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Brief Report

Retinal arteriolar narrowing and incidence of knee replacement for osteoarthritis: a prospective cohort study

S.M. Hussain †, Y. Wang †, J.E. Shaw ‡, D.J. Magliano ‡, T.Y. Wong §, A.E. Wluka †, S. Graves ‖ ¶, R.J. Tapp # ††, F.M. Cicuttini † *

† *Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Alfred Hospital, Melbourne, VIC 3004, Australia*
‡ *Baker IDI Heart and Diabetes Institute, Melbourne, VIC 3004, Australia*
§ *Singapore Eye Research Institute, Singapore National Eye Center, Duke-NUS Graduate Medical School, National University of Singapore, Singapore*
‖ *Department of Surgery, Flinders University Adelaide, SA, Australia*
¶ *Australian Orthopaedic Association National Joint Replacement Registry, Discipline of Public Health, School of Population Health & Clinical Practice, University of Adelaide, SA 5005, Australia*
# *Department of Optometry and Vision Sciences, The University of Melbourne, Australia*
†† *Indigenous Eye Health Unit, Melbourne School of Population and Global Health, The University of Melbourne, Australia*

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SUMMARY

Objectives: The role of the microcirculation in the pathogenesis of osteoarthritis (OA) remains unclear. This prospective cohort study examined the association between retinal vascular calibre and incidence of knee replacement for OA.
Design: 1838 participants of the Australian Diabetes, Obesity and Lifestyle (AusDiab) Study had retinal vascular calibre measured using a nonmydriatic digital fundus camera in 1999–2000 and were aged ≥40 years at joint replacement data collection commencement. The incidence of knee replacement for OA during 2002–2011 was determined by linking cohort records to the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR).
Results: 77 participants underwent knee replacement for OA. They had narrower retinal arteriolar calibre compared with those without knee replacement (166.1 ± 24.8 μm vs 174.3 ± 24.5 μm, $P = 0.004$). For every one standard deviation reduction in retinal arteriolar calibre, the incidence of knee replacement increased by 25% (HR 1.25, 95% confidence interval (CI) 1.00–1.56). Participants in the narrower two-thirds of arteriolar calibre had twice the risk of knee replacement compared with those in the widest one-third (HR 2.00, 95% CI 1.07–3.74, $P = 0.03$) after adjustment for sex, body mass index (BMI), physical activity and HbA1c. There was no association for retinal venular calibre.
Conclusions: Retinal arteriolar narrowing is associated with increased risk of knee replacement for OA suggesting that further work is warranted to determine the role of the microcirculation in the pathogenesis of knee OA.

Introduction

There is increasing evidence suggesting an association between vascular disease and osteoarthritis (OA)[1,2]. The Rotterdam study found that increased intima media thickness of the carotid artery, a subclinical marker of large vessel atherosclerosis, was associated with increased prevalence of knee OA and progression of hand OA in women[1]. In the women of the AGES Reykjavik Study, carotid plaque and coronary calcification were associated with increased severity of hand OA[2]. Increased popliteal artery wall thickness, another measure of large vessel atherosclerosis, was associated

* Address correspondence and reprint requests to: F.M. Cicuttini, School of Public Health and Preventive Medicine, Monash University, Alfred Hospital, Melbourne VIC 3004, Australia. Tel: 61-3-990-30158; Fax: 61-3-990-30556.
E-mail addresses: monira.hussain@monash.edu (S.M. Hussain), yuanyuan.wang@monash.edu (Y. Wang), jonathan.shaw@bakeridi.edu.au (J.E. Shaw), dianna.magliano@bakeridi.edu.au (D.J. Magliano), tien_yin_wong@nuhs.edu.sg (T.Y. Wong), anita.wluka@monash.edu (A.E. Wluka), segraves@aoanjrr.org.au (S. Graves), robyn.tapp@unimelb.edu.au (R.J. Tapp), flavia.cicuttini@monash.edu (F.M. Cicuttini).

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with generalized OA[3]. These findings suggest that macrovascular disease is involved in the pathogenesis of OA possibly through reduced nutrition to the joint. However, little work has examined the role of microcirculation in OA.

The microcirculation, including the arterioles, capillaries, and venules, optimizes nutrient and oxygen supply within tissues in response to metabolic demand variations[4]. Some of the earliest manifestation of cardiovascular disease occurs in the microcirculatory bed[4]. Abnormal microcirculation is common among the conventional cardiovascular risk factors, including hypertension, diabetes, obesity, and dyslipidemia[4] which are risk factors for OA[5]. The retinal vasculature provides a unique window to assess the microcirculation noninvasively and directly[6] and it has been associated with clinical and subclinical cardio-metabolic outcomes including hypertension[7,8], dyslipidaemia[7], and diabetes[8]. The purpose of this study was to examine the association between retinal vascular calibre and the incidence of knee replacement for OA.

Patients and methods

The Australian Diabetes, Obesity and Lifestyle (AusDiab) Study is a population-based, national prospective cohort study of 11,247 people, aged ≥25 years, recruited during 1999–2000[9]. 2476 participants (having diabetes or impaired glucose metabolism, and a random sample with normal glucose tolerance) who participated in the baseline complications survey had retinal vascular calibre measured and were included in this study[10]. They were older (60.5 ± 12.0 vs 54.8 ± 11.9 years), had higher HbA1c level (5.7 ± 1.2 vs 5.2 ± 0.5), systolic blood pressure (138.9 ± 20.1 vs 130.0 ± 18.6 mm Hg), and body mass index (BMI) (28.7 ± 5.6 vs 26.8 ± 4.7 kg/m^2) (all $P < 0.001$) than non-participants. We restricted our analysis to those aged ≥40 years at joint replacement data collection commencement ($n = 1838$) since joint replacement as treatment of OA is very uncommon under this age.

Data on date of birth, sex, and physical activity (sufficient, ≥150 min per week, insufficient, <150 min per week, or sedentary, 0 min per week) were collected by trained interviewers[9]. Height and weight were measured using standard protocols; systolic blood pressure measured with dinamap/mercury sphygmomanometer; HbA1c measured by Boronate affinity high performance liquid chromatography; serum total cholesterol measured by enzymatic method; and urine protein measured by immunoturbidimetric method (Olympus AU600 analyser)[9].

Retinal photographs of both eyes were taken using a non-mydriatic digital fundus camera[10]. Retinal vascular calibre was measured using a validated computer-based program[10]. For each photograph, the average arteriolar and venular calibre was summarized as central retinal artery equivalent and central retinal vein equivalent, respectively[10]. Reproducibility of this method was high, with intra- and inter-grader intra-class correlation coefficients 0.78–0.99[10].

The Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) collects information on prostheses, patient demographics, type and reason for joint replacement, with almost complete data on joint replacement in Australia[11]. Linking AusDiab records to AOA NJRR identified those who had a primary joint replacement performed between 1 January 2002 and 31 December 2011. Knee OA was defined as the first primary knee replacement for OA. For those with multiple joint replacements, only the first recorded knee replacement was considered. Data linkage study was approved by the Alfred Hospital, University of Adelaide and Monash University Human Research Ethics Committees. All participants gave written informed consent.

Cox proportional hazard regression models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the incidence of knee replacement due to OA associated with retinal vascular calibre, with age as the time scale. Follow-up for joint replacement (calculation of person-time) began 1 January 2002, and ended at the date of first knee replacement for OA or date of censoring. Participants were censored at either the date of first knee replacement for indications other than OA, the date of death, or end of follow-up (December 31, 2011), whichever came first. Retinal vascular calibre was standardized so that HR represents the effect of a one-standard-deviation difference in calibre. Retinal vascular calibre was also categorized into tertiles based on the analysis sample with widest tertile used as the referent category. Linear association between retinal vascular calibre and knee replacement risk was examined using the likelihood ratio test. Each analysis was adjusted for sex and BMI, and further adjusted for physical activity, HbA1c, and cardiovascular risk factors (systolic blood pressure, total cholesterol and microalbuminuria). All statistical analyses were performed using Stata 12.0 (StataCorp LP., College Station, TX, USA).

Results

Over the 8.7 (SD 2.7) years of follow-up, 77 knee replacements for OA were identified. Characteristics of the study participants are presented in Table I.

After adjusting for sex, BMI, HbA1c and physical activity, 1 standard deviation reduction in retinal arteriolar calibre was associated with a 25% increased incidence of knee replacement (HR 1.25, 95% CI 1.00–1.56) (Table II). When retinal arteriolar calibre was examined as a categorical variable, HR was 1.98 (95% CI 1.00–3.92) for the narrowest and HR 2.02 (95% CI 1.03–3.94) for the middle tertile, with widest tertile the referent group. Further adjustment for the cardiovascular risk factors did not change the associations. As there was no evidence for a linear association, the narrower two tertiles were combined and compared with the widest tertile. Participants with narrower two-thirds of arteriolar calibre had a 2 times increased risk of knee replacement compared with those with widest one-third of arteriolar calibre (HR 2.04, 95% CI 1.10–3.79, $P = 0.02$) (Supplementary Fig. 1). This association remained unchanged after adjustment for sex, BMI, physical activity and HbA1c (HR 2.00, 95% CI 1.07–3.74, $P = 0.03$). There was no association observed for retinal venular calibre.

Discussion

We found that narrower retinal arteriolar calibre, but not retinal venular calibre, predicted an increased risk of knee replacement for

Table I
Characteristics of study population

	No knee replacement ($n = 1761$)	Knee replacement ($n = 77$)	*P* value
Age at baseline (years)	60.3 ± 12.1	65.0 ± 7.5	0.001
Age at 1 January 2002 (years)	62.5 ± 12.1	67.4 ± 7.5	0.001
Female, *n* (%)	965 (54.8)	39 (50.7)	0.47
BMI (kg/m^2)	28.6 ± 5.6	31.4 ± 5.5	<0.001
Physical activity, *n* (%)			0.20
Sedentary	376 (21.5)	23 (29.9)	
Insufficient	572 (32.7)	24 (31.2)	
Sufficient	803 (45.9)	30 (39.0)	
HbA1c (%)	5.7 ± 1.2	5.8 ± 1.1	0.35
Systolic blood pressure (mm Hg)	138.4 ± 20.2	149.0 ± 18.3	<0.001
Total cholesterol (mmol/L)	5.7 ± 1.0	5.7 ± 1.0	0.63
Microalbumin (mg/L)	33.5 ± 118.0	20.1 ± 55.6	0.34
Retinal arteriolar calibre (μm)	174.3 ± 24.5	166.1 ± 24.8	0.004
Retinal venular calibre (μm)	205.0 ± 23.2	198.4 ± 21.6	0.01

Data presented as mean ± SD or no (%).