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Basic science

Association between popliteal artery wall thickness and structural progression in patients with symptomatic knee osteoarthritis

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Abstract

Objective: There is increasing evidence for the involvement of vascular disease in the pathogenesis of knee OA. Popliteal artery wall thickness can be used as a surrogate marker of atherosclerosis. We examined the association between popliteal artery wall thickness and knee cartilage volume in individuals with symptomatic knee OA.

Methods: This prospective cohort study analysed 176 participants from a randomized placebo-controlled trial examining the effect of atorvastatin on structural progression in knee OA. The participants underwent MRI of the study knee at baseline and 2-year follow-up. Popliteal artery wall thickness and tibial cartilage volume were measured from MRI using validated methods. The top quartile of the rate of tibial cartilage volume loss was defined as rapid progression.

Results: At baseline, every 10% increase in popliteal artery wall thickness was associated with 120.8 mm^3 (95% CI 5.4, 236.2, $P=0.04$) lower of medial tibial cartilage volume and 151.9 mm^3 (95% CI 12.1, 291.7, $P=0.03$) lower of lateral tibial cartilage volume. Longitudinally, for every 10% increase in popliteal artery wall thickness, the annual rate of medial tibial cartilage volume loss was increased by 1.14% (95% CI 0.09%, 2.20%, $P=0.03$), and there was a 2.28-fold (95% CI 1.07, 4.83, $P=0.03$) risk of rapid progression of medial tibial cartilage loss, adjusted for age, sex, BMI, tibial bone area, smoking, vigorous physical activity, and intervention group allocation.

Conclusion: The findings support a role for vascular pathology in the progression of knee OA. Targeting atherosclerosis has the potential to improve outcomes in knee OA.

Keywords: knee osteoarthritis, vascular pathology, cartilage volume, progression

Rheumatology key messages

- Increased popliteal artery wall thickness was associated with structural progression in knee osteoarthritis.
- Targeting vascular pathology may be important in slowing structural progression in knee osteoarthritis and reducing the burden of the disease

Introduction

OA is the most common chronic joint disease, affecting >300 million people, and is a major contributor to physical disability worldwide [1]. OA is a multifactorial disease involving all the joint structures. Despite the high prevalence and substantial health-care burden of the disease, there is no approved disease-modifying drug to slow disease progression, and end-stage OA is treated with costly total joint replacement surgery to relieve pain and restore joint function. Understanding the biological pathways involved in the development and progression of OA has the potential to inform preventive and therapeutic strategies.

There is increasing evidence for a role for vascular pathology in the pathogenesis of knee OA [2, 3]. Reduced retinal

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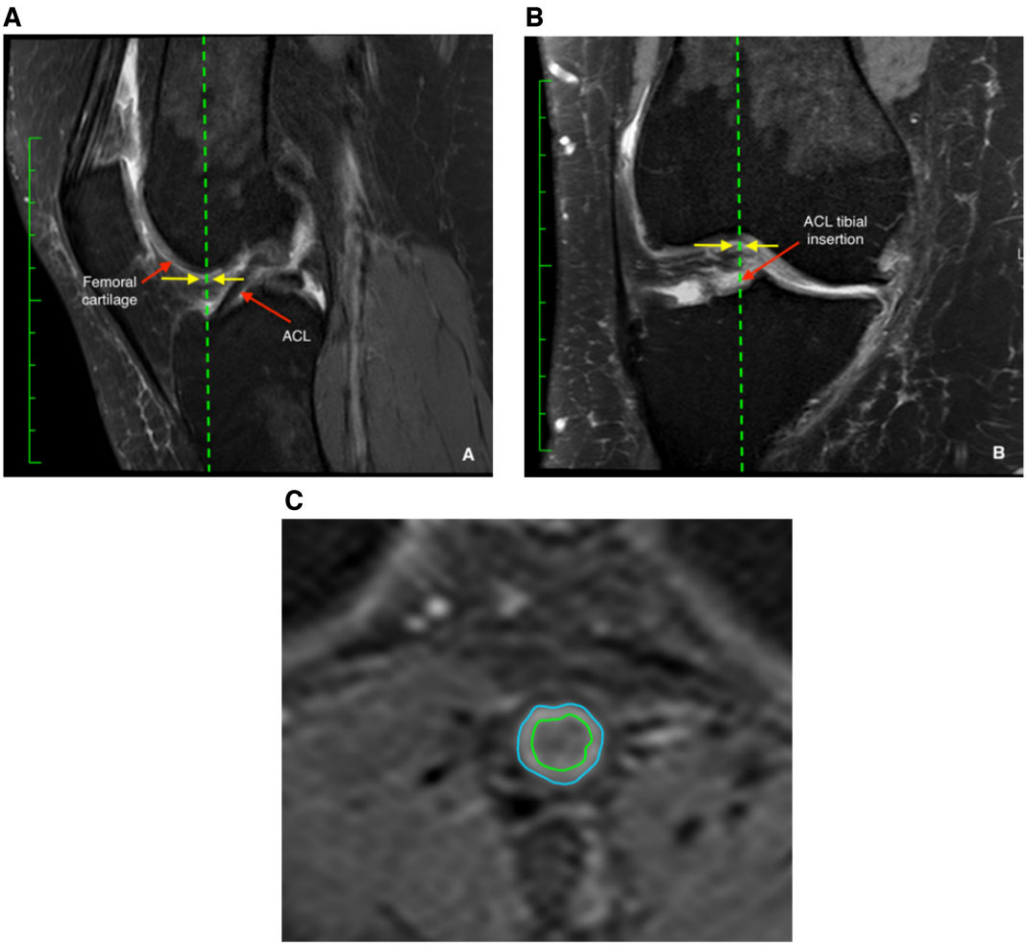

Figure 1. Measurement of popliteal artery wall thickness

(**A**) Identification of the level of the femoral intercondylar notch inferior to the cartilage from the sagittal image. (**B**) Identification of the level of the femoral intercondylar notch inferior to the cartilage from the coronal image. (**C**) Segmentation of the outer and inner popliteal artery wall from the axial image at the level identified in (A) and (B).

arteriolar calibre is associated with increased risk of total knee replacement for OA [4, 5]. Increased carotid intima-media thickness is associated with increased prevalence of radiographic knee OA [6]. We also found that increased popliteal artery wall thickness was associated with accelerated cartilage volume loss in two independent studies of asymptomatic populations without clinical knee OA [7, 8]. In contrast, the Netherlands Epidemiology of Obesity study found no association between popliteal vessel wall thickness and prevalence of clinical knee OA or structural knee OA [9]. Using a different assessment of vascular disease, the Rotterdam Study did not find an association between coronary artery calcification and prevalence or progression of knee OA [10].

Popliteal artery wall thickness can be used as a surrogate marker of atherosclerosis. Increased popliteal artery wall thickness is associated with prevalent cardiovascular disease and classical risk factors for cardiovascular disease, which include dyslipidaemia, history of diabetes mellitus, elevated systolic blood pressure, plasma fibrinogen level, smoking, and excess alcohol use [11–13]. Popliteal artery wall thickness can be measured from MRI with excellent reproducibility [7, 14]. Our previous findings that increased popliteal artery wall thickness is associated with cartilage volume loss in asymptomatic populations suggest a role of vascular pathology in the pathogenesis of knee OA in the early stages of the disease [7, 8]. However, it is unknown whether the association persists in populations with established knee OA. This information would be useful for identifying patients with knee OA at higher risk of disease progression for early intervention targeting atherosclerosis. Therefore, we aimed to examine the association between popliteal artery wall thickness and structural progression in those with symptomatic knee OA.

Patients and methods

Study design and participants

This study analysed data collected from the Osteoarthritis of the Knee Statin (OAKS) study, a multicentre randomized, double-blind, placebo-controlled trial determining the effect of atorvastatin on slowing structural progression over 2 years in patients with symptomatic knee OA [15, 16]. In brief, inclusion criteria were (1) men and women aged 40–70 years, (2) symptomatic knee OA (i.e. knee OA with knee pain in most of the days in the last month) for $\geq$6 months, (3) pain score of $\geq$20 mm on a 100 mm visual analogue scale, and (4) meeting the ACR clinical criteria for knee OA [17]. Exclusion criteria were severe radiographic knee OA (grade 3 joint space narrowing according to Altman's atlas [18]), severe knee pain (on

standing >80 mm on 100 mm visual analogue scale), inflammatory arthritis, significant knee injury, accepted indications for statin therapy (familial hypercholesterolaemia, known atherosclerotic cardiovascular disease, and diabetes mellitus), current use of lipid-lowering therapy, previous adverse reaction to statins, absolute cardiovascular risk estimated using the Framingham Risk Equation of >15% within the next 5 years, fasting total cholesterol level >7.5 mmol/l, clinically significant renal disease or abnormal liver function, arthroscopy or open surgery in the index knee in the last 12 months, or contraindication to MRI scanning [15, 16]. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12613000190707). Ethics approval was obtained from the Alfred Hospital Ethics Committee, Monash University Human Research Ethics Committee, the Tasmania Health and Medical Human Research Ethics Committee, and The Queen Elizabeth Hospital Human Research Ethics Committee. All participants provided written informed consent. Three hundred and four participants were recruited from 2013 to 2016 in Melbourne, Hobart and Adelaide, Australia, and the trial was completed in 2018. The current study included 176 participants recruited in Melbourne who had popliteal artery wall thickness measured from MRI.

Study procedure

Participants were randomly assigned in a 1:1 ratio to receive either 40 mg atorvastatin once daily or an inactive matching placebo once daily. Details of the randomization, blinding, and study procedure have been reported previously [15, 16]. All participants were provided usual care by their treating health practitioners. At screening, participants completed questionnaires, underwent physical examination, and had knee X-ray and biochemical testing to assess eligibility. Subsequent study visits were scheduled at baseline, 6, 12 and 24 months.

Anthropometric measurements, physical activity and smoking

At baseline, height and weight were measured to the nearest 0.1 cm using a stadiometer and to the nearest 0.1 kg using an electric scale, respectively. BMI, weight/height^2 (kg/m^2) was calculated. Physical activity was measured using the International Physical Activity Questionnaire short version [19]. Vigorous activity was assessed by asking the following questions: "During the last 7 days, on how many days did you do vigorous activities such as lifting, digging, aerobics, or fast bicycling?" Participation in vigorous physical activity was classified as yes if participants provided data on how many days per week without ticking "No vigorous physical activity". Data on smoking history were collected in the baseline questionnaire in which participants were asked to select only one from "current", "former" and "never". Current and former smokers were classified as smokers.

MRI acquisition

MRI of the study knee was performed at baseline (2013–2016) and ~2 years later (2015–2018) using 1.5 T or 3 T whole-body MRI units with a commercial transmit–receive knee coil. Details of the MRI units, sequences and parameters have been published previously [16].

Measurement of popliteal artery wall thickness

Original axial fat-suppressed proton density MRI is essential for measuring popliteal artery wall thickness, which was only available at the Melbourne site (repetition time/echo time 2703/30 msec, slice thickness 2.5 mm, interslice gap 2 mm, flip angle 90 degrees, field of view 15 cm, 960 × 960 matrix). The popliteal artery wall thickness was measured on baseline MRIs using the OsiriX software for macOS [20, 21], at the midpoint of the knee on the level of the femoral intercondylar notch inferior to the femoral cartilage, as confirmed by both sagittal and coronal images (Fig. 1 A, B). The outer and inner contours of the popliteal artery wall were manually traced, and the cross-sectional areas of the popliteal artery and the arterial lumen were obtained separately (Fig. 1 C). The popliteal artery wall area was calculated by subtracting the luminal area from the arterial area. To account for individual variation in popliteal artery size, the popliteal artery wall area–to–arterial area ratio was used to assess popliteal artery wall thickness, which was calculated by (arterial area – luminal area)/arterial area, expressed as a percentage; the greater the ratio, the thicker the artery wall in relation to the arterial size. The measurement was performed by a single trained observer (E.W.P.), who was blinded to participant characteristics and intervention group allocation. The intra-observer intraclass correlation coefficient was 0.95. The measurement was considered feasible if the luminal and outer boundaries of the popliteal artery wall could be identified and traced properly with no issues about the quality of the images.

Tibial cartilage volume measurement

The volumes of medial and lateral tibial cartilage plates were measured on sagittal T1-weighted images using the OsiriX software [20, 21], by manually tracing the disarticulation contours around the cartilage boundaries [22]. Two trained observers performed the measurement independently with the average results taken as the final measure; the inter-observer intraclass correlation coefficient was 0.91. The annual percentage change of tibial cartilage volume was calculated by (follow-up cartilage volume – baseline cartilage volume)/(baseline cartilage volume × years between MRI scans), expressed as a percentage, where a negative value indicates cartilage volume loss, and a positive value indicates an increase in cartilage volume.

Tibial bone area measurement

The cross-sectional areas of medial and lateral tibial plateau were measured from axial images as previously described [23]. The coefficients of variation for the medial and lateral tibial plateau areas were 2.3% and 2.4%, respectively [23].

Statistical analysis

With 176 participants, this study had 80% power to detect a correlation coefficient as low as 0.21 between popliteal artery wall thickness and structural outcomes (alpha 0.05, 2-sided significance). Popliteal artery wall thickness was examined as a continuous variable and, as well, as a categorical variable. Due to the significant difference in popliteal artery wall thickness between men and women, sex-specific quartiles of popliteal artery wall thickness were created, and participant characteristics were compared among the quartiles using analysis of variance (ANOVA) or the χ^2 test, when appropriate. The associations of popliteal artery wall thickness (as a

Table 1. Baseline characteristics of study participants

	Total population	Sex-specific popliteal artery wall thickness[a]				
	$N = 176$	Bottom quartile $N = 45$	Second quartile $N = 43$	Third quartile $N = 44$	Top quartile $N = 44$	P[b]
Age, years	56.5 (7.2)	56.1 (7.0)	55.7 (7.5)	57.2 (7.0)	56.9 (7.4)	0.76
Women, *n* (%)	100 (56.8)	25 (55.6)	25 (58.1)	25 (56.8)	25 (56.8)	1.00
BMI, kg/m^2	29.4 (5.8)	30.1 (5.5)	29.0 (6.2)	30.2 (6.2)	28.3 (5.0)	0.32
Smoker, *n* (%)	76 (43.2)	23 (51.1)	15 (34.9)	23 (52.3)	15 (34.1)	0.15
Vigorous physical activity, *n* (%)	106 (60.2)	29 (64.4)	26 (60.5)	27 (61.4)	24 (54.6)	0.81
Statin group, *n* (%)	88 (50.0)	17 (37.8)	23 (53.5)	25 (56.8)	23 (52.3)	0.28
Tibial cartilage volume, mm^3						
Medial	1766 (519)	1941 (577)	1754 (479)	1764 (563)	1603 (391)	0.02
Lateral	1933 (628)	2102 (705)	2007 (661)	1760 (552)	1862 (543)	0.05
Tibial bone area, cm^2						
Medial	22.7 (4.0)	24.3 (4.1)	22.5 (3.9)	22.3 (4.0)	21.9 (3.7)	0.03
Lateral	13.2 (2.8)	14.3 (2.7)	12.5 (2.2)	13.2 (3.2)	12.7 (2.5)	0.01
Popliteal artery wall thickness[a], %	46.3 (5.9)	39.9 (3.1)	44.7 (2.6)	47.9 (3.5)	52.6 (5.1)	<0.0001

Data presented as mean (S.D.) or *n* (%).
[a] Assessed by popliteal artery wall area–to–arterial area ratio, calculated by (arterial area – luminal area)/arterial area, expressed as a percentage; the greater the ratio, the thicker the artery wall in relation to the arterial size.
[b] For differences among participants in each quartile of popliteal artery wall thickness.

continuous variable) with baseline tibial cartilage volume and annual percentage change in tibial cartilage volume were examined using multiple linear regression, adjusted for age, sex, BMI, smoking, vigorous physical activity, compartment-specific tibial bone area, and intervention group allocation (the last only for change in tibial cartilage volume). Annual percentage change in tibial cartilage volume was further categorized into quartiles, with cartilage volume loss at the top quartile being defined as rapid progression. The associations between popliteal artery wall thickness (as a continuous and a categorical variable) and rapid progression were examined using logistic regression, adjusted for age, sex, BMI, smoking, vigorous physical activity, compartment-specific tibial bone area, and intervention group allocation. The interaction between sex or intervention group allocation and popliteal artery wall thickness for their association with tibial cartilage volume measures was examined.

A meta-analysis was also performed based on the results from two previous studies examining the relationship between popliteal artery wall thickness and tibial cartilage volume loss in populations without clinical knee OA [7, 8]. The effect estimates were synthesized using a random-effects model, assuming that clinical and methodological heterogeneity are likely to exist and have an effect on the results, with heterogeneity assessed by the I^2 statistic [24]. The magnitude of association between popliteal artery wall thickness and tibial cartilage volume loss in pre-OA and OA populations was compared.

A two-sided P-value of <0.05 was considered statistically significant. All statistical analyses were performed using Stata 16.0 (StataCorp, College Station, TX, USA).

Results

All of the 176 participants had popliteal artery wall thickness measurement at baseline, and 152 (86.4%) of them completed the 2-year follow-up. The mean follow-up time was 2.1 (S.D. 0.2) years. Participant characteristics at baseline are shown in Table 1. The mean age was 56.5 (S.D. 7.2) years, and the mean BMI was 29.4 (S.D. 5.8) kg/m^2; 100 (56.8%) were women. Women had greater popliteal artery wall thickness compared with men [48.9% (S.D. 5.7%) *vs* 42.8% (S.D. 4.2%), $P < 0.001$]. Tibial cartilage volume and bone area were significantly different among participants in each sex-specific quartile of popliteal artery wall thickness. There were no significant differences in BMI, sex, smoking status, or vigorous physical activity between the participants who completed the study and those who did not, except that participants who completed the study were older than those who did not [57.4 (S.D. 6.9) *vs* 50.7 (S.D. 6.0) years, $P < 0.001$].

Association between popliteal artery wall thickness at baseline and tibial cartilage volume

When baseline tibial cartilage volume was examined, greater popliteal artery wall thickness was associated with lower medial and lateral tibial cartilage volume at baseline in univariable analysis (all $P < 0.001$), as shown in Table 2. The association remained significant after adjustments for age, sex, BMI, compartment-specific tibial bone area, smoking and vigorous physical activity for both medial (per 10% increase in popliteal artery wall thickness: regression coefficient –120.8 mm^3, 95% CI –236.2 to –5.4) and lateral (regression coefficient –151.9 mm^3, 95% CI –291.7 to –12.1) tibial cartilage volume.

When annual percentage change in tibial cartilage volume was examined (Table 2), greater popliteal artery wall thickness at baseline was associated with an increased rate of medial tibial cartilage volume loss in multivariable analysis adjusted for age, sex, BMI, tibial bone area, smoking, vigorous physical activity and intervention group allocation (per 10% increase in popliteal artery wall thickness: regression coefficient –1.14%, 95% CI –2.20% to –0.09%). There was no significant association between popliteal artery wall thickness and annual percentage change in lateral tibial cartilage volume (regression coefficient –0.36%, 95% CI –1.16% to 0.43%).

Table 2. Association between popliteal artery wall thickness at baseline and cartilage volume

	Univariable analysis		Multivariable analysis	
	Regression coefficient (95% CI)	*P*	Regression coefficient (95% CI)	*P*
Tibial cartilage volume at baseline, mm^3[a]				
Medial	–415.5 (–530.2, –300.7)	<0.001	–120.8 (–236.2, –5.4)	0.04
Lateral	–463.9 (–605.9, –322.0)	<0.001	–151.9 (–291.7, –12.1)	0.03
Annual % change in tibial cartilage volume[b]				
Medial	–0.82 (–1.68, 0.03)	0.06	–1.14 (–2.20, –0.09)	0.03
Lateral	–0.38 (–1.04, 0.28)	0.25	–0.36 (–1.16, 0.43)	0.37

All regression coefficients were for every 10% increase in popliteal artery wall thickness.
[a] Multivariable analyses adjusted for age, sex, BMI, compartment-specific tibial bone area, smoking, and vigorous physical activity.
[b] For annual % change in tibial cartilage volume, a negative value indicates cartilage volume loss, and a positive value indicates an increase in cartilage volume. Multivariable analyses adjusted for age, sex, BMI, compartment-specific tibial bone area, smoking, vigorous physical activity, and intervention group allocation.

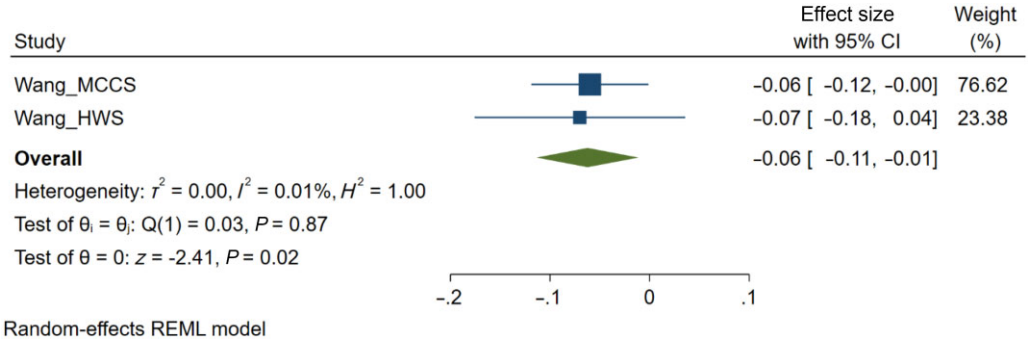

Figure 2. Meta-analysis of association between popliteal artery wall thickness and tibial cartilage volume in pre-OA populations

Random-effects meta-analysis of the regression coefficient for the association between popliteal artery wall thickness and annual percentage change in medial tibial cartilage volume in pre-OA populations.

There was no interaction between sex or intervention group allocation and popliteal artery wall thickness for their association with tibial cartilage volume measures (all *P* values for interaction >0.3). However, the significant association between popliteal artery wall thickness and annual percentage change in medial tibial cartilage volume was observed in the atorvastatin group (regression coefficient –2.90%, 95% CI –4.67% to –1.12%) but not the placebo group (0.02%, 95% CI –1.26% to 1.31%) in multivariable analysis.

The meta-analysis of the association between popliteal artery wall thickness and annual percentage change in medial tibial cartilage volume in pre-OA populations [7, 8] showed a regression coefficient (per 1% increase in popliteal artery wall thickness) of –0.06% (95% CI –0.11% to –0.01%) (Fig. 2). The magnitude of the association was less than in this current study of a population with OA [regression coefficient (per 1% increase in popliteal artery wall thickness) –0.11%, 95% CI –0.22% to –0.01%], although the difference was not statistically significant ($P = 0.40$).

Association between popliteal artery wall thickness at baseline and rapid progression

Greater popliteal artery wall thickness at baseline was associated with higher risk of rapid progression in multivariable analysis adjusted for age, sex, BMI, compartment-specific tibial bone area, smoking, vigorous physical activity and intervention group allocation (per 10% increase in popliteal artery wall thickness: odds ratio 2.28, 95% CI 1.07, 4.83) (Table 3).

When sex-specific quartiles of popliteal artery wall thickness were examined, with the bottom quartile as the reference, the odds ratio of rapid progression was 1.40 (95% CI 0.45, 4.36) for the second quartile, 2.65 (95% CI 0.87, 8.04) for the third quartile, and 2.92 (95% CI 0.91, 9.32) for the top quartile, with *P* for trend of 0.04.

Discussion

In a population with symptomatic knee OA, greater popliteal artery wall thickness was associated with lower tibial cartilage volume at baseline, and increased rate of medial tibial cartilage volume loss and increased risk of rapid progression of medial tibial cartilage loss over 2 years. These results in a population with knee OA are consistent with findings in populations with pre-clinical OA [7, 8], further strengthening the evidence for a role for vascular pathology in the pathogenesis of knee OA across the disease spectrum from pre-clinical early stage through to established symptomatic disease.

We previously showed that greater popliteal artery wall thickness was associated with less cartilage volume and increased rates of cartilage loss in two independent cohort studies of asymptomatic populations without clinical knee OA [7, 8]. This was further supported by other studies examining vascular pathology using different methods, including carotid intima-media thickness and retinal arteriolar calibre, for their relationship with different OA outcomes (i.e. radiographic OA or total knee replacement for OA) [4–6]. We found that

Table 3. Association between popliteal artery wall thickness at baseline and rapid progress in medial tibial cartilage volume loss

	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Popliteal artery wall thickness (per 10%)	1.50 (0.82, 2.75)	0.19	2.28 (1.07, 4.83)	0.03
Popliteal artery wall thickness, quartiles				
Bottom quartile	1.00		1.00	
Second quartile	1.21 (0.40, 3.63)	0.74	1.40 (0.45, 4.36)	0.56
Third quartile	2.02 (0.72, 5.67)	0.18	2.65 (0.87, 8.04)	0.08
Top quartile	2.09 (0.73, 6.01)	0.17	2.92 (0.91, 9.32)	0.07
P for trend		0.11		0.04

Multivariable analysis adjusted for age, sex, BMI, compartment-specific tibial bone area, smoking, vigorous physical activity, and intervention group allocation.

the magnitude of the association between increased popliteal artery wall thickness and the rate of cartilage loss was higher in those with knee OA than in the pre-clinical populations [7, 8] (regression coefficient –0.11% *vs* –0.06%), although the results were not significantly different. With different measures of artery wall as a surrogate measure of atherosclerosis, such as intima-media thickness, diameter and wall area of the carotid artery measured from US, there was a difference of 7–20% in these measures between those with and without myocardial infarction, and a difference of 12–46% in carotid intima-media thickness between those with and without cardiovascular disease at follow-up [25, 26]. These results provide support for the clinical significance of a 10% increase in artery wall thickness. In our present study population, with a 10% increase in popliteal artery wall thickness, the annual rate of medial tibial cartilage loss increased by 1.14%. This is clinically significant, as a 1% increase in the annual rate of tibial cartilage volume loss increased the risk of knee replacement by 20% over 3 years [27]. These findings suggest the clinical and public health implications of targeting vascular pathology in reducing the progression of knee OA and the consequent requirement of total knee replacement, which result in significant health-care burden. Given the bidirectional relationship between vascular pathology and OA with several shared risk factors, targeting these conditions in parallel on the shared risk factors has the potential to improve the outcomes of both conditions.

It is likely that the mechanism for the adverse effect of increased popliteal artery wall thickness on cartilage loss is due to the reduced blood flow to the knee joint. The subchondral bone regions are highly vascularized, and higher blood flow is associated with increased rate of bone remodelling [28, 29]. Articular cartilage is avascular and relies on subchondral bone and synovium for nutrition. The popliteal artery supplies blood to the knee joint, and is also a surrogate marker for generalized atherosclerosis [11–13]. Increased popliteal wall thickness is likely to result in decreased blood flow to the subchondral bone of the knee and reduced interstitial fluid flow within the subchondral bone. This will result in subchondral bone ischaemia, compromising the oxygen and nutrient supply to the articular cartilage and leading to apoptosis of osteocytes, which further initiates osteoclastic bone resorption, alters the mechanical property and impairs the shock absorption ability of the subchondral bone [3]. All these changes will make the articular cartilage more susceptible to damage and result in cartilage degeneration.

There are limitations in our study. Popliteal artery wall thickness was measured on a single MRI slice, which may not represent the condition of the whole artery. However, popliteal artery wall thickness measured on one single slice or site of MRI and US reflected the variance in popliteal artery wall thickness in a population, being associated with classical risk factors for cardiovascular disease, prevalence of cardiovascular disease, and cartilage loss [7, 12, 13]. These data provide evidence for validation of this measurement. Second, although the sample size of our study was moderate, the study was powered to detect a correlation coefficient as low as 0.21 between popliteal artery wall thickness and cartilage volume. The strengths of our study included the validated measurement of popliteal artery wall thickness and knee cartilage volume, both of which showed excellent reproducibility. Our study had 2 years of follow-up with good retention rate, allowing the detection of cartilage volume loss and examination of its association with popliteal artery wall thickness. Finally, our study included a meta-analysis that confirmed the associations observed in each individual study and enabling the comparison of the magnitude of the association in pre-OA and OA populations.

In conclusion, increased popliteal artery wall thickness was associated with structural progression in knee OA, evidenced by lower medial and lateral tibial cartilage volume at baseline and increased rate of medial tibial cartilage volume loss and increased risk of rapid progression over 2 years. Our findings suggest the involvement of vascular disease in the development and progression of knee OA and that targeting vascular pathology may be important in slowing the structural progression in both pre-OA and OA populations and reducing the burden of the disease.

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Data availability statement

The data generated from this study will not be deposited in a public repository due to privacy and consent restrictions. De-identified data can be made available from the corresponding author on reasonable request, subject to a data sharing agreement.

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