4-1-2018

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Citation of this paper:

- PMID: 29406252
- DOI: 10.1016/j.joca.2018.01.011

Osteoarthritis and Cartilage 26 (2018) 462–470

Osteoarthritis and Cartilage

Review

Osteoarthritis, cerebrovascular dysfunction and the common denominator of inflammation: a narrative review

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ARTICLE INFO

Article history:
Received 13 October 2017
Accepted 13 January 2018

Keywords:
Osteoarthritis
Cerebrovascular dysfunction
Vascular dysfunction
Comorbidities
Inflammation
Aging

SUMMARY

Objective: Population-based cohort studies suggest an association between osteoarthritis (OA) and cerebrovascular disease, yet the mechanisms underlying vascular comorbidities in OA remain unclear. The purpose of this narrative review is to discuss the literature examining inflammation in OA with a focus on physiological mechanisms, and whether overlapping mechanisms exist in cerebrovascular dysfunction.
Method: A literature search was conducted in PubMed using combinations of search terms: *osteoarthritis*, *cerebrovascular (disease/dysfunction/risk)*, *cardiovascular (disease/dysfunction/risk)*, *aging/ageing*, *inflammation*, *inflammatory mediators*, *cytokine*, *c-reactive protein*, *interleukin*, *advanced glycation end-products*, *metabolic syndrome*, *reactive oxidative species*, *cognitive impairment*, *(vascular-related) dementia*, *small cerebral vessel disease*, *endothelial function*, *blood–brain barrier*, *gender/sex*, *hypertension*, *peripheral vascular health*, and *physical activity*. Reference lists of identified articles were also researched manually.
Results: Overlapping inflammatory factors that may contribute to onset and progression of both OA and cerebrovascular dysfunction are presented. We describe oxidative mechanisms involving pro-inflammatory cytokines and oxidative species, advanced glycation end-products, sex hormones, microvascular dysfunction and osteoprotegerin, and their specific roles in potentially contributing to OA and cerebrovascular dysfunction.
Conclusion: Synthesis of the current literature suggests future investigations may benefit from directly testing cerebrovascular hemodynamics and cognitive function in individuals with or at risk of OA to elucidate common physiological mechanisms.

Introduction

Musculoskeletal and cardiovascular diseases (CVDs) together contribute substantially to the global economic burden of illness[1], and may possess overlapping mechanisms in disease progression. Individuals with osteoarthritis (OA), the most prevalent joint-related disorder[2], are prone to developing hypertension[3], a risk factor for cardiovascular and cerebrovascular disease (CeVD) onset. While CVD is the leading cause of death for most living with OA[4], driven mainly by decreased mobility[5,6], those with OA are also more likely to experience stroke[7]. With a rise in the aging, obese, and less active population, incidence and prevalence of OA[8] and vascular co-morbidities[9] are likely to increase. These concerning projections emphasize the need to understand the progression of these disorders to inform preventative and therapeutic strategies. The overlap in the prevalence of OA with vascular diseases also raises the possibility of shared disease mechanisms (Fig. 1). In this narrative review, we focus on shared mechanisms in OA and CeVD.

Pathophysiological mechanisms of OA and vascular diseases are complex, suggesting that any potential interaction between OA and cardiovascular pathology is likely multi-factorial. For example, physical inactivity due to OA-attributed discomfort and pain may, at least in part, explain the increased prevalence of CVD in hip and

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https://doi.org/10.1016/j.joca.2018.01.011

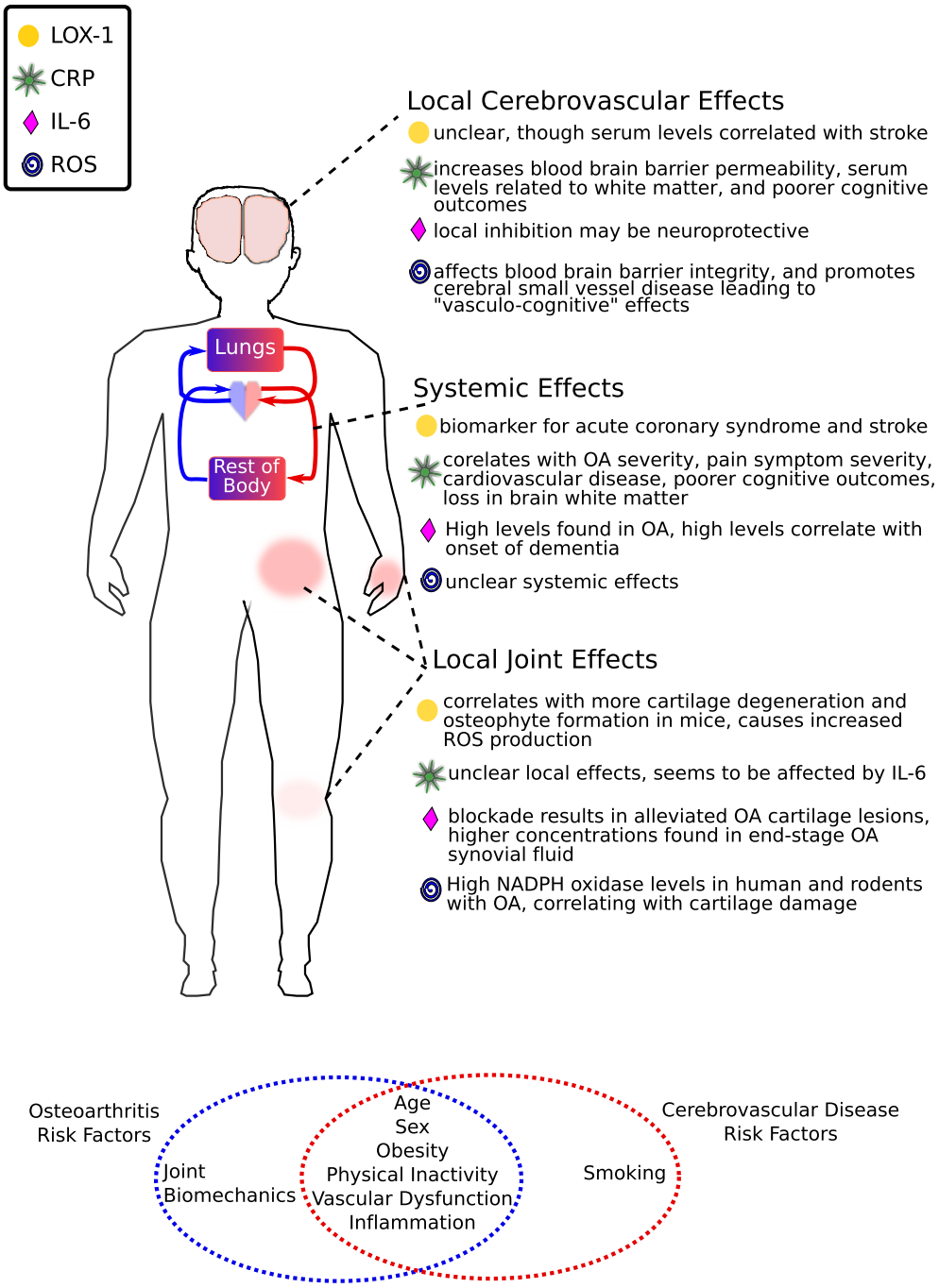

Fig. 1. Schematic highlighting local and systemic mediators of, and shared risk factors for osteoarthritis (OA) and cerebrovascular dysfunction. The hip, knee and hand (most prevalent sites for OA incidence) represent OA disease, and the brain highlights location for cerebrovascular dysfunction. Shared risk factors are indicated in the Venn diagram on bottom.

knee OA[5], yet the association of symptomatic (but not asymptomatic) hand OA with cardiovascular events remains after accounting for levels of physical activity[10]. However, additional factors for the association between vascular co-morbidities and OA may exist[11].

Chronically or intermittently-elevated levels of systemic inflammation may be an additional link between OA and vascular disease. The traditional consideration that OA represents a non-inflammatory condition is now reconsidered with the view that chronic, low-grade local inflammation underlies the OA process, driven by several inflammatory mechanisms[12,13]. Local inflammation exists at the joint (e.g., synovitis and inflammatory mediators in the synovial fluid); however, whether systemic inflammatory mechanisms also exist remains controversial, but some evidence exists. For example, chronic and low-grade inflammation occurs with aging (i.e., "inflammaging")[14], and OA becomes more prevalent with age[15]. Independent of aging, blood immune composition changes (affected sub-phenotypes of T and B-cells) occur in those with OA which suggests a systemic change in inflammatory processes accompanying OA[16]. The clinical significance of such immunological shifts, however, is uncertain. Similarly, plasma levels of prostaglandin E2 and 15-hydroxyeicosatetraenoic acid, derivatives of the arachidonic acid cascade, were elevated in patients with symptomatic knee OA, and correspond with OA progression (i.e., joint space narrowing)[17]. These studies suggest that

several low-grade chronic inflammatory processes occurring locally in joints affected by OA are also reflected systemically.

Several shared inflammatory mediators between OA and CVD include inflammatory cytokines (e.g., interleukin-6)[18,19], oxidative pathways[20,21], and C-reactive protein (CRP)[22–24]. Inflammation leads to vascular endothelium dysfunction, where endothelial dysfunction predicts cardiovascular event incidence[25]. Impaired flow-mediated dilation responses seen in those with OA indicate poor vascular endothelial function[26], which may serve as an early sign of peripheral vascular dysfunction. Endothelial function is also integral to cerebrovascular health, with the endothelial cells forming tight junctions in the blood–brain barrier (BBB). Endothelial dysfunction is involved in both cardiovascular (e.g., atherosclerosis and myocardial infarction) and CeVD (e.g., stroke)[27]. Therefore, since endothelial dysfunction and the incidence of both CVD and stroke are higher in those with OA[7], cerebrovascular dysfunction (i.e., when mechanisms for regulating cerebral blood flow are compromised) may also be an under-recognized form of vascular dysfunction in OA.

Cardiovascular and CeVD share several risk factors including age, diet, physical activity, sex, hypertension[28]. Impaired cerebrovascular reactivity predicts stroke in those with carotid artery disease[29], and OA progression is associated with carotid artery disease onset[30]. Moreover, while population-based cohort studies suggest an association between OA and CeVD (Table I), whether or not a causative relationship exists is unknown. As an essential step in elucidating the association between OA and CVD/CeVD, this narrative review will discuss the literature examining whether inflammation, and specific physiological mechanisms in OA are shared with cerebrovascular dysfunction.

What is cerebrovascular dysfunction?

Functional cerebral vessels ensure that brain tissue receives a continuous blood supply. Functional cerebral vessels include intact: 1) BBB, 2) myogenic mechanism (i.e., reflex vasoreactivity), and 3) functional hyperemia (i.e., increase in blood flow accompanying tissue activity)[31]. Cerebral endothelial cells form tight junctions which underlie an intact BBB, where endothelial dysfunction leads to CeVD onset (e.g., stroke)[27]. The myogenic response reflects the capacity of cerebrovascular smooth muscle cells to respond to local changes in intravascular pressure, as a form of autoregulation, to keep blood flow constant within the cerebral vessels. Functional hyperemia is operationally-defined by cerebrovascular reactivity, or respective changes in blood flow to endogenous and/or exogenous vasoactive agents (i.e., dilators and/or constrictors)[31]. Both the myogenic mechanism and functional hyperemia contribute to cerebrovascular autoregulation, which describes the brain's ability to maintain cerebral blood flow in the face of perfusion pressure changes[32]. Thus, cerebrovascular dysfunction occurs when adaptive mechanisms for regulating cerebral blood flow are compromised, potentially resulting in inadequate cerebral blood flow distribution. Dysfunctional cerebrovascular autoregulation[33] and reactivity[29] are both involved in predicting poor cerebrovascular outcomes for those at risk.

Besides smoking, which seems to have a positive relationship with cerebrovascular disorders[34] and an inverse relationship with OA progression[35], several other risk factors and underlying mechanisms are shared between cerebrovascular dysfunction and OA (discussed below).

Potential shared inflammatory mechanisms between OA and cerebrovascular dysfunction

At the local tissue level, tissue damage in OA is explained, at least in part, by an increase in various inflammatory mediators, such as pro-inflammatory cytokines and Reactive Oxygen Species (ROS)[13]. In this section, we will discuss some of the overlapping inflammatory and oxidative mechanisms involved in local and/or systemic progression of OA and cerebrovascular dysfunction (Fig. 1).

LOX-1

Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is found on the surface of the vascular endothelium and is the receptor for oxidized low-density lipoprotein (oxLDL), a more reactive form of low-density lipoproteins (LDL). LOX-1 receptor activation by oxLDL binding causes altered production of nitric oxide by the endothelium, in part via superoxide production[36]. oxLDL binding to LOX-1 receptors on the endothelium leads to intimal layer thickening and lipid deposition[37].

Evidence of a systemic role

Through proteolytic cleavage, LOX-1 may release into the bloodstream as soluble LOX-1, and act as a systemic biomarker for early diagnosis of acute coronary syndrome[38]. In an age-and sex-matched study (age 40–79 years), acute stroke patients showed higher serum levels of LOX-1, indicating that soluble LOX-1 may also act as a systemic biomarker for acute stroke[39].

Evidence of a local role

Oxidized LDL (ox-LDL) binding to LOX-1 causes increased activation of nuclear factor-kappa B (NF-kB) signaling and production of ROS in bovine articular chondrocytes[40]. This effect may be mitigated partly by synovial cells, since ox-LDL injection into mouse knee joints did not induce an inflammatory response[41]. Nevertheless, using a murine model of post-traumatic OA, via destabilization of the medial meniscus (DMM) experimental model, Hashimoto *et al.* concluded that LOX-1 is critical in OA progression, as LOX-$1^{+/+}$ mice had more knee joint damage (i.e., cartilage degeneration and osteophyte formation) compared to LOX-$1^{-/-}$ mice[42]. It is unclear from the above experiments whether the observed effects of LOX-1 receptor are a result of variations in LOX-1 receptor expression or changes in the ox-LDL ligand concentration.

Adaptations in lipid metabolism may underlie OA progression, as indicated by increased serum cholesterol levels and lipid deposition within the joint during early OA[43]. Although serum LOX-1 levels are greater in stroke patients, further research is necessary to determine whether LOX-1 is also higher in individuals before stroke and whether this correlates with cerebrovascular dysfunction. Future work could determine whether heightened levels of circulating lipids and/or LOX-1 receptor expression affect

Table I
Epidemiological studies highlighting vascular comorbidities (including cerebrovascular disease) in those with osteoarthritis

Author (year)	Osteoarthritis patient sample	Type of study	Vascular-comorbidities event
Hsu (2017)	Severe OA: knee or hip replacement required Mild to Moderate OA: no surgery required	Retrospective population-based cohort	Hemorrhagic or thrombotic stroke
Hawker (2014)	Moderate to severe Hip, knee	Population-based cohort	Acute myocardial infarction, coronary revascularization, heart failure, stroke or transient ischemic attack

cerebrovascular function in those with OA and whether loss or inhibition of LOX-1 has a protective effect on cerebrovascular outcomes as it does in experimental OA.

hs-CRP

As part of the inflammatory process, hepatocytes and adipocytes release C-reactive protein (CRP) via cytokine-regulated mechanisms[44]. Increased plasma levels of CRP [measured through high-sensitivity CRP (hs-CRP) immunoassays] introduce low-grade systemic inflammation which threatens the functional integrity of the vascular endothelial layer. Besides indicating systemic inflammation, CRP modulates innate immunity via complement binding and fixation. Interestingly, CRP has also been shown to be a ligand of LOX-1, although the effect of this interaction remains unclear[45].

Evidence of a systemic role

CRP serum levels correlate with radiographic severity of OA[46]. hs-CRP serum levels correlate with pain symptom severity (using WOMAC pain scale) over a 5-year period[47]. CRP is also associated with CVD progression, as seen in those with coronary artery disease, where the endothelial function is also compromised[48]. As well, systemic hs-CRP levels remain elevated for as many as 28 days following a stroke, at levels higher than hypertensive and normotensive individuals[49]. CRP is also related to cognitive outcomes, as Miralbell *et al.* showed that CRP levels were negatively correlated with cognitive functions like verbal fluency performance[50]. Miralbell *et al.* also showed that CRP levels were associated with loss in brain white matter integrity in individuals without a history of symptomatic CVD[51], which suggests CRP is associated with preclinical changes in cerebral anatomy that may have an impact on long-term cognitive outcomes. In another study, after adjusting for age, gender, BMI, smoking status, and circulating lipids, higher serum levels of IL-6 and CRP were associated with poorer physical and cognitive performance and even predicted the risk of mortality[52]. Although the local role of CRP on human cerebrovasculature is unknown, it is possible that levels of CRP could rise in patients with OA and affect the endothelium and BBB.

Evidence of a local role

In response to injury, local inflammatory cells release cytokines, like IL-6, into the bloodstream, and the liver responds by releasing acute phase reactants such as CRP[53]. Higher levels of hs-CRP (~2.5 mg/L) increase paracellular permeability in a mouse model of adult-onset obesity[54]. These data suggest that both OA and CeVD may share a common component of systemic inflammation. Future studies should seek to test this question as a potential mechanism mediating co-morbid effects of systemic inflammation between OA and CeVD.

It is important to note that CRP is also often high in obese individuals[55], and that metabolic syndrome (MetS; i.e., a combination of obesity, hypertension, dyslipidemia, insulin resistance) is associated with increased risk of knee OA. To explore whether CRP was inherent to OA independent of confounding MetS components, Engström *et al.* found that the association of CRP levels with knee OA incidence was attenuated after risk factor adjustments and initial associations were largely due to body mass index[56].

Interleukin-6 (IL-6)

Specific inflammatory mediators play a prominent role in OA progression. As an example, synovial fluid cytokine levels of IL-6 and IL-8 were higher in patients with end-stage OA than a traumatic knee injury group without OA, despite a similar need for knee replacement surgery[18].

Evidence of a systemic role

Higher serum cytokine levels of IL-6 and IL-8[57] and plasma levels of IL-6[58] are found in those with OA. In the context of cerebrovasculature, a 7 year-long observational study conducted in 803 Japanese participants with vascular risk factors, those with higher circulating levels of IL-6 were more likely to develop dementia[59]. Additionally, the association of IL-6 with incidental vascular-related dementia remained significant despite multivariable analyses accounting for other conventional risk factors (e.g., gene variants and CRP levels)[59].

Evidence of a local role

In an OA-induced (via DMM) mouse model, systemic IL-6 blockade alleviated OA cartilage lesions, and it was determined that downstream signaling during IL-6 activation mediates the catabolic effects of IL-6 on cartilage, namely via signal transducer and activator of transcription-3 (Stat3) phosphorylation[60]. Similarly, in hypoxic-ischemia brain injury in neonatal mice, selective inhibition of the glycogen synthase kinase 3 isoform (i.e., GSK3ß) was neuroprotective by reducing Stat3 phosphorylation which can, in part, be attributed to the ability of GSK3ß inhibition in decreasing IL-6 production[61].

Recently, the term “vascular contributions to cognitive impairment and dementia” (VCID) was used to explain the role of cerebrovascular functionality on cognitive decline[62]. With these findings, we speculate that the heightened IL-6 levels in those with OA, and known vascular risk factors, may be one way in which those with OA might be put at higher risk for developing dementia. Together, these data provide evidence that IL-6 may have a role in the progression of both OA and cerebrovascular dysfunction. Further studies are required to investigate the role of IL-6 as a candidate systemic biomarker of cerebrovascular-related cognitive decline in OA.

Reactive oxygen species (ROS)

Increased ROS production can induce oxidative stress which then impacts cellular activity. The production of ROS is increased with ageing, hypertension, endothelial dysfunction, and vascular inflammation[63]. Both cerebral vascular cells and chondrocytes have the ability to produce ROS (see below), where excessive ROS production leads to cerebral microvascular dysfunction and the promotion of osteoarthritis, respectively. As an example, in the brain, cerebral endothelial nitric oxide synthase can produce superoxide anion (a member of the ROS family) that impairs the nitric oxide signaling pathway[64] underlying healthy vascular function. As well, in cerebral small vessel disease, there is an increase in local ROS production, primarily via NADPH oxidase activity[65]. In this section, we discuss the local effects of ROS production at the cerebrovascular level and during OA progression.

Evidence of a local role

With regards to OA progression, a higher mRNA level of NADPH oxidase isoform was found in a rodent model of OA, where consumption of alpha-lipoic acid (an ROS scavenger) provided chondroprotective effects via decreased NADPH oxidase production[66]. In congruence with the OA rodent study, higher age-related levels of plasma NADPH oxidase activity in humans with knee OA correlated with greater cartilage degradation and Kellgren–Lawrence grade[67]. As well, ROS activity was indicated by an accumulation of nitrotyrosine (a product formed after nitric oxide reacts with ROS) in histological sections of knee and ankle articular cartilage samples taken from human adults with OA[68]. ROS production also affects BBB integrity and is implicated in several BBB diseases[69], which may result in ROS accumulation near the cerebral vessels and

ultimately cause fatal neurological and/or cerebrovascular dysfunction. As discussed, ROS production is a major cause of cerebral small vessel disease which leads to the development of subsequent "vasculo-cognitive" defects.

It is unknown whether the NADPH oxidase activity accompanying OA progression is predictive of, or associated with, cerebrovascular dysfunction. Whether mechanisms that cause higher ROS production in chondrocytes during OA are also implicated in cerebrovascular dysfunction remain to be determined. As such, future studies may want to investigate how ROS production pathways implicated during hypercholesterolemia, or aging, may affect OA progression and whether these pathways implicate cerebrovascular dysfunction.

Potential mechanisms related to shared risk factors between OA and CeVD

Aging

Although OA becomes more prevalent with age, the mechanistic processes responsible for onset and progression of OA remain insufficiently understood. Aging is associated with increases in catabolic factors and cytokines that increase ROS production and oxidative stress, thereby promoting progression of OA[70]. As well, elevated low-grade systemic inflammation detected in OA, also can be observed with aging in general[8]. This phenomenon has been coined "inflammaging"[71]. One theory regarding inflammation and OA progression with aging considers the role of advanced glycation end products (AGEs), which are produced in aging tissue, and weaken cartilage by altering its mechanical properties[12,72]. AGE receptors (RAGE) are present on chondrocytes[73], and upon AGE-binding, RAGE activation leads to increased production of pro-inflammatory cytokines, specifically IL-6 and IL-8, thereby increasing inflammation[19]. AGEs interfere with human BBB permeability, and leads to the enhanced release of IL-6 and IL-8[74]. As described above, BBB integrity is imperative for intact cerebrovascular function.

Similar to RAGE activation during OA progression, RAGE gene overexpression is present in vascular disease[75]. In the case of CeVD, the polymorphism rs1035798 of the RAGE gene was associated with increased risk of hemorrhagic stroke in those under the age of 50[76]. In a 9-year follow-up study, systemic serum levels of N$\sum$-(carboxymethyl)lysine (CML), a robust AGE whose circulating levels are representative of overall AGE burden, were correlated with the incidence of coronary heart disease and stroke[77]. Higher stroke-risk individuals may also have greater levels of RAGE and AGE that could weaken cartilage and lead to OA progression. Taken together, aging may contribute to onset and/or progression of OA and cerebrovascular dysfunction through direct and/or indirect actions of inflammaging, and specifically due to the role of AGEs. Further prospective studies should focus on determining whether local and/or systemic levels of AGEs in OA predict incidence of stroke.

Sex differences

According to the World Health Organization, women have a higher lifetime risk of experiencing stroke, which suggests that they are at a higher risk of developing cerebrovascular dysfunction, as in most cases, cerebrovascular dysfunction precedes stroke[29]. In The Framingham Osteoarthritis Study, the rate of knee OA incidence was 1.7 times higher in elderly (~70 years) women than in men, and the disease progression was also higher in women (relative risk = 1.4, compared to men)[78].

Estrogen and its receptor subtypes are key players in the gender-based disparity for both OA progression and stroke risk. Both estrogen receptor subtypes, ERα and ERβ, are co-expressed in brain and bone tissues. OA prevalence increases with menopause[79,80], and the decrease in estrogen accompanying menopause is not only shown to affect articular cartilage, but also subchondral bone, synovium, periarticular muscles, and the articular capsule[80]. Similarly, the cardio-protective role of estrogen is explained in part by increased nitric oxide synthase production, angiogenesis, and decreased ROS production[79]. Inflammatory insult presents greater BBB disturbances in older female mice compared to young female mice[81]. The role of sex hormones in BBB disruption was supported by similar outcomes in ovariectomized young female mice, an effect that was reversible with estradiol replacement, where estradiol protected the BBB via maintenance of key barrier features (e.g., paracellular permeability and tight junction integrity). The role of NADPH in both small cerebral vessel disease and osteoarthritis (via ROS production), considered alongside the fact that older women are more likely to develop OA, suggests that post-menopausal women are especially at a high-risk of CeVD due to increased ROS production and potential loss of BBB integrity.

Shared mechanisms in progression of OA and vascular dysfunction: the "chicken or egg"

Cardiovascular events are higher in OA than age-matched controls[82], especially in women with OA affecting two or more joints[83]. Specifically, those with OA are over twice as likely to develop ischemic heart disease or heart failure[84], and even after accounting for cardiovascular risk factors, atherosclerosis is more prevalent in women with knee and hand OA[30]. Potential associations between OA and vascular comorbidities are outlined schematically, highlighting the potential relationship(s) between OA and cerebrovascular dysfunction (Fig. 1). The proposed relationship(s) introduce(s) an interesting "chicken or egg" thought on the directionality and/or simultaneous progression of OA and vascular impairment. Here, we suggest possible overlapping systemic and local *vascular-related mechanisms* between OA and vascular dysfunction.

Systemic vascular mechanisms

Osteoprotegerin (OPG) is a key modifier of bone resorption (via osteoclast regulation), and is also associated with vascular endothelial function and is predictive of early atherosclerosis in coronary artery disease patients[85]. As a circulating glycoprotein, OPG acts to antagonize receptor activator nuclear factor kappa-B ligand (RANKL), thereby affecting osteoclasts and preventing further bone breakdown[86]. A higher level of OPG was also found in serum levels of those with OA where levels were correlated with the Kellgren–Lawrence scale for radiographic OA severity[87]. The role of OPG in both atherosclerosis and bone remodeling suggests a possible overlapping mechanism in the progression of OA and CVD. These higher levels of OPG may serve to progress OA, and may occur in tandem (or before/after) development of dysfunctional vascular remodeling.

Local (Joint) vascular mechanisms

Limited data exist which consider the potential role of vascular dysfunction in the progression of OA. While it is suggested that local vascular pathology potentiates osteoarthritis progression via subchondral bone ischemia[88], the systemic macrovascular changes present during CVD may also contribute to OA progression. Arteriosclerosis may influence the fate of bone health, where vascular calcification may share overlapping mechanisms with skeletal bone remodeling[89].

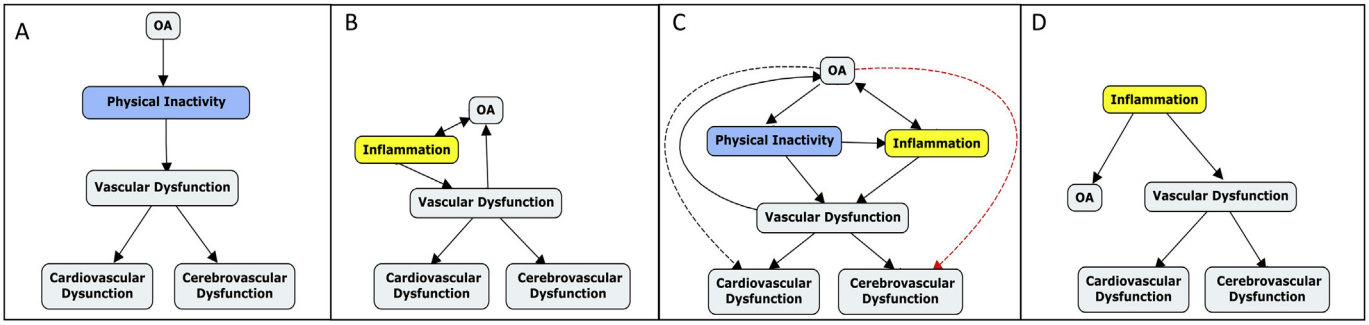

Fig. 2. Simplified schematic describing the proposed relationship between osteoarthritis and cerebrovascular dysfunction. Cmap© software (Institute for Human and Machine Cognition, FL, USA) was used to create the schematic. Panel A: Osteoarthritis (OA) effects on vascular dysfunction (i.e., cardiovascular and cerebrovascular function) may in part be explained via physical inactivity. Panel B: Inflammatory processes both drive and are driven by OA (bi-directionality indicated by double headed arrow). Inflammation promotes vascular dysfunction independent of OA, and vascular dysfunction exacerbates OA. Panel C: Combining Panel A with Panel B, OA not only reduces the capacity to perform vasculo-protective physical activity, but also progresses vascular dysfunction via inflammation. The role of inflammation on vascular function, together with the observed cardiovascular complications associated with OA (black dashed line), suggest the hypothesis (red dashed line) that OA is also associated with cerebrovascular dysfunction. Panel D: Inflammation drives the independent progression of OA and vascular dysfunction, and no causal or associative relationship exists between OA and vascular dysfunction.

Potential cognitive outcomes in OA from the perspective of cerebrovascular dysfunction

Cerebrovascular outcomes in those with OA may lead to neurological damage, which may include, but is not limited to, changes in cognition, gait, or autonomic control. In most cases, cerebral microvascular dysfunction is the leading cause of cerebral small vessel disease and ultimately leads to impaired perfusion within the brain that is followed by changes in cognitive function[90]. Similarly, in a transgenic mouse model of Alzheimer's disease, mice that were induced with OA (via viral injection into knees) presented with greater Aß plaques and neuroinflammation than those without OA, which suggest that peripheral inflammation may also be linked with Alzheimer's disease pathology[91]. Cerebrovascular impairment can be assessed through characteristic changes in this disease such as white matter hyperintensities, brain atrophy, and small hemorrhaging[92]. Those with OA who have undergone joint replacements have greater volume of white matter hyperintensities, despite a lack of history of cardiac or cerebrovascular events[93]. It is important to note that myocardial infarction[94] and stroke[95] incidences are higher with major surgery such as hip and/or knee replacement; thus, the effect of surgery need to be assessed as a potential confounder when determining white matter hyperintensities in these patients. Future OA studies should investigate the presence of subclinical cerebral microvascular damage and whether there is an association between cerebral microvascular damage and cognitive outcomes in these patients.

Radiographic knee OA severity correlates negatively with mobility, as indicated by a negative correlation between a higher score on the Kellgren–Lawrence OA severity grading scale and physical performance[96]. In a systematic assessment of gait in older adults with mild cognitive impairment syndromes, velocity, stride length, cadence values were lower in the cognitively-impaired group[97], suggesting that early cognitive decline may affect physical function. As summarized in a study looking at pain and decreased cognition in older adults with OA, pain may influence cognition, which then, in turn, may affect physical function[98]. Decreased performance on executive function tests corresponded with slower gait speed and stair climbing, and after adjusting for performance scores on executive function testing, pain scores were no longer correlated with physical test scores. Together, these studies highlight the importance of OA-associated cognitive decline, as cognitive ability may affect mobility and independence in OA patients.

Summary

This narrative review presents a synthesis of studies, suggesting that cerebrovascular dysfunction may be present in OA patients and may underlie the observed increased risk of stroke in those with OA. The shift from describing OA as a joint-centric disease in the literature has opened discussion on underlying mechanisms of OA progression and affiliated co-morbidities. The well-documented association of OA with increased CVD, cognitive impairment, brain white matter hyperintensities, increased systemic inflammation, together create the ideal milieu for the onset of cerebrovascular dysfunction.

Perspective and future research

We highlighted the potential relationships between OA and cerebrovascular dysfunction (Fig. 2). Future studies should aim to confirm and determine if: 1) mechanisms are common to both diseases, 2) OA-related inflammatory mechanisms directly increase the risk of vascular dysfunction, 3) if vascular dysfunction leads to the OA progression, or 4) if an external driver (e.g., metabolic syndrome) promotes parallel disease progression. Future investigations may quantify parameters grounded in cognitive, hemodynamic, and cellular data. Building on the current cross-sectional correlational studies, future studies should focus on prospective studies designed to delineate whether progression of both diseases occurs in tandem, or whether a (bi-)directional relationship exists between OA and cerebrovascular health outcomes.

Author contributions

BKA conceptualized, organized and drafted the manuscript. CTA, FB, TBB, and JKS contributed to the content, organization, and editing of the manuscript.

Conflict of interest

The authors have no conflicts of interest to report.

Acknowledgments

BKA was funded by the Bone & Joint Institute Collaborative Training Program in Musculoskeletal Health (R2922A32), and a MITACS Elevate Postdoctoral Fellowship in partnership with the Children's Health Foundation (IT08316).

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