




Vascular Pathology and Osteoarthritis: A Systematic Review

Sultana Monira Hussain , Chloe Dawson, Yuanyuan Wang , Andrew M. Tonkin, Louisa Chou, Anita E. Wluka , and Flavia M. Cicuttini 

ABSTRACT. Objective. Vascular pathology (changes in blood vessels) and osteoarthritis (OA) are both common chronic conditions associated with aging and obesity, but whether vascular pathology is a risk factor for OA is unclear. The aim of this study was to systematically review the evidence for an association between vascular pathology and risk of joint-specific OA.

Methods. Scopus, Ovid Medline, and EMBASE were searched from inception to February 2019. MeSH terms and keywords were used to identify studies examining the association between vascular pathology and OA. Two reviewers independently extracted the data and assessed the methodological quality. Qualitative evidence synthesis was performed.

Results. Fifteen studies with high (n = 3), fair (n = 3), or low (n = 9) quality were included. Features of vascular pathology included atherosclerosis, vascular stiffness, and endothelial dysfunction in different vascular beds. There was evidence for an association between vascular pathology and risk of hand OA in women but not men, and between vascular pathology and risk of knee OA in both men and women. Only 2 studies examined hip OA showing no association between vascular pathology and risk of hip OA.

Conclusion. There is evidence suggesting an association between vascular pathology and risk of hand and knee OA, with a potential causal relationship for knee OA. Based on the limited evidence, it is hard to conclude an association for hip OA. Further stronger evidence is needed to determine whether there is a causal relationship. (First Release November 1 2019; J Rheumatol 2020;47:748–60; doi:10.3899/jrheum.181236)

Key Indexing Terms:

VASCULAR PATHOLOGY ATHEROSCLEROSIS ARTERIAL WALL THICKNESS
CAROTID INTIMA-MEDIA THICKNESS CAROTID PLAQUE OSTEOARTHRITIS

Osteoarthritis (OA) is a major cause of pain and disability, resulting in 128.9 million years lived with disability globally

From the School of Public Health and Preventive Medicine, Monash University, Alfred Hospital, Melbourne; Australian National University (ANU) College of Health and Medicine, Canberra; The Alfred Hospital, Melbourne, Australia.

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S.M. Hussain, PhD, Research Fellow, School of Public Health and Preventive Medicine, Monash University, Alfred Hospital; C. Dawson, MPH, Medical Student, School of Public Health and Preventive Medicine, Monash University, Alfred Hospital, and ANU College of Health and Medicine; Y. Wang, PhD, Senior Research Fellow, School of Public Health and Preventive Medicine, Monash University, Alfred Hospital; A.M. Tonkin, PhD, Professor, School of Public Health and Preventive Medicine, Monash University, Alfred Hospital; L. Chou, FRACP, Consultant, School of Public Health and Preventive Medicine, Monash University, Alfred Hospital, and The Alfred Hospital; A.E. Wluka, PhD, Professor, School of Public Health and Preventive Medicine, Monash University, Alfred Hospital; F.M. Cicuttini, PhD, Professor, School of Public Health and Preventive Medicine, Monash University. S.M. Hussain and C. Dawson are joint first authors.

Address correspondence to Prof. F.M. Cicuttini, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria 3004, Australia. E-mail: flavia.cicuttini@monash.edu

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in 2015, an increase of 35% since 2005¹. OA affects the whole joint involving cartilage, subchondral bone, synovium, capsule, ligaments, and surrounding muscles². No treatments for OA have been proven to have a disease-modifying effect, with joint replacement being the only option for endstage OA. Thus, prevention is important and will be optimized with a better understanding of the modifiable factors involved in the pathogenesis of OA.

Pathological changes in blood vessels (vascular pathology), particularly atherosclerosis or thickening of arterial wall, and OA are both common chronic conditions associated with aging and obesity². People with OA are at higher risk of death from cardiovascular disease compared with the general population. Knee OA is more prevalent among hypertensive individuals compared with nonhypertensive individuals³. Higher levels of serum cholesterol are associated with increased risk of knee and generalized OA^{4,5}. However, the association between vascular pathology and OA remained inconclusive because some studies reported a positive association between arterial narrowing and risk of hand and knee OA^{3,6,7,8,9}, while others found no association between arterial stiffness and knee OA^{10,11}.

Emerging evidence suggests that different joints are susceptible to different risk factors for OA. The knee and

hand joints are more affected by obesity-associated inflammation¹² and metabolic factors¹³. In contrast, alterations in bony shape or geometry are linked to hip OA, with weak or inconsistent associations for metabolic or inflammatory factors¹⁴. We aimed to systematically review the evidence for the relationships between vascular pathology and risk of joint-specific OA.

MATERIALS AND METHODS

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines¹⁵.

Search strategy. These databases were searched: Ovid Medline (between January 1946 and February 2019), Scopus (between January 1937 and February 2019), and EMBASE (between January 1974 and February 2019), using MeSH terms and keywords to identify studies examining the role of vascular involvement in the pathogenesis of OA. The search terms are outlined in Supplementary Data 1 (available with the online version of this article). Searches were limited to human studies published in English. Identified manuscripts were reviewed manually and references searched for additional relevant studies.

Study selection. SMH and CD independently assessed the eligibility of studies using a 3-stage determination method, reviewing the title, abstract, and then full text. Any disagreement between the 2 authors was resolved by discussion. We included studies examining knee, hip, or hand OA using a validated definition including the American College of Rheumatology criteria, Kellgren–Lawrence (KL) score, and arthroplasty for OA. We also included studies that examined magnetic resonance imaging (MRI) structural changes associated with OA. Studies were included that assessed the exposure of interest, measuring vascular pathology comprising atherosclerosis, arteriolar or arterial wall thickness, vascular stiffness, microvascular derangement, endothelial dysfunction, and venous drainage. We excluded case reports, conference abstracts, review articles, and studies without a comparison group. We also excluded studies with heterogeneous populations that were a mix of participants with OA of the knee, hip, or hand, because previous studies showed that different sets of joint-specific risk factors are associated with the onset and progression of the disease^{16,17,18,19} and much of the genetic basis for OA occurs on a joint-specific basis^{20,21,22,23,24}.

Data extraction and synthesis. SMH and CD extracted data on study design, number/sex/age of study participants, type/definition/prevalence of OA, length of followup (Table 1), measures of vascular pathology, confounding factors being adjusted for, and associations (all available mean differences, risk ratios, OR, HR, regression coefficients) between vascular pathology and OA (Table 2 and Table 3). Qualitative synthesis was performed owing to the heterogeneity of the included studies.

Risk of bias assessment. SMH and LC independently assessed risk of bias of included studies using the US National Heart, Lung, and Blood Institute quality assessment tool for observational studies²⁵. The tool includes 14 criteria for cohort and cross-sectional studies and 12 criteria for case-control studies. Each criterion was rated as yes, no, cannot determine, not applicable, or not reported, with overall quality of studies being scored as high (low risk of bias), fair (moderate risk of bias), or low (high risk of bias).

RESULTS

Search results. The search of the 3 electronic databases identified 8296 records until September 2017 (2137 from Scopus, 2345 from Ovid Medline, and 3814 from EMBASE) and a further 30 records from September 2017 to February 2019, with 6952 articles remaining after removal of duplicates. By screening titles and abstracts, 6868 articles were

excluded because they assessed risk of OA in relation to markers or risk factors of cardiovascular disease (serum cholesterol, fatty acids, hyperuricemia, obesity, hypertension, diabetes, lipid abnormalities, or metabolic syndrome). Eighty-four articles were retrieved, with 64 studies excluded because they were abstracts, conference papers, or review articles, or the outcome was self-reported joint pain or stiffness. Full-text screening was performed for 20 articles, with 5 excluded because they had no comparison group, had an inappropriate comparison group (e.g., patients with rheumatoid arthritis), examined heterogeneous populations (i.e., where they were mixed regarding type of OA), or did not measure vascular pathology objectively (Figure 1). No additional article was found after searching the references of review articles.

Description of included studies. Table 1 provides an overview of the included studies. The studies were published between 2007 and 2019, including 6 cohorts^{3,6,8,26,27,28}, 3 case-control studies^{9,29,30}, and 6 cross-sectional studies^{7,10,11,31,32,33}. Four studies originated from Australia^{3,8,27,32}, 3 from Turkey^{29,30,31}, 3 from Iceland^{7,10,28}, 2 each from the Netherlands^{6,26} and the United States^{11,33}, and 1 from Greece⁹. The mean age of participants ranged from 50 to 76 years. Twelve studies included both men and women^{3,6–11,26,28,30,32,33}, and 3 studies included women only^{27,29,31}.

Assessment of OA. OA was examined in hand^{6,7,9,11,31}, knee^{3,6,8,10,26,27,29,30,32}, hip^{6,10}, and facet joint³³ by using the KL scores^{6,11,26,29,30,31}, bone erosion from radiographs⁹, computed tomography (CT)^{7,10,28,33}, scored hand photographs^{7,10,28}, presence of cartilage defects or bone marrow lesions on MRI^{8,27,32}, or arthroplasty for OA^{3,10,28}.

Assessment of vascular pathology. Vascular pathology was examined for atherosclerosis^{3,6–10,26,27,29,31,32}, vascular stiffness^{6,7,10,11,26}, aortic elasticity and stiffness³⁰, change in retinal vascular caliber^{3,28,32}, and endothelial dysfunction⁹, in a number of different vascular beds including common carotid artery^{6,9,26,31}, coronary artery^{7,10,11,31}, abdominal aorta^{30,33}, common femoral artery^{9,29}, tibial artery²⁹, popliteal artery^{8,27}, or retinal vessels^{3,28,32}. The variables used to measure vascular pathology were carotid intima-media thickness (IMT)^{6,7,9,10,26}, carotid plaque severity^{6,9,26}, coronary and/or aortic calcifications^{7,10,26}, plasma levels of biomarkers (soluble CD40 ligand, vascular cell adhesion molecule 1, and vascular endothelial growth factor)²⁶, Gensini scoring of coronary angiogram³¹, popliteal artery wall thickness^{8,27}, retinal microvasculature^{3,28,32}, arterial pulse wave velocity (PWV)^{11,29}, flow volume²⁹, flow-mediated dilatation and sublingual glyceryl trinitrate-induced dilatation of the brachial artery⁹, or transthoracic echocardiography of aorta³⁰.

Data synthesis. The prevalence of OA at individual joints could be established in 9 studies^{3,6,7,10,11,26,28,31,33}, which varied depending on the definition of OA. The prevalence of

Table 1. General characteristics of included studies.

Author, Country, Year	Study Population (% Women)	Age of Study Population, Yrs, Mean ± SD	Type, Definition, Key Outcome of OA	Prevalence, % OA	Followup Time, Yrs, Mean ± SD	Quality of Study
Cohort studies						
Jonsson, <i>et al</i> ²⁸ , Iceland, 2019	4757 participants (57)	76 ± 5	Hand OA Knee OA Hand OA high-quality digital photographs Knee replacement due to OA	Hand OA (43% male, 48% female) Knee OA (prevalence: 5% male, 7% female; incidence: 3% male, 4% female)	5	Fair
Hoeven, <i>et al</i> ²⁶ , Netherlands, 2015	975 subjects in the serum biomarker study (56) 1669 subjects in the coronary artery calcification study (52)	73.1 ± 7.5	Knee OA Radiograph, KL score	18 (11% male, 23% female)	4.5 ± 0.5	High
Hussain, <i>et al</i> ³ , Australia, 2015	1838 subjects (52)	Knee replacement 65.0 ± 7.5 No knee replacement 60.3 ± 12.1	Knee OA Knee replacement due to OA	4	8.7 ± 2.7	High
Wang, <i>et al</i> ²⁷ , Australia, 2015	142 subjects (100)	52.2 ± 6.7	Knee structural changes predictive of OA Tibial cartilage volume on MRI	NR	2.2 ± 0.1	Fair
Wang, <i>et al</i> ⁸ , Australia, 2015	278 subjects (62)	57.8 ± 5.3	Knee structural changes predictive of OA Tibial cartilage volume and bone marrow lesions on MRI	NR	2.3 ± 0.4	Fair
Hoeven, <i>et al</i> ⁶ , Netherlands, 2013	5650 subjects (58)	68.2 ± 8.0	Knee OA Hand OA Hip OA Radiograph, KL score	Knee: 15 (9% male, 20% female) Hand: NR Hip: 6 (5% male, 7% female)	10	High
Case-control studies						
Belen, <i>et al</i> ³⁰ Turkey, 2016	160 subjects, 80 cases, 80 controls (unknown)	Cases 56.81 ± 5.36; controls 57.18 ± 7.6	Radiograph, KL score	N/A	N/A	Low
Boyaci, <i>et al</i> ²⁹ , Turkey, 2015	69 subjects, 39 cases, 30 controls (100)	Cases 51.74 ± 5.23; controls 50.93 ± 5.99	Knee OA Radiographs, KL score	N/A	N/A	Low
Koutroumpas, <i>et al</i> ⁹ , Greece, 2013	48 subjects, 24 cases, 24 controls (92)	Cases: 62.5 ± 6.6; controls: 60.7 ± 5.8	Erosive hand OA ACR criteria for hand OA and radiograph IP joint central erosions in the form of “gull-wing” or “saw-teeth”	N/A	N/A	Low
Cross-sectional studies						
Cemeroglu, <i>et al</i> ³¹ , Turkey, 2014	61 subjects (100)	65.5 ± 8.0	Hand OA Radiograph, KL score	64	N/A	Low
Davies-Tuck, <i>et al</i> ³² , Australia, 2012	289 subjects (61)	58.0 ± 5.5	Knee structural changes predictive of OA MRI of dominant knee, cartilage, and bone marrow lesions	N/A	N/A	Low
Jonsson, <i>et al</i> ¹⁰ , Iceland, 2011	5170 subjects (58)	76.0 ± 6.0	Knee OA Hand OA Hip OA Knee & hip OA: arthroplasty due to OA Hand OA, CT scans and high-quality hand photographs (HOAScore)	Knee 4 Hand NR Hip 6	N/A	Low

Table 1. Continued.

Author, Country, Year	Study Population (% Women)	Age of Study Population, Yrs, Mean \pm SD	Type, Definition, Key Outcome of OA	Prevalence, % OA	Followup Time, Yrs, Mean \pm SD	Quality of Study
Suri, <i>et al</i> ³³ , USA, 2010	441 subjects (46)	54.5 \pm 11.5	CT scans	70	N/A	Low
Jonsson, <i>et al</i> ⁷ , Iceland, 2009	5342 subjects (58)	76 \pm 6 (range 66–96)	Hand OA CT scans and high-quality hand photographs (HOAScore)	68	N/A	Low
Saleh, <i>et al</i> ¹¹ , USA, 2007	256 subjects (48)	Hand OA 67.2 \pm 8.9; no hand OA 43.2 \pm 14.8	Hand OA Radiograph, KL	20	N/A	Low

NR: not reported; N/A: not applicable; OA: osteoarthritis; CT: computed tomography; MRI: magnetic resonance imaging; KL: Kellgren-Lawrence arthritis grading scale; ACR: American College of Rheumatology; IP: interphalangeal joint; HOAScore: photographic hand OA score.

knee OA was 4–7% when defined by arthroplasty for OA^{3,10,28} and 14–18% when defined using the KL score from radiographs^{6,26}. The prevalence of hip OA was 6% from radiographs and arthroplasty^{6,10}. Two studies reported the prevalence of hand OA: 64% from radiographs³¹ and 68% from hand photographs⁷. One study reported the prevalence of OA of distal interphalangeal (33%), proximal interphalangeal (12%), metacarpophalangeal (MCP; 5%), and carpometacarpal/trapezoscaphoid joints (27%)⁶. The prevalence of facet joint OA was 30% using CT scans³³. Three studies reported sex-specific prevalence of OA^{6,7,26,28}. Knee OA was more prevalent in women than in men (20% vs 9%⁶, 23% vs 11%²⁶, and 7% vs 5%²⁸), while hand (69.8% vs 67.4% and 48% vs 43%²⁸)⁷ and hip (7% vs 5%)⁶ OA had similar prevalence in women and men.

Risk of bias. There were 3 high-quality^{3,6,26} and 3 fair-quality^{8,27,28} cohort studies. All the 3 case-control and 6 cross-sectional studies were of low quality^{7,9,10,11,29,30,31,32,33}. The study population and research question were defined clearly in most studies. The main issues were the lack of sample size justification, and measurement of exposures at only 1 timepoint for cohort studies. The overall quality assessment is shown in Table 1, with details of quality assessment presented in Supplementary Table 1 (available with the online version of this article) for cohort and cross-sectional studies, and Supplementary Table 2 for case-control studies. The initial agreement between the 2 reviewers was 78%.

Vascular pathology and hand OA. Six studies examined the relationship between vascular pathology and risk of hand OA^{6,7,9,11,28,31} (Table 2). In a high-quality cohort study, baseline IMT was associated with the progression of MCP OA in women but not the prevalence of hand OA⁶. Baseline carotid plaque was associated with greater baseline prevalence of distal interphalangeal and MCP OA in women but not the progression of hand OA⁶. After correction for multiple testing, the association persisted as statistically significant between baseline carotid plaque and prevalent

distal interphalangeal OA⁶. There were no significant associations in men in all analyses⁶. One case-control and 2 cross-sectional studies found that atherosclerosis of carotid and coronary artery was associated with higher prevalence of hand OA^{7,9,31}. Two studies also showed that those who had more severe atherosclerosis measured by IMT⁹ and Gensini score of angiogram³¹ were more likely to have hand OA, although they did not adjust for confounders. In the AGES-Reykjavik study, narrow retinal arteriolar caliber was associated with hand OA for both men and women²⁸. Among the Framingham population, the association between PWV (a measure of vascular stiffness) and hand OA was no longer significant after adjustment for age¹¹.

Vascular pathology and knee OA. Ten studies examined the association between vascular pathology and risk of knee OA^{3,6,8,10,26–30,32} (Table 3). Among the 6 cohort studies, 4 studies examined the association between baseline vascular pathology and risk of knee OA^{6,26,28} or knee structure⁸ both cross-sectionally and longitudinally. Higher baseline levels of atherosclerosis markers (i.e., CD40L²⁶ and carotid IMT⁶) were associated with higher prevalence of knee OA measured by radiological KL score in women; greater baseline popliteal artery wall thickness was associated with reduced medial tibial cartilage volume on MRI⁸; and narrow retinal arteriolar caliber was associated with knee replacement due to OA in men and women²⁸. Three cohort studies examined the longitudinal relationship between baseline vascular pathology and risk of OA or knee structure and showed significant associations: retinal arteriolar narrowing was associated with increased risk of knee arthroplasty for OA in the AusDiab study population³; similarly, in the AGES-Reykjavik study, retinal arteriolar narrowing was associated with incident knee replacement for OA²⁸, and greater popliteal arterial wall thickness was associated with increased rate of tibial cartilage volume loss on MRI²⁷. In a low-quality study, aortic stiffness was associated with the prevalence and severity of knee OA measured by radiological KL score³⁰. Wider retinal venular diameter was associated with increased prevalence of bone

Table 2. Association between vascular pathology and hand osteoarthritis (OA).

Author, Year	Exposure and Exposure Measurement	Confounder Adjusted for	Results	Conclusion
Cohort studies				
Hoeven, <i>et al</i> ⁶ , 2013	Common carotid artery: atherosclerosis by IMT and atheromatous plaques	Age, BMI, total cholesterol/HDL ratio, diabetes, hypertension, and smoking	<p>Cross-sectional analysis: Women, carotid plaque DIP: OR 1.4, 95% CI 1.19–1.65 PIP: OR 1.1, 95% CI, 0.90–1.40 MCP: OR 1.5, 95% CI 1.09–2.18 CMC/TS: OR 1.0, 95% CI 0.88–1.24</p> <p>Women, carotid IMT DIP: OR 1.4, 95% CI 0.93–2.10 PIP: OR 1.3, 95% CI 0.81–2.22 MCP: OR 1.6, 95% CI 0.84–2.94 CMC/TS: OR 1.0, 95% CI 0.68–1.59</p> <p>Men, carotid plaque DIP: OR 1.0, 95% CI 0.76–1.18 PIP: OR 0.9, 95% CI 0.66–1.24 MCP: OR 1.3, 95% CI 0.78–1.80 CMC/TS: OR 1.0, 95% CI 0.78–1.28</p> <p>Men, carotid IMT DIP: OR 1.1, 95% CI 0.67–1.64 PIP: OR 0.8, 95% CI 0.40–1.40 MCP: OR 1.0, 95% CI 0.46–2.06 CMC/TS: OR 0.9, 95% CI 0.56–1.54</p> <p>Longitudinal analysis: progression Women, carotid plaque DIP: OR 1.1, 95% CI 0.86–1.34 PIP: OR 1.0, 95% CI 0.77–1.29 MCP: OR 0.9, 95% CI 0.67–1.22 CMC/TS: OR 0.9, 95% CI 0.68–1.13</p> <p>Women, carotid IMT DIP: OR 1.3, 95% CI 0.65–2.66 PIP: OR 0.6, 95% CI 0.26–1.34 MCP: OR 2.9, 95% CI 1.18–6.93 CMC/TS: OR 0.6, 95% CI 0.25–1.27</p> <p>Men No significant association was shown either with carotid plaque or carotid IMT Data were not presented</p>	Carotid plaque was associated with DIP and MCP, but not PIP or CMC/TS OA in women but not men. IMT but not plaque was associated with progression of MCP OA in women only.
Case-control studies				
Koutroumpas, <i>et al</i> ⁹ , 2013	IMT and atheromatous plaques in the common carotid and common femoral arteries The endothelium-dependent, flow-mediated dilatation (FMD) and endothelium-independent, NMD of the brachial artery	Age and sex	<p>Erosive hand OA IMT > 1 mm (OR 3.33, 95% CI 1.02–10.9) Plaque (OR 1.41, 95% CI 0.46–4.46) Difference between FMD and NMD increased in erosive OA (p = 0.026)</p>	Subclinical atherosclerosis was associated with erosive hand OA.

Table 2. Continued.

Author, Year	Exposure and Exposure Measurement	Confounder Adjusted for	Results	Conclusion
Cross-sectional studies				
Jonsson, <i>et al</i> ²⁸ , 2019	Generalized vascular pathology Retinal vascular caliber (arteriolar and venular)	Age, sex, BMI	Total population Arteriolar caliber: OR 1.08, 95% CI 1.02–1.15 Venular caliber: OR 1.08, 95% CI 1.02–1.14 Women Arteriolar caliber: OR 1.08, 95% CI 1.00–1.17 Venular caliber: OR 1.09, 95% CI 1.01–1.18 Men Arteriolar caliber: OR 1.22, 95% CI 1.00–1.51 Venular caliber: OR 1.06, 95% CI 0.97–1.16 Gensini score: hand OA vs no hand OA (21.5 ± 17.1 vs 11.8 ± 9.2, respectively; p = 0.017) Correlation between Gensini score and OA score: r = 0.332; p = 0.009	There was a positive association between narrow arteriolar caliber and hand OA in both men and women. Further, there was a positive association for narrower venular caliber and hand OA only for women. Atherosclerosis was associated with the presence of hand OA.
Cemeroglu, <i>et al</i> ³¹ , 2014	Gensini scoring of coronary angiogram was used to evaluate the patients for atherosclerosis and its severity	Not adjusted for confounders		
Jonsson, <i>et al</i> ⁷ , 2009	IMT and plaque severity in common carotid artery Calcium in the coronary arteries CT scan of entire thoracic aorta	Age, smoking, cholesterol, triglycerides, BMI, pulse pressure, and statin use.	Women Carotid plaque: OR 1.25, 95% CI 1.04–1.49; the proportion of women with moderate or severe carotid plaque increased with the severity of hand OA, p for trend < 0.0002. Coronary calcification: OR 1.42, 95% CI 1.14–1.76; the proportion of women with no detectable coronary calcification decreased with the severity of hand OA, p for trend = 0.027. Aortic calcification (mm) hand OA/no hand OA: 7.66 (0.04)/7.57 (0.06), p > 0.05 Men Carotid plaque: OR 1.02, 95% CI 0.83–1.25 Coronary calcification: OR 1.13, 95% CI 0.67–1.83 Aortic calcification (mm) hand OA/no hand OA: 7.51 (0.05)/7.4 (0.06), p > 0.05 PWV regression coefficient 9.2, 95% CI –64.2, 82.5	There was a linear association between severity of atherosclerosis and the severity of hand OA in women but not men.
Saleh, <i>et al</i> ¹¹ , 2007	Vascular stiffness by arterial PWV in right common carotid artery and right femoral artery	Age, BMI, sex, systolic and diastolic blood pressure, smoking, and diabetes status		There was no association between PWV and hand OA.

BMI: body mass index; IMT: intima-media thickness; HDL: high-density lipoprotein; PWV: pulse wave velocity; FMD: flow-mediated dilatation; NMD: sublingual glyceryl trinitrate-induced dilatation; DIP: distal interphalangeal joint; PIP: proximal IP joint; MCP: metacarpophalangeal joint; CMC/TS: carpometacarpal/trapeziosaphoid; CT: computed tomography.

Table 3. Association between vascular pathology and knee, hip, and facet osteoarthritis (OA).

Author, Year	Exposure and Exposure Measurement	Confounder Adjusted for	Results	Conclusion
Knee OA				
Cohort studies				
Jonsson, <i>et al</i> ²⁸ , 2019	Generalized vascular pathology Retinal vascular caliber (arteriolar and venular)	Age, sex, BMI	Cross-sectional analysis All participants Arteriolar caliber: OR 1.21, 95% CI 1.07–1.37 Venular caliber: OR 1.05, 95% CI 0.93–1.19 Women Arteriolar caliber: OR 1.17, 95% CI 1.00–1.37 Venular caliber: OR 1.12, 95% CI 0.95–1.31 Men Arteriolar caliber: OR 1.26, 95% CI 1.04–1.53 Venular caliber: OR 0.95, 95% CI 0.77–1.15 Longitudinal analysis All participants Arteriolar caliber: OR 1.24, 95% CI 1.01–1.52 Venular caliber: OR 1.08, 95% CI 0.88–1.33 Women Arteriolar caliber: OR 1.18, 95% CI 0.91–1.53 Venular caliber: OR 1.10, 95% CI 0.85–1.43 Men Arteriolar caliber: OR 1.35, 95% CI 0.98–1.87 Venular caliber: OR 1.04, 95% CI 0.74–1.47	Per unit SD decrease in arteriolar caliber was associated with prevalence of total knee replacement.
Hoeven, <i>et al</i> ²⁶ , 2015	Atherosclerosis CAC Plasma level of: CD40L VCAM-1 VEGF protein that stimulates angiogenesis	Age, BMI, total cholesterol/ HDL ratio, diabetes, hypertension, and smoking	Cross-sectional analysis Women CD40L: OR 1.3, 95% CI 1.1, 1.6 VCAM-1: OR 1.3, 95% CI 1.1, 1.6 VEGF: OR 1.08, 95% CI 0.93, 1.24 CAC: OR 1.11, 95% CI 0.95, 1.30 Men CD40L: OR 1.05, 95% CI 0.80, 1.37 VCAM-1: OR 1.08, 95% CI 0.82, 1.42 VEGF: OR 1.07, 95% CI 0.90, 1.28 CAC: OR 1.11, 95% CI 0.86, 1.43 Longitudinal analysis: progression Women CD40L: OR 1.2, 95% CI 0.9–1.6 VCAM-1: OR 0.9, 95% CI 0.6–1.4 VEGF: OR 0.3, 95% CI 0.1–1.1 CAC: OR 1.02, 95% CI 0.81–1.28 Men CD40L: OR 1.8, 95% CI 1.1–2.9 VCAM-1: OR 1.1, 95% CI 0.8–1.7 VEGF: OR 0.8, 95% CI 0.3–1.8 CAC: OR 1.17, 95% CI 0.76–1.80	Markers of atherosclerosis were associated with prevalent knee OA in women but not in men. There was no association between CAC and presence of knee OA. CD40L was associated with progression of knee OA in men. There was no association between markers of atherosclerosis and progression of knee OA in women. There was no association between CAC and progression of knee OA.

Table 3. Continued.

Author, Year	Exposure and Exposure Measurement	Confounder Adjusted for	Results	Conclusion
Hussain, <i>et al</i> ³ , 2015	Generalized vascular pathology Retinal vascular caliber (arteriolar and venular)	Age, sex, BMI, physical activity, HbA1c	Arteriolar caliber: HR 1.25, 95% CI 1.00–1.56 (continuous) Narrower two-thirds vs rest: HR 2.00, 95% CI 1.07–3.74, <i>p</i> = 0.03 (dichotomous) Venular caliber: HR 0.86, 95% CI 0.67–1.10 Annual cartilage volume loss, mean (SE) Medial tibia: 1.62 (0.45), 2.18 (0.43), and 2.98 (0.48); <i>p</i> for trend = 0.04 Lateral tibia: 1.50 (0.43), 1.24 (0.40), 2.02 (0.44); <i>p</i> for trend = 0.41	Retinal arteriolar narrowing was associated with increased risk of knee replacement for OA. Venular caliber was not associated with risk of knee replacement for OA. Greater popliteal artery wall thickness was associated with increased rate of medial tibial cartilage volume loss but not lateral tibial cartilage volume loss.
Wang, <i>et al</i> ²⁷ , 2015	Atherosclerosis Popliteal artery wall thickness on MRI	Age, BMI, tibial bone area, physical activity, diabetes, and hypertension	Cross-sectional analysis Cartilage volume Medial tibia: β coefficient –6.7, 95% CI –12.9, –0.6; <i>p</i> = 0.03 Lateral tibia: β coefficient –5.4, 95% CI –12.9, 2.0; <i>p</i> = 0.15 Prevalence of bone marrow lesion Medial tibiofemoral: OR 0.95, 95% CI 0.88–1.03; <i>p</i> = 0.21 Lateral tibiofemoral: OR 0.99, 95% CI 0.92–1.07; <i>p</i> = 0.81 Longitudinal analysis Annual change in cartilage volume Medial tibia: β coefficient 0.06, 95% CI 0.01–0.12; <i>p</i> = 0.03 Lateral tibia: β coefficient –0.003, 95% CI –0.05, 0.05; <i>p</i> = 0.92 Worsening of BML Medial tibia: OR 1.07, 95% CI 0.995–1.15; <i>p</i> = 0.07 Lateral tibia: OR 0.99, 95% CI 0.91–1.07; <i>p</i> = 0.72	Greater popliteal artery wall thickness was associated with reduced medial tibial cartilage volume but not lateral tibial cartilage volume or prevalence of BML. Greater popliteal artery wall thickness was associated with increased medial tibial cartilage volume loss but not with lateral tibial cartilage volume loss or changes in BML.
Wang, <i>et al</i> ⁸ , 2015	Atherosclerosis Popliteal artery wall thickness on MRI	Age, sex, BMI, tibial bone area, physical activity, diabetes, and hypertension	Cross-sectional analysis Women Plaque: OR 1.0, 95% CI 0.81–1.24 IMT: OR 1.7, 95% CI 1.1–2.7 Men Plaque: OR 0.9, 95% CI 0.60–1.19 IMT: OR 1.3, 95% CI 0.68–2.36 Longitudinal analysis: progression Women Plaque: OR 1.3, 95% CI 0.97–1.67 IMT: OR 1.9, 95% CI 0.83–4.39 Men No association with either carotid plaque or carotid IMT Data were not presented	Carotid IMT but not plaque was associated with knee OA in women but not men. Neither carotid IMT nor plaque was associated with knee OA progression in women or men.
Hoeven, <i>et al</i> ⁶ , 2013	Atherosclerosis Measured by carotid IMT and carotid plaque, by ultrasonography	Age, BMI, total cholesterol/HDL ratio, diabetes, hypertension, and smoking		

Table 3. Continued.

Author, Year	Exposure and Exposure Measurement	Confounder Adjusted for	Results	Conclusion
Case-control studies				
Boyaci, <i>et al</i> ²⁹ , 2015	Blood velocity measured by color Doppler imaging in external iliac, common femoral, superficial femoral, deep femoral, popliteal, anterior and posterior tibial, and distal superficial femoral arteries Femoral artery IMT	Unadjusted	Patients' blood flow volume in the external iliac and superficial femoral artery were greater than those of controls ($p < 0.05$). There were no significant differences in patients' blood flow volume in the common femoral artery, anterior, and posterior ($p > 0.05$) compared with controls The diameters of the popliteal, and anterior and posterior tibial arteries, were narrower in patients with OA ($p < 0.05$) There were no statistically significant differences in the diameter of the superficial femoral artery, deep femoral artery, or external iliac artery ($p > 0.05$)	Vascular abnormalities were associated with knee OA.
Belen, <i>et al</i> ³⁰ , 2016	Arterial stiffness measurements by echocardiograph	Age, sex, LDL, HDL, CRP, eGFR, blood glucose	Aortic strain: OR 0.77, 95% CI 0.63–0.93 Aortic distensibility: OR 0.85, 95% CI 0.70–1.03 Aortic stiffness: OR 1.58, 95% CI 1.01–2.47 Systolic diameter of the ascending aorta: OR 1.19, 95% CI 0.93–1.53 Diastolic diameter of the ascending aorta: OR 1.15, 95% CI 0.92–1.44	There was a close relationship between presence and severity of knee OA and aortic stiffness and the aortic strain.
Cross-sectional studies				
Davies-Tuck, <i>et al</i> ² , 2012	Generalized vascular pathology Changes in retinal microvasculature – retinal arteriolar and venular diameter measured using a retinal photograph	Age, sex, BMI, and either CRAE or CRVE	Arterial diameter BML vs no BML: $147.5 \pm 2.1 \mu\text{m}$ vs $143.9 \pm 0.84 \mu\text{m}$; $p = 0.11$ Venular diameter: $214.1 \pm 2.8 \mu\text{m}$ vs $207.5 \pm 1.1 \mu\text{m}$; $p = 0.03$	Wider retinal venular diameter was associated with BML.
Jonsson, <i>et al</i> ¹⁰ , 2011	Atherosclerosis Measured by IMT and plaque severity (ultrasound), coronary and aortic calcifications (CT), PVH on MRI, and a history of cardiac and cerebral events	Age, BMI, high-sensitivity CRP, BMD of the spine, triglycerides, cholesterol, smoking history, statin use, and pulse pressure	Women Carotid plaque: OR 1.49, 95% CI 0.98–2.27 Men Carotid plaque: OR 0.92, 95% CI 0.55–1.51	No significant associations between vascular pathology and total knee replacement in either women or men.
Hip OA Cohort studies Hoeven, <i>et al</i> ⁶ , 2013	Atherosclerosis Measured by carotid IMT and carotid plaque, through ultrasonography	Age, BMI, total cholesterol/HDL ratio, diabetes, hypertension, and smoking	Women IMT: OR 1.4, 95% CI 0.71, 2.60 Plaque: OR 0.8, 95% CI 0.55, 1.06 Men IMT: OR 1.0, 95% CI 0.48, 2.03 Plaque: OR 0.9, 95% CI 0.70, 1.63	No association between atherosclerosis and hip OA in women or men.
Cross-sectional studies				
Jonsson, <i>et al</i> ¹⁰ , 2011	Atherosclerosis Measured by IMT and plaque severity (ultrasound), coronary and aortic calcifications (CT), periventricular white matter hyperintensities PVH on MRI, and a history of cardiac and cerebral events	Age, BMI, high-sensitivity CRP, BMD of the spine, triglycerides, cholesterol, smoking history, statin use, and pulse pressure	Women Carotid plaque: OR 1.07, 95% CI 0.76–1.5 Men Carotid plaque: OR 1.02, 95% CI 0.64–1.62	No significant associations with total hip replacement and vascular pathology in women or men.

Table 3. Continued.

Author, Year	Exposure and Exposure Measurement	Confounder Adjusted for	Results	Conclusion
Facet joint OA Cross-sectional study Suri, <i>et al</i> ³³ , 2010	Abdominal aortic calcification measured by abdominal multidetector CT	Age, sex, BMI, diabetes, hypertension, hypercholesterolemia, and smoking	No AAC: reference Low AAC: OR 1.81, 95% CI 1.01–3.27 High AAC: OR 2.34, 95% CI 0.99–5.23	AAC were associated with facet joint OA in a community-based population.

BMI: body mass index; IMT: intima-media thickness; CAC: coronary artery calcification; PWV: pulse wave velocity; BML: bone marrow lesion; LDL: low-density lipoprotein; HDL: high-density lipoprotein; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; AAC: abdominal aortic calcification; VCAM-1: vascular cell adhesion molecule 1; CRAE: central retinal artery equivalent; CRVE: central retinal vein equivalent; PVH: periventricular white matter hyperintensities; CT: computed tomography; VEGF: vascular endothelial growth factor; SE: standard error; MRI: magnetic resonance imaging; BMD: bone mineral density.

marrow lesions on MRI in a cross-sectional study³², and lower extremity arterial blood flow was associated with increased risk of knee OA in a case-control study²⁹. In contrast, there was insufficient evidence to suggest either carotid IMT or plaque was associated with knee OA progression in women or men⁶. No significant association was found between the following: presence or progression of knee OA and baseline coronary artery calcification²⁶; knee replacement for OA and retinal venular caliber³; knee arthroplasty and coronary and aortic calcification, periventricular white matter hyperintensities¹⁰; presence and progression of bone marrow lesion and popliteal artery wall thickness^{8,27}; or presence of bone marrow lesion in the knee and arterial diameter³².

Vascular pathology and hip and facet joint OA. Two studies examined the association between vascular pathology and risk of hip OA^{6,10}. There was no association between the prevalence of hip OA assessed by radiological KL score and coronary artery calcification or carotid plaque⁶, or between the incidence of hip arthroplasty for OA and coronary and aortic calcification, periventricular white matter hyperintensities, cardiac, or cerebral events¹⁰. One study examined the association between vascular pathology and risk of facet joint OA and found that abdominal aortic calcifications were associated with facet joint OA in a community-based population³³.

DISCUSSION

This study systematically reviewed the evidence for an association between vascular pathology and risk of joint-specific OA, with syntheses derived from 15 studies. There was evidence, irrespective of the quality of the studies, that vascular pathology was associated with risk of hand and knee OA but not hip OA. Further, there was evidence that vascular pathology was associated with a spectrum of knee OA outcomes, including progression of structural changes that predict development of knee OA, progression of radiographic OA, and endstage OA requiring a joint replacement.

Five studies, including one high-quality cohort study, found that vascular pathology was associated with hand OA^{6,7,9,28,31}. The only cohort study showed that in women carotid plaque was associated with higher prevalence of hand OA and carotid IMT with progression of hand OA⁶. Atherosclerosis measured in the carotid and coronary artery was associated with hand OA in a case-control⁹ and 2 cross-sectional studies^{7,31}. Similarly, generalized vascular pathology was associated with prevalence of hand OA²⁸. In contrast, a low-quality cross-sectional study that included subjects across a wide age range (19–93 yrs) and used PWV, a less accurate method to assess atherosclerosis³⁴, did not show a relationship between arterial stiffness and risk of hand OA¹¹.

Different measures of vascular pathology were associated

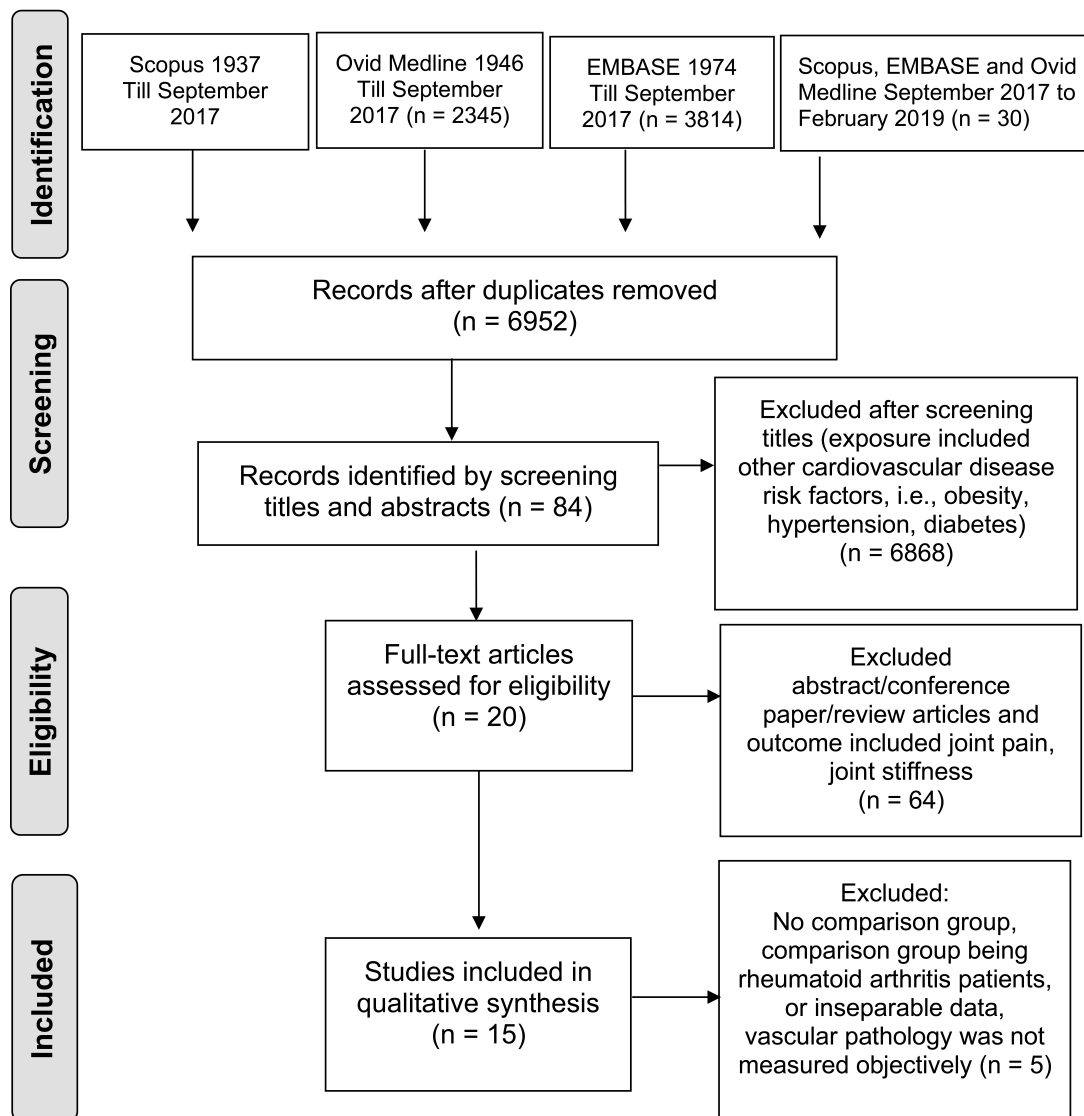


Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram of included articles.

with increased risk of knee OA and early knee structural changes predictive of knee OA, based on 9 studies including 3 high-quality and 3 fair-quality cohort studies^{3,6,8,26–30,32}. The vascular pathologies included narrowing of large arteries (carotid artery, coronary artery, aorta, or popliteal artery), narrowing of small arteries, or dilation of small veins (retinal arterioles and venules). No association between arterial calcification and risk of knee OA could be established²⁶. Measurements of IMT and arterial calcification are often discordant³⁵, with IMT being more sensitive than arterial calcification for the detection of atherosclerosis³⁶. In contrast, there was no association between vascular pathology and the risk of hip OA as evidenced from 1 high-quality cohort⁶ and 1 cross-sectional study¹⁰. Only 1 study examined the association between vascular pathology and facet joint OA and found a positive association³³.

The results of this systematic review lend support to the

hypothesis that vascular pathology may be involved in OA initiation and progression³⁷, with consistent evidence for an association of vascular pathology with hand and knee OA. Among the 6 cohort studies of the knee, 2 examined early knee structural changes in people free from clinical OA^{8,27}, and the other 4 studies included people with different stages of OA^{3,6,26,28}. A positive association was found between the severity of vascular pathology and the likelihood of having hand or knee OA^{3,6,7,8,26,27,29,32}. The association between vascular pathology and risk of OA was joint-specific, which was seen for hand and knee OA^{3,6–9,26–29,31,32} but not hip OA^{6,10}. However, caution is needed given the limited number of studies on hip OA.

We applied the Bradford Hill criteria³⁸ to further explore whether there was a causal relationship between vascular pathology and OA. The criteria, along with a description of how an association was established, are included in

Supplementary Table 3 (available with the online version of this article). All the Bradford Hill criteria were met for knee OA. However, none of the high- and fair-quality studies were designed with the primary aim of examining the association between vascular pathology and OA. Thus, although the evidence supports a causal link, further high-quality studies are needed to determine whether targeting vascular pathology will reduce the burden of OA.

These findings cannot be simply explained by reverse causation, in which pain resulted from OA may reduce physical activity and thus increase the risk of obesity and metabolically driven inflammation and vascular disease. This is because 6 cohort studies included in this review showed that vascular pathology at baseline predicted structural progression of OA over the subsequent 2–10 years^{3,6,8,26,27,28} (Supplementary Table 4, available with the online version of this article). The 2 cohort studies of asymptomatic participants without clinical knee OA found an association between vascular pathology and early structural changes that are predictive of knee OA development^{8,27}. Animal studies, where vascular changes were induced in a laboratory environment, showed that vascular pathology is involved in the initiation of OA^{39,40}. Data from human cohort studies showed that statins used to treat atherosclerosis were associated with reduced progression of knee OA²¹ and reduced risk of OA at any site⁴¹. Taken together, these findings suggest that vascular pathology may be on the causal pathway of OA development and progression. Further, all the high- and fair-quality studies and most of the low-quality studies controlled for obesity, dyslipidemia, hypertension, and diabetes as confounders in the statistical analyses. It is less likely that the observed association is due to residual confounding, because we observed consistent results in all the included studies with a variety of study designs, study populations, methods, and stages of OA.

In this review, conducting a metaanalysis was not possible owing to the heterogeneous characteristics of study populations, definition of OA, and measurement of vascular pathology. The extent to which individual studies measured and adjusted for potential confounders varied. The quality of the included studies was generally low. As with any systematic reviews, our study is subject to the potential of publication bias that may have inflated the association between vascular pathology and the risk of OA. To minimize this, we performed an extensive search for all relevant studies in 3 databases, examined biological plausibility (with obesity, lipids, glucose) and animal data, and considered the Bradford Hill criteria. Nonetheless, we carefully assessed the risk of bias for each included study using established tools.

Articular cartilage is avascular and depends on synovial fluid secreted by synovium⁴² and subchondral bone for nutrition and gas exchange³⁷. Narrower arterioles in synovium may result in localized hypoxia that stimulates angiogenesis, development of an immature vasculature and

inflammation predictive of cartilage damage, and catabolic effects on chondrocytes⁴². The growth, repair, and metabolism as well as modeling and remodeling of subchondral bone may depend on blood flow and hemopoiesis³⁷. Decreased blood flow may initiate osteoclastic resorption resulting in impaired integrity of subchondral bone, leading to reduced bony support for the overlying cartilage and subsequent higher susceptibility of cartilage to damage³⁷. Arterial narrowing may also affect the integrity of ligaments⁴³, tendons⁴⁴, and skeletal muscles⁴⁵, which are important structures for joint health. Venous occlusion and stasis may result in increased intraosseous pressure. Compromised venous drainage may decrease interstitial fluid flow; as a result, the removal of waste products is reduced, an extremely deleterious situation for osteocytes and surrounding tissues^{37,46}.

There is evidence of an association between vascular pathology and the risk of hand and knee OA, but not hip OA. Although these findings need to be confirmed by further high-quality studies, including longitudinal studies of disease-free participants at study inception, our systematic review provides support for the heterogeneity in the pathogenesis of OA. Understanding this will be important in optimizing the prevention and treatment of OA.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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