood flow measured by 3D PCASL as biomarker of vascular cognitive impairment and dementia (VCID) in a cohort of elderly Latinx subjects at risk of small vessel disease. Front Neurosci 2021; 15: 627627.
59. Baezner H, Blahak C, Poggesi A, et al. Association of gait and balance disorders with age-related white matter changes. Neurology 2008; 70: 935–42.
60. Naraoka M, Matsuda N, Shimamura N, Asano K, Ohkuma H. The role of arterioles and the

microcirculation in the development of vasospasm after aneurysmal SAH. Biomed Res Int 2014; 2014: 1–9.
61. Li Q, Yang Y, Reis C, et al. Cerebral small vessel disease. Cell Transplant 2018; 27: 1711–22.
62. Allen KD, Thoma LM, Golightly YM. Epidemiology of osteoarthritis. Osteoarthritis Cartilage 2022; 30: 184–95.
63. Li Y, Kalpouzos G, Laukka EJ, et al. Progression of neuroimaging markers of cerebral small vessel disease in older adults: A 6-year follow-up study. Neurobiol Aging 2022; 112: 204–11.
64. Lee WJ, Chou KH, Lee PL, et al. Cerebral small vessel disease phenotype and 5-year mortality in asymptomatic middle-to-old aged individuals. Sci Rep 2021; 11: 23149.
65. Ansari MY, Ball HC, Wase SJ, Novak K, Haqqi TM. Lysosomal dysfunction in osteoarthritis and aged cartilage triggers apoptosis in chondrocytes through BAX mediated release of Cytochrome c. Osteoarthritis Cartilage 2021; 29: 100–12.
66. Petrea RE, O'Donnell A, Beiser AS, et al. Mid to late life hypertension trends and cerebral small vessel disease in the framingham heart study. Hypertension 2020; 76: 707–14.
67. Lo K, Au M, Ni J, Wen C. Association between hypertension and osteoarthritis: A systematic review and meta-analysis of observational studies. J Orthop Translat 2022; 32: 12–20.
68. Tchetina E V, Markova GA, Sharapova EP. Insulin resistance in osteoarthritis: Similar mechanisms to type 2 diabetes mellitus. J Nutr Metab 2020; 2020: 1–16.
69. Yu X, Yu Y, Wei C, et al. Association between small dense low-density lipoprotein cholesterol and neuroimaging markers of cerebral small vessel disease in middle-aged and elderly Chinese populations. BMC Neurol 2021; 21: 436.
70. World Health Organisation (WHO). Obesity and overweight. WHO 2024. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed Dec 25, 2024.
71. Raud B, Gay C, Guiguet-Auclair C, et al. Level of obesity is directly associated with the clinical and functional consequences of knee osteoarthritis. Sci Rep 2020; 10:3601.
72. Zhang R, Huang P, Wang S, et al. Decreased cerebral blood flow and delayed arterial transit are independently associated with white matter hyperintensity. Front Aging Neurosci 2022; 14: 762745.
73. Xu Z, Li F, Xing D, et al. A novel imaging biomarker for cerebral small vessel disease associated with cognitive impairment: The deep-medullary-veins score. Front Aging Neurosci 2021; 13: 720481.
74. Yu C, Lu W, Qiu J, et al. Alterations of the whole cerebral blood flow in patients with different total cerebral small vessel disease burden. Front Aging Neurosci. 2020; 12: 175.
75. Zhu S, Ji L, He Z, et al. Association of smoking and osteoarthritis in US (NHANES 1999–2018). Sci Rep 2023; 13: 3911.
76. Immanuel J, Yun S. Vascular inflammatory diseases and endothelial phenotypes. Cells 2023; 12: 1640.
77. Drożdż D, Drożdż M, Wójcik M. Endothelial dysfunction as a factor leading to arterial hypertension. Pediatric Nephrology 2023; 38: 2973–85.
78. Botts SR, Fish JE, Howe KL. Dysfunctional vascular endothelium as a driver of atherosclerosis: Emerging insights into pathogenesis and treatment. Front Pharmacol 2021; 12: 787541.
79. Agrawal S, Schneider JA. Vascular pathology and pathogenesis of cognitive impairment and dementia in older adults. Cereb Circ Cogn Behav 2022; 3: 100148.
80. Shabir O, Berwick J, Francis SE. Neurovascular dysfunction in vascular dementia, Alzheimer's and atherosclerosis. BMC Neurosci 2018; 19: 62.
81. Wang R, Wang ZM, Xiang SC, et al. Relationship between 25-hydroxy vitamin D and knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. Front Med (Lausanne) 2023; 10: 1200592.
82. Kim HA, Perrelli A, Ragni A, et al. Vitamin D deficiency and the risk of cerebrovascular disease. Antioxidants 2020; 9: 327.
83. Guo H, Wang Y, Qiu L, et al. Structural and functional abnormalities in knee osteoarthritis pain revealed with multimodal magnetic resonance imaging. Front Hum Neurosci 2021; 15: 783355.
84. Cheng S, Dong X, Zhou J, et al. Alterations of the white matter in patients with knee osteoarthritis: A diffusion tensor imaging study with tract-based spatial statistics. Front Neurol 2022; 13: 835050.
85. Hsiao CT, Chen YC, Liu YT, Soong BW, Lee YC. Acute simultaneous multiple lacunar infarcts as the initial presentation of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. J Chinese Med Assoc 2015; 78: 424–6.
86. Sharma R, de Havenon A, Rivier C, et al. Impaired mobility and MRI markers of vascular brain injury:

Atherosclerosis Risk in Communities and UK Biobank studies. BMJ Neurol Open 2024; 6: e000501.
87. Shen Y, Li F, Cao L, et al. Hip osteoarthritis and the risk of lacunar stroke: A two-sample Mendelian randomization study. Genes (Basel) 2022; 13: 1584.
88. Obrecht M, Zurbruegg S, Accart N, et al. Magnetic resonance imaging and ultrasound elastography in the context of preclinical pharmacological research: significance for the 3R principles. Front Pharmacol 2023; 14: 1177421.
89. Salazar-Méndez J, Cuyul-Vásquez I, Viscay-Sanhueza N, et al. Structural and functional brain changes in people with knee osteoarthritis: a scoping review. PeerJ 2023; 11: e16003.
90. Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune–metabolic viewpoint for age-related diseases. Nat Rev Endocrinol 2018; 14: 576–90.
91. Fulop T, Larbi A, Pawelec G, et al. Immunology of aging: the birth of inflammaging. Clin Rev Allergy Immunol 2021; 64: 109–22.
92. Low A, Mak E, Rowe JB, Markus HS, O'Brien JT. Inflammation and cerebral small vessel disease: A systematic review. Ageing Res Rev 2019; 53: 100916.
93. Del Cuore A, Pacinella G, Riolo R, Tuttolomondo A. The role of immunosenescence in cerebral small vessel disease: A review. Int J Mol Sci 2022; 23: 7136.
94. Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage 2013; 21: 16–21.
95. Abramoff B, Caldera FE. Osteoarthritis. Med Clin North Am 2020; 104: 293–311.
96. Babaei M, Javadian Y, Narimani H, et al. Correlation between systemic markers of inflammation and local synovitis in knee osteoarthritis. Caspian J Intern Med 2019; 10: 383–7.
97. Attur M, Krasnokutsky S, Statnikov A, et al. Low-Grade inflammation in symptomatic knee osteoarthritis: Prognostic value of inflammatory plasma lipids and peripheral blood leukocyte biomarkers. Arthritis Rheumatol 2015; 67: 2905–15.
98. Hoeven TA, Kavousi M, Ikram MA, et al. Markers of atherosclerosis in relation to presence and progression of knee osteoarthritis: a population-based cohort study. Rheumatology 2015; 54: 1692–8.
99. Motta F, Barone E, Sica A, Selmi C. Inflammaging and osteoarthritis. Clin Rev Allergy Immunol 2022; 64: 222–38.
100. Mobasheri A, Matta C, Zákány R, Musumeci G. Chondrosenescence: Definition, hallmarks and potential role in the pathogenesis of osteoarthritis. Maturitas 2015; 80: 237–44.
101. Long D, Blake S, Song XY, Lark M, Loeser RF. Human articular chondrocytes produce IL-7 and respond to IL-7 with increased production of matrix metalloproteinase-13. Arthritis Res Ther 2008; 10: R23.
102. Rezuş E, Cardoneanu A, Burlui A, et al. The link between inflammaging and degenerative joint diseases. Int J Mol Sci 2019; 20: 614.
103. Millerand M, Berenbaum F, Jacques C. Danger signals and inflammaging in osteoarthritis. Clin Exp Rheumatol 2019; 37 Suppl 120: 48-56..
104. Rosenberg JH, Rai V, Dilisio MF, Agrawal DK. Damage-associated molecular patterns in the pathogenesis of osteoarthritis: potentially novel therapeutic targets. Mol Cell Biochem 2017; 434: 171–9.
105. Prati C, Demougeot C, Guillot X, Godfrin-Valnet M, Wendling D. Endothelial dysfunction in joint disease. Joint Bone Spine 2014; 81: 386–91.
106. Eroglu E, Kocyigit I, Lindholm B. The endothelin system as target for therapeutic interventions in cardiovascular and renal disease. Clinica Chimica Acta 2020; 506: 92–106.
107. Steyers C, Miller F. Endothelial dysfunction in chronic inflammatory diseases. Int J Mol Sci 2014; 15: 11324–49.
108. Poredos P, Poredos AV, Gregoric I. Endothelial dysfunction and its clinical implications. Angiology 2021; 72: 604–15.
109. Andresen J, Shafi NI, Bryan RM. Endothelial influences on cerebrovascular tone. J Appl Physiol 2006; 100: 318–27.
110. Kim MJ, Kim HJ, Hong YH, et al. Age-related NADPH oxidase (arNOX) activity Correlated with cartilage degradation and bony changes in age-related osteoarthritis. J Korean Med Sci 2015; 30: 1246.
111. Wang J, Sun H, Fu Z, Liu M. Chondroprotective effects of alpha-lipoic acid in a rat model of osteoarthritis. Free Radic Res 2016; 50: 767–80.
112. De Silva TM, Miller AA. Cerebral small vessel disease: Targeting oxidative stress as a novel therapeutic strategy? Front Pharmacol 2016; 7: 61.
113. Hussain SM, Dawson C, Wang Y, et al. Vascular pathology and osteoarthritis: A systematic review. J Rheumatol 2020; 47: 748–60.
114. Ma S, Wang C, Mao X, Hao Y. B cell dysfunction associated with aging and autoimmune diseases. Front Immunol 2019; 10: 318.

115.Frasca D, Blomberg BB. Adipose tissue inflammation induces B cell inflammation and decreases B cell function in aging. Front Immunol 2017; 8: 1003.
116.Jian B, Hu M, Cai W, Zhang B, Lu Z. Update of immunosenescence in cerebral small vessel disease. Front Immunol 2020; 11: 585655.
117.Hu WT, Howell JC, Ozturk T, et al. CSF cytokines in aging, multiple sclerosis, and dementia. Front Immunol 2019; 10: 480.
118.Plaza-Zabala A, Sierra-Torre V, Sierra A. Autophagy and microglia: Novel partners in neurodegeneration and aging. Int J Mol Sci 2017; 18: 598.
119.Ronaldson PT, Davis TP. Blood-brain barrier integrity and glial support: mechanisms that can be targeted for novel therapeutic approaches in stroke. Curr Pharm Des 2012; 18: 3624-44.
120.Kimura A, Sakurai T, Yamada M, et al. Anti-endothelial cell antibodies in patients with cerebral small vessel disease. Curr Neurovasc Res 2012; 9: 296–301.
121.Ponchel F, Burska AN, Hensor EM, et al. Changes in peripheral blood immune cell composition in osteoarthritis. Osteoarthritis Cartilage 2015; 23: 1870-8.
122.Zhu W, Zhang X, Jiang Y, et al. Alterations in peripheral T cell and B cell subsets in patients with osteoarthritis. Clin Rheumatol 2020; 39: 523–32.
123.Li YS, Luo W, Zhu SA, Lei GH. T Cells in osteoarthritis: Alterations and beyond. Front Immunol 2017; 8: 356.
124.Xie X, Doody GM, Shuweihdi F, Conaghan PG, Ponchel F. B-cell capacity for expansion and differentiation into plasma cells are altered in osteoarthritis. Osteoarthritis Cartilage 2023; 31: 1176–88.
125.Gao Y, Cai W, Zhou Y, et al. Immunosenescence of T cells: a key player in rheumatoid arthritis. Inflamm Res 2022; 71: 1449–62.
126.Zhang S, Feng Y, Yin X, et al. Genetic evidence suggesting the predicted causality between osteoarthritis and cardiovascular diseases. Rheumatol Autoimmu 2023; 3: 230–9.
127.Al-Khazraji BK, Badrov MB, Kadem M, et al. Exploring cerebrovascular function in osteoarthritis: "Heads-up." Physiol Rep 2019; 7: e14212.
128.Bian L, Zhou Y, Zhang D, et al. Negative correlation between serum pyruvate kinase M2 and cognitive function in patients with cerebral small vessel disease. Clin Neurol Neurosurg 2023; 225: 107586.
129.Jiang T, Zhou Y, Zhang D, et al. Association of serum interleukin-34 and insulin resistance with cognitive impairment in patients with cerebral small vessel disease. Curr Neurovasc Res 2021; 18: 446–55.
130.Schulz M, Malherbe C, Cheng B, Thomalla G, Schlemm E. Functional connectivity changes in cerebral small vessel disease - a systematic review of the resting-state MRI literature. BMC Med 2021; 19: 103.
131.Fan D, Zhao H, Liu H, et al. Abnormal brain activities of cognitive processes in cerebral small vessel disease: A systematic review of task fMRI studies. J Neuroradiol 2024; 51: 155–67.
132.Cardoso J, Sibille K, Glover T, et al. Cognitive performance is associated with pain and function among individuals with or at risk of knee osteoarthritis. J Pain 2018; 19: S102.
133.Xin H, Liang C, Fu Y, et al. Disrupted brain structural networks associated with depression and cognitive dysfunction in cerebral small vessel disease with microbleeds. Prog Neuropsychopharmacol Biol Psychiatry 2024; 131: 110944.
134.Wei HL, Wei C, Yu YS, et al. Dysfunction of the triple-network model is associated with cognitive impairment in patients with cerebral small vessel disease. Heliyon 2024; 10: e24701.
135.Gonçalves S, Hathway GJ, Woodhams SG, Chapman V, Bast T. No evidence for cognitive impairment in an experimental rat model of knee osteoarthritis and associated chronic pain. J Pain 2023; 24: 1478–92.
136.Nastić K, Pecikoza U, Labudović-Borović M, et al. The antidepressant drugs vortioxetine and duloxetine differentially and sex-dependently affect animal well-being, cognitive performance, cardiac redox status and histology in a model of osteoarthritis. Biomed Pharmacother 2023; 166: 115360.
137.Eitner A, Hofmann GO, Schaible HG. Mechanisms of osteoarthritic pain. Studies in humans and experimental models. Front Mol Neurosci 2017; 10: 349.
138.Magni A, Agostoni P, Bonezzi C, et al. Management of osteoarthritis: Expert opinion on NSAIDs. Pain Ther 2021; 10: 783–808.
139.Lim YZ, Wong J, Hussain SM, et al. Recommendations for weight management in osteoarthritis: A systematic review of clinical practice guidelines. Osteoarthr Cartil Open 2022; 4: 100298.
140.Mo L, Jiang B, Mei T, Zhou D. Exercise therapy for knee osteoarthritis: A systematic review and network meta-analysis. Orthop J Sports Med 2023; 11: 232596712311727.

141.Zeng CY, Zhang ZR, Tang ZM, Hua FZ. Benefits and mechanisms of exercise training for knee osteoarthritis. Front Physiol 2021; 12: 794062.
142.Endisha H, Datta P, Sharma A, et al. MicroRNA-34a-5p promotes joint destruction during osteoarthritis. Arthritis Rheumatol 2021; 73: 426–39.
143.Ali SA, Gandhi R, Potla P, et al. Sequencing identifies a distinct signature of circulating microRNAs in early radiographic knee osteoarthritis. Osteoarthritis Cartilage 2020; 28: 1471–81.
144.Rousseau JC, Millet M, Croset M, et al. Association of circulating microRNAs with prevalent and incident knee osteoarthritis in women: the OFELY study. Arthritis Res Ther. 2020; 22: 2.
145.Chen C. Serum hsa_circ_101178 as a Potential biomarker for early prediction of osteoarthritis. Clin Lab 2020; 66: p1577.
146.Fernández-Moreno M, Soto-Hermida A, Vázquez-Mosquera ME, et al. A replication study and meta-analysis of mitochondrial DNA variants in the radiographic progression of knee osteoarthritis. Rheumatology 2017; 56: 263–70.
147.Fernández-Moreno M, Soto-Hermida A, Vázquez-Mosquera ME, et al. Mitochondrial DNA haplogroups influence the risk of incident knee osteoarthritis in OAI and CHECK cohorts. A meta-analysis and functional study. Ann Rheum Dis 2017; 76: 1114–22.
148.Fang H, Zhang F, Li F, et al. Mitochondrial DNA haplogroups modify the risk of osteoarthritis by altering mitochondrial function and intracellular mitochondrial signals. Biochim Biophys Acta 2016; 1862: 829–36.
149.Koo BS, Song Y, Lee S, et al. Association of Asian mitochondrial DNA haplogroup B with new development of knee osteoarthritis in Koreans. Int J Rheum Dis 2019; 22: 411–6.
150.Søndergaard CB, Nielsen JE, Hansen CK, Christensen H. Hereditary cerebral small vessel disease and stroke. Clin Neurol Neurosurg 2017; 155: 45–57.
151.Longstreth WT. Brain Vascular disease overt and covert. Stroke 2005; 36: 2062–3.
152.Falcone GJ, Malik R, Dichgans M, Rosand J. Current concepts and clinical applications of stroke genetics. Lancet Neurol 2014; 13: 405–18.
153.Tikka S, Baumann M, Siitonen M, et al. CADASIL and CARASIL. Brain Pathol 2014; 24: 525-44.
154.Brady RO, Gal AE, Bradley RM, et al. Enzymatic defect in Fabry's disease. N Engl J Med 1967; 276: 1163–7.
155.Jeanne M, Gould DB. Genotype-phenotype correlations in pathology caused by collagen type IV alpha 1 and 2 mutations. Matrix Biology 2017; 57–58: 29–44.
156.Bugiani M, Kevelam SH, Bakels HS, et al. Cathepsin A–related arteriopathy with strokes and leukoencephalopathy (CARASAL). Neurology 2016; 87: 1777–86.
157.Wang Y, Shi C, Li Y, et al. Genetic study of cerebral small vessel disease in Chinese Han population. Front Neurol 2022; 13: 829438.