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The presence of total knee or hip replacements due to OA enhances the positive association between hand OA and atherosclerosis in females: The AGES-Reykjavik Study

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Abstract

Objective—This study examines the relationship between total knee replacements (TKR), total hip replacements (THR) or replacements of either joint (TJR) due to osteoarthritis (OA) and atherosclerosis in a large population-based study.

Methods—The participants were 2195 males and 2975 females, mean age 76±6 years. The OA data were analysed in relation to measures of atherosclerosis, including carotid artery intima media thickness and plaque severity (ultrasound), coronary and aortic calcifications (CT), cerebral white matter lesions (MRI) and history of previous cardiac and cerebral events.

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Results—The prevalence of TKR was 223(4.3%) and THR 316(6.1%). The presence of TJR's in females was associated with a nonsignificant trend towards increased carotid plaque severity, coronary calcifications and periventricular white matter hyperintensities (PVHs) but not with history of cardiac or cerebral events. No associations were seen in males. When TJR's were grouped according to the presence or absence of HOA there was a highly significant association in the order $-TJR/-HOA < +TJR/-HOA < -TJR/+HOA < +TJR/+HOA$, for carotid plaque severity, coronary calcifications and PVHs.

Conclusion—The presence of TJR's did not show a significant independent association with atherosclerosis but enhanced the strength of the positive association between HOA and subclinical atherosclerosis in females.

Keywords

Hand osteoarthritis; Total knee replacements; Total hip replacements; atherosclerosis; AGES-Reykjavik Study

BACKGROUND

A number of investigators have speculated on the relationship between the vascular system and the development and progression of osteoarthritis (OA).[1] There have been reports associating OA with increased cardiovascular comorbidity, increased arterial stiffness and even cardiovascular deaths.[2,3,4,5] Others have described both venous and arterial pathology in the subchondral bone as well as a systemic dysregulation of coagulation and fibrinolysis in OA.[6]

In a recent study, we described increased coronary calcifications and carotid plaque severity in elderly females with hand OA (HOA). This association was linear with increasing atherosclerosis with HOA severity.[7] Kornaat and associates have also recently described increased popliteal arterial wall thickness in patients with OA at multiple joint sites compared with a non-OA control group.[8]

In this study we used total knee replacements (TKR), total hip replacements (THR) or replacements of either joint (TJR) due to OA as surrogate markers for severe OA at these sites and applied the same methods as before to analyse the relationship between TJR and atherosclerotic vascular disease in the AGES-Reykjavik Study.[7]

METHODS

The AGES-Reykjavik Study (Age, Gene/Environment Susceptibility - Reykjavik Study) is a population based study of elderly individuals from the 40 year long Reykjavik Study. Participants were aged between 66 and 96 and were randomly recruited between 2002 and 2006 from surviving Reykjavik Study members. Informed consent was obtained from all participants. Details of the investigations are described in the study's baseline article.[9]

Knee and hip joint replacements (TKR, THR) were recorded on the basis of computerized tomography (CT) anterior scout scans. A total of 5250 individuals had both CT scans and high quality hand photographs for the assessment of HOA, and a total of 581 of those had total joint replacements (TJR). In order to identify those with total joint replacements (TJR) presumably due to osteoarthritis, subjects with evidence of inflammatory arthritis on the CT scans or photographs were excluded (n=27). Furthermore, additional 53 photographs could not be scored for HOA due to contractures, deformities or thumb positioning. This left a study group of 5170 with a total of 559 subjects with TJR. Finally, this group was then compared with a verified fracture registry for this group based on medical records,[10]

excluding TJR's due to fractures. This left a study group of 5170 subjects (2195 males and 2975 females) 508 of whom had total joint replacements that were presumed to be caused by OA. The average age of the participants was 76 ± 6 years.

The presence and severity of HOA was read from high quality digital photographs and scored as 0-3 for the distal interphalangeal joints (DIP), the proximal interphalangeal joints (PIP) and the first carpometacarpal joint (CMC1) joints creating an aggregate score of 0-9. This score was subsequently truncated to 0,1,2,3 and 4+ (HOAScore) as previously described.[7] In the analysis, HOA was defined as no evidence of OA (HOAScore=0) and some evidence of OA (HOAScore ≥ 1).

The atherosclerosis variables have been described previously [7] with the exception of white matter hyperintensities (WMH) and PVHs. MRI detected WMH were considered present in the case of signal intensity higher than normal white and gray matter on both T2-weighted and FLAIR images. The load of WMH in the subcortical and periventricular regions is separately rated according to a scale with known properties.[11] The total load of subcortical WMH of the whole brain was calculated as the weighted sum of the number and size of lesions. A total load of periventricular WMH (PVHs) was calculated as the sum of lesion scores on a size scale of 0-3. [11,12]. Information about previous stroke was based on questionnaire as in the previous study,[7] but history of myocardial infarction was now based on a national registry maintained by the Icelandic Heart Association, defining MI, PCI or CABG as a coronary event.

Statistics

We performed multiple linear regression analysis for the atherosclerosis variables in relation to the presence/absence of TKR and THR in each gender, adjusting for previously indicated risk factors, including age, BMI, hs-CRP, triglycerides, cholesterol, statin use, bone mineral density of the spine, pulsepressure and smoking history. In the case of the binary variables, a binary logistic regression was chosen. In analyzing the relationship between selected variables and the presence or absence of HOA we combined TKR and THR into a single variable; TJR (present/absent). Tests for linear trends over subgroups were done using orthogonal contrasts. The statistical analysis was done using the SPSS 16.0 statistical software package.

RESULTS

The total number of THR presumed to be due to OA was 316 (6.1%), 206 females and 110 males. 31 participants had both hip and knee replacements. The total number of individuals with TKR was 223 (4.3%), 142 females and 81 males.

The presence of TKR and THR in females was associated with a nonsignificant trend towards increased coronary calcifications and PVH's (Table 1a) and increased carotid plaque severity but not with history of cardiac or cerebral events (Table 1b). No associations were seen in males.

Thus, apart from a marginally increased aortic calcium in females with TKR there were no statistical differences in those with and without TKR or THR. Aortic calcium was not statistically increased in participants with HOA .[7] When the presence or absence of TJR's were grouped according to the presence or absence of HOA in females there was a significant trend in the order $-TJR/-HOA < +TJR/-HOA < -TJR/+HOA < +TJR/+HOA$, for the association with coronary calcifications, PVHs and the fraction of those with moderate or severe carotid plaque severity. (Figure 1). The magnitude of the difference between the mean values of the lowest group ($-TJR/-HOA$) and the highest ($+TJR/+HOA$)

was approximately 10% for these three variables. However, since coronary calcifications measurements are presented on a logarithmic scale ($\ln+1$) for statistical purposes, back transformation of this variable corresponds to a 57% difference in true measurement values.

DISCUSSION

In this cross-sectional, population-based study of 5170 elderly individuals, we found only a weak nonsignificant trend towards increased atherosclerosis in participants with TKR or THR due to OA. However, when these data were coupled to evidence of HOA there was a clearly significant positive association in females, with those having both TJR and HOA exhibiting the highest level of atherosclerosis.

In comparison with our previous report showing a linear association between HOA severity and coronary calcifications and carotid plaques, the information on knee and hip OA was limited to subjects having had joint replacements due to OA, here used as surrogate markers for severe knee and hip OA. Thus, the comparison was limited to the presence or absence of TJR and this was analysed in comparison with the remainder of the study group. It is possible that analysis of quantitative data would have shown a stronger association with OA severity in these joints. In our previous study however,[7] the most severe phenotype of HOA had significantly more atherosclerosis compared with the remainder (data not shown) which may indicate that the systemic association between HOA and atherosclerosis may be stronger than the association between TJR and atherosclerosis. In our previous study there was no analysis of MRI data so the association between PVH's and OA has not been described previously. This variable exhibits very similar associations with OA as do coronary calcifications and carotid plaque severity but adds a further dimension to the systemic nature of the association now detected in different organ sites with three different imaging methods, ultrasound, CT and MRI. The magnitude of the OA related difference in the atherosclerosis variables is also highly relevant, corresponding in effect size to that observed between AGES-Reykjavik Study participants with and without hypertension (hypertension defined by either self reports, use of antihypertensive medications or measurements at study visit).

The mechanisms behind the association between osteoarthritis and atherosclerosis are still unknown. Several genes, including the KLOTHO gene [13,14] have been associated with both conditions and a variety of other mechanisms may be involved including inflammation, [15] and the accumulation of advanced glycation end-products.[16] In the AGES-Reykjavik study, current hsCRP is associated with atherosclerosis but no association is seen with HOA severity.[7] Some other theoretical mechanisms involve adipokines [17], Cathepsin cysteine proteases,[18] ADAMTS proteases [19] and the involvement of extracellular membrane vesicles,[20] all known to be involved in the pathophysiological processes of OA and atherosclerosis.

The AGES-Reykjavik Study, with its large number of elderly subjects is highly suitable for analyzing relationships involving organ damage acquired during lifetime. The governmental health care system in Iceland is socialized with universal access to medical care including joint replacements, and the study itself is population-based, indicating that the current findings are probably representative of the Icelandic population. Possible caveats of this study relate primarily to the diagnostic methods, photography to diagnose and grade HOA and the assumption that joint replacements not attributable to inflammatory arthritis or fractures represent severe OA.

The findings in the current study are in agreement with our previous findings in women, indicating an overlap between the pathological processes of OA and atherosclerosis. They

also indicate the existence of a systemic form of osteoarthritis that needs to be defined further. We are currently analyzing a number of “midlife” biomarkers and inflammatory markers available from previous visits in the 40-year long Reykjavik Study in an attempt to clarify this relationship.

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Figure 1.

A schematic presentation of the relationship between total joint replacements and hand osteoarthritis in females and their association with selected markers of atherosclerosis. The available numbers for each variable were not the same and are therefore listed separately. All values are adjusted for age, BMI, hsCRP, bone mineral density of the spine, triglycerides, cholesterol, smoking history, statin use and pulsepressure as well as HOA severity. The linear trends for the order $-TJR/-HOA < +TJR/-HOA < -TJR/+HOA < +TJR/+HOA$ are all highly significant, for coronary calcium, $p=0,003$ for PVHs $p<0,001$ and for carotid plaque $p=0,011$.

Table 1a

Measurement of atherosclerosis markers in relation to hip and knee joint replacements. Values represent means (SE). All variables were adjusted for age, BMI, hsCRP, bone mineral density of the spine, triglycerides, cholesterol, smoking history, statin use and pulsepressure.

		Males without/with joint replacement	Females without/with joint replacement
CCA-IMT (mm) *	Hip	1,02(1,01-1,02)/ 1,0(0,97-1,02)	0,96(0,95-0,96)/ 0,96(0,94-0,98)
	Knee	1,01(1,01-1,02)/ 1,02(0,99-1,05)	0,96(0,95-0,96)/0,96(0,94-0,98)
Coronary calcium (Agatston units (log))	Hip	5,96(5,86-6,06)/ 6,1(5,75-6,45)	4,58(4,48-4,68)/ 4,71(4,39-5,03)
	Knee	5,97(5,87-6,07)/ 5,85(5,45-6,25)	4,58(4,48-4,68)/4,96(4,57-5,35)
Aortic calcium (Agatston units (log))	Hip	7,48(7,4-7,56)/ 7,45(7,16-7,74)	7,64(7,58-7,7)/ 7,7(7,51-7,89)
	Knee	7,48(7,4-7,56)/ 7,54(7,23-7,87)	7,63(7,57-7,69)/ 7,89(7,66-8,12) ****
PVHs **	Hip	6,13(6,0-6,25)/ 6,36(5,86-6,86)	6,17(6,06-6,28)/ 6,35(5,88-6,72)
	Knee	6,12(5,88-6,25)/ 6,63(6,04-7,22)	6,17(6,06-6,29)/6,41(5,97-6,85)
WMHs ^{1/3} ***	Hip	1,31(1,27-1,34)/ 1,26(1,13-1,38)	1,38(1,35-1,41)/ 1,38(1,29-1,47)
	Knee	1,3(1,27-1,34)/1,33(1,18-1,48)	1,38(1,35-1,41)/1,4(1,3-1,51)

* Carotid intimal thickness in mm.

** Periventricular hyperintensities score.

*** Subcortical white matter hyperintensities.

p=0.024

Table 1b

Odds ratios for the association between binary cardiovascular outcome variables and total hip and knee joint replacements due to osteoarthritis.

		Males OR(95%CI)	Females OR(95%CI)
Carotid Plaque Moderate or higher	Hip	1.02(0.64-1.62)	1.07(0.76-1.5)
	Knee	0.92(0.55-1.51)	1.49(0.98-2.27)
History of myocardial Infarction (yes/no)	Hip	1.24(0.72-2.13)	1.06(0.6-1.87)
	Knee	0.67(0.34-1.33)	1.02(0.49-2.09)
History of stroke (yes/no)	Hip	1.39(0.8-2.44)	0.78(0.44-1.37)
	Knee	1.18(0.59-2.36)	0.9(0.46-1.76)