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Brief Report

Osteoarthritis bone marrow lesions at the knee and large artery characteristics

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SUMMARY

Objective: There is evidence to suggest vascular involvement in the initiation and progression of osteoarthritis (OA). The relationship between large artery characteristics and pathogenesis of OA has not been investigated and was the aim of this study.
Design: Large artery characteristics (i.e., aortic stiffness, brachial and central blood pressure (BP) variables) and bone marrow lesions (BMLs; measured by magnetic resonance imaging as a surrogate index of OA) were recorded in 208 participants (aged 63 ± 7 years; mean ± SD) with symptomatic knee OA. Relationships between large artery characteristics and BML were assessed by multiple regression adjusting for age, sex and body mass index.
Results: There was a high prevalence of BML presence in the study population (70%), but no significant difference between participants with and without BML for all large artery and BP variables ($P > 0.05$ all). Furthermore, there were no significant relationships between BML size and aortic stiffness ($r = -0.033$, $P = 0.71$), central pulse pressure ($r = 0.028$, $P = 0.74$), augmentation index ($r = 0.125$, $P = 0.14$), brachial pulse pressure ($r = 0.005$, $P = 0.95$) or brachial systolic BP ($r = -0.066$, $P = 0.44$). When participants were stratified according to high or low aortic stiffness, there was no significant difference between groups regarding the proportion of those with a BML (64% vs 70% respectively; $P = 0.69$).
Conclusions: Variables indicative of large artery characteristics are not significantly correlated with BML size or presence in people with symptomatic knee OA. Thus, large artery characteristics may not have a causative influence in the development of OA, but this needs to be confirmed in prospective studies.

Introduction

A high proportion of patients with osteoarthritis (OA) have cardiovascular comorbidities that have been suggested to play a contributory role in OA pathogenesis[1]. Despite this, a causative connection between OA and conventional cardiovascular risk factors has remained elusive. Accumulating evidence alludes to vascular involvement in the initiation and progression of OA[2]. Indeed, a recent investigation found that abnormalities of the retinal microvasculature were independently associated with bone marrow lesions (BMLs) and knee cartilage volume in a community sample of 289 asymptomatic people (61% women) aged 50–79 years[3]. Altogether, data suggests that examination of vascular structure and function using techniques that are more sensitive than conventional cardiovascular risk factors could advance understanding on the OA–cardiovascular disease relationship. Microvascular abnormalities precede development of atherosclerosis and are associated with large artery dysfunction (e.g., increased aortic stiffness)[4]. With this in mind, there remains the possibility that large artery dysfunction may also have a role in the pathogenesis of OA, but this has not been investigated before. The aim of this study was to determine the association between BMLs (as a surrogate index of OA) and large artery characteristics as determined by aortic stiffness and central blood pressure (BP) variables related to systemic arterial stiffness (i.e., augmentation index and central pulse pressure).

Methods

Participants and protocol

The study sample comprised 208 participants with symptomatic knee OA who were recruited as part of a clinical trial (ClinicalTrials.

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gov identifier: NCT01176344; Australian New Zealand Clinical Trials Registry: ACTRN12610000495022)[5]. Data presented here is from the baseline examination (prior to randomisation) of participants in the Tasmanian study arm. Procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. All participants provided written informed consent. Inclusion criteria were: participants aged 50–79 years with symptomatic knee OA for at least 6 months with a pain visual analogue scale (VAS) of at least 20 mm out of 100 mm (higher score out of 100 mm indicates more pain)[6]. Participants were also required to meet the American College of Rheumatology criteria for symptomatic knee OA assessed by a Rheumatologist and have relatively good health (0–2 according to the investigator's global assessment of disease status on a 5-point Likert scale, range 0 [very well] to 4 [very poor]). In addition, serum 25-(OH)D levels must have ranged between 12.5 and 60 nmol/L which is in the low-normal to moderate vitamin D deficiency range, using a cut-off of 50 nmol/L to define deficiency. Exclusion criteria were as follows: severe radiographic knee OA, grade 3 according to Altman's atlas[7]; severe knee pain on standing (more than 80 mm on 100 mm VAS); contraindication to MRI; rheumatoid or psoriatic arthritis, lupus or cancer; severe cardiac or renal impairment; hypersensitivity to vitamin D; any condition possibly affecting oral drug absorption; significant trauma to knees, including arthroscopy or significant injury to ligaments or menisci of the knee within 1 year preceding the study; anticipated need for knee or hip surgery within the next 2 years; history of taking vitamin D supplements or an investigational drug within the previous 30 days.

Large artery characteristics and BP

Electrocardiogram-gated, sequential applanation tonometry at the carotid and femoral arteries (pulse wave velocity (PWV); SphygmoCor 8.1, AtCor Medical, Sydney, New South Wales) was used to measure supine aortic stiffness as per recommended guidelines[8]. Seated central BP was measured in duplicate by radial tonometry using the SphygmoCor 8.1 system with a validated transfer function[9]. Augmentation index was calculated from the difference between the first and second systolic peaks of the central waveform as a percentage of pulse pressure[8]. This is a composite measure of left ventricular load and systemic arterial stiffness. Central pulse pressure was calculated as the difference between central systolic and central diastolic pressure values. Seated brachial BP was recorded in duplicate after 5 min rest using an automated oscillometric device (Omron HEM 907) and these values were used to calibrate the radial tonometric pressure waveform.

BMLs

An MRI scan using a T_2-weighted fat-saturated fast spin echo sequence of the symptomatic knee was undertaken for determination of tibial and femoral BMLs. A BML was defined as an area of increased signal intensity adjacent to subcortical bone in the medial and lateral areas of the tibial and femoral bones. If more than one BML was present, the BML of greatest size was used in analysis. BML area was measured using Osiris software as previously described[1].

Statistical methods

All analyses were performed using IBM SPSS statistics 19 for windows. Data were expressed as mean ± SD unless otherwise stated. Pearson's product moment correlations were used to assess relationships between variables. Comparison of variables between those with and without BMLs were analysed using independent Student's *t* tests or the Chi square tests for independence. Partial correlation analysis was used to determine the relationship between BML area and large artery characteristics (aortic stiffness and BP variables), adjusting for age, sex and body mass index. Increased aortic stiffness was defined as per age and BP-specific normative values, calculated using standardised PWV measures[10] as well as according to the European Society of Hypertension (ESH) suggested cutpoint of ≥12 m/s. Standard diagnostic checks of model adequacy and unusual observations were performed for all models. BML area was not normally distributed and was normalized by logarithmic transformation. Statistical significance was defined as $P < 0.05$.

Results

Mean age of the study population was 63 ± 7 years. BMLs were present in 146 of the 208 participants. Characteristics of study participants (for those with and without BMLs), as well as aortic stiffness and BP variables are summarised in Table I. No significant difference in age, sex or body mass index was found between the two groups. There was no significant difference between participants with and without BMLs for aortic stiffness, central pulse pressure, augmentation index or brachial pulse pressure. Furthermore, there were no significant relationships between BML size and aortic stiffness ($r = -0.033$, $P = 0.71$), central pulse pressure ($r = 0.028$, $P = 0.74$), augmentation index ($r = 0.125$, $P = 0.14$), brachial pulse pressure ($r = 0.005$, $P = 0.95$) or brachial systolic BP ($r = -0.066$, $P = 0.44$). No significant difference in mean BML size was found when the ESH guidelines proposed threshold for increased aortic stiffness was used to compare groups (233 ± 403 vs 193 ± 241 mm^2; $P = 0.51$; Fig. 1). Furthermore, there was no significant difference ($P = 0.69$) in the percentage of those with a BML in the group with increased aortic stiffness (64%) compared with the group of lower aortic stiffness (70%). There was also no significant difference in BML area for those who had aortic PWV above calculated age- and BP-specific normative values[10]. These findings were unchanged when analysed separately for men and women.

Discussion

The aim of this study was to determine associations between large artery characteristics and BMLs in participants with OA. The rationale for undertaking the work was that conventional cardiovascular risk factors often coexist in OA, yet examination of new (and more sensitive) large artery risk factors as potential contributory variables in OA has not been undertaken. The measurements of large artery characteristics used in this investigation (i.e., aortic PWV, augmentation index and central BP), are known correlates of

Table I
Participant characteristics between those with and without tibial or femoral BMLs

Variable	BML present ($n = 146$)	No BML ($n = 62$)	*P* value
Age (years)	63 ± 7	64 ± 8	0.66
Sex (*n* (% male))	75 (51)	26 (42)	0.27
Body mass index (kg/m^2)	29.8 ± 5	29.2 ± 5	0.45
Aortic stiffness (m/s)	9.3 ± 2	9.0 ± 2	0.49
Peripheral systolic pressure (mmHg)	130 ± 15	127 ± 14	0.21
Peripheral diastolic pressure (mmHg)	74 ± 10	72 ± 9	0.13
Central systolic pressure (mmHg)	118 ± 15	116 ± 15	0.29
Peripheral pulse pressure (mmHg)	56 ± 12	55 ± 12	0.65
Central pulse pressure (mmHg)	43 ± 11	43 ± 12	0.89
Augmentation index (%)	25 ± 10	26 ± 9	0.46

P value is for differences between groups; values are mean ± SD.