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Brief Report

Is local or central adiposity more strongly associated with incident knee osteoarthritis than the body mass index in men or women?

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SUMMARY

Objective: To determine whether central (abdominal) or peripheral (thigh) adiposity measures are associated with incident radiographic knee osteoarthritis (RKOA) independent of body mass index (BMI) and whether their relation to RKOA was stronger than that of BMI.

Design: 161 Osteoarthritis Initiative (OAI) participants (62% female) with incident RKOA (Kellgren/Lawrence grade 0/1 at baseline, developing an osteophyte and joint space narrowing (JSN) grade ≥1 by year-4) were matched to 186 controls (58% female) without incident RKOA. Baseline waist-height-ratio (WHtR), and anatomical cross-sectional areas of thigh subcutaneous (SCF) and intermuscular fat (IMF) were measured, the latter using axial magnetic resonance images. Logistic regression assessed the relationship between each adiposity measure and incident RKOA before and after adjustment for BMI, and area under receiver operating characteristic curves (AUC) for each adiposity measure was compared to that of BMI using chi-squared tests.

Results: BMI, WHtR, subcutaneous fat (SCF) and IMF were all significantly associated with incident RKOA when analysed separately, with similar effect sizes (odds ratio range 1.30−1.53). After adjusting for BMI, odds ratios (ORs) for WHtR, SCF and IMF were attenuated and no longer statistically significant. No measure of central or peripheral adiposity was significantly more strongly associated with incident RKOA than BMI. Results were similar for men and women.

Conclusions: Although both central (WHtR) and peripheral (SCF and IMF) adiposity were significantly associated with incident RKOA, neither was more strongly associated with incident RKOA than BMI. The simple measure of BMI appears sufficient to capture the elevated risk of RKOA associated with greater amounts of localised adiposity.

Introduction

Obesity is the strongest risk factor for the development of radiographic knee osteoarthritis (RKOA) in women, and is second only to knee injury in men[1]. Although mechanical overload of the knee that may lead to altered biomechanics and cartilage breakdown was thought to explain most of the increased risk for RKOA among persons who are obese, recent evidence has suggested that the relationship between obesity and RKOA may also be driven by metabolic factors (i.e., release of pro-inflammatory adipokines such as leptin)[1].

The body mass index (BMI) is a simple anthropometric measure most commonly used to define obesity but cannot discriminate adipose from non-adipose body mass, and does not account for patterns of fat distribution throughout the body. This is important as, contrary to adipose tissue, greater muscle mass (that also contributes to greater BMI) is beneficial for knee osteoarthritis[2], and adiposity at specific locations (i.e., abdominal or thigh) have distinct properties that may have different associations with disease[3]. While excessive central adiposity (i.e., abdominal fat including both visceral and subcutaneous depots)[4] has been found

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to be an independent risk factor for end-stage RKOA (i.e., knee replacement surgery)[5] and thigh intermuscular fat (IMF) was observed to be associated with RKOA presence and knee functional deficits[6], little is known about the impact of central adiposity and peripheral adiposity (i.e., specific thigh fat depots including IMF and subcutaneous fat (SCF)[4]), on incident RKOA.

In previous work[7], we found BMI to be a strong predictor of incident RKOA, in both sexes, although potentially by different mechanisms in men and women (i.e., with increased BMI, muscle quality (specific strength) appears to decrease due to elevated local adiposity in women, but not in men). Determining which measures of body composition are most closely associated with subsequent RKOA development, and whether these differ between men and women, is thus potentially important in the clinical management of the disease at an early (pre-radiographic) stage, and in its prognosis. Further, these relationships may provide clues to better understand the pathogenesis of the disease in view of obesity-related risk factors. Therefore, the aim of this study was to test the hypothesis that central or peripheral adiposity, and specifically intermuscular and subcutaneous adipose tissue, confer greater odds of incident RKOA than BMI, and to explore whether there was any significant difference in the relationship of these adiposity measures with incident RKOA.

Methods

Participants

This study was ancillary to the Osteoarthritis Initiative (OAI), a multicentre longitudinal study of men and women aged 45–79 years designed to identify risk factors for RKOA incidence and progression (http://oai.epi-ucsf.org/). In the current analysis, we studied all OAI participants who developed incident RKOA, as defined and outlined in a recent report on thigh muscle cross-sectional area and RKOA risk[7]. Briefly, 186 knees with incident RKOA (i.e., cases), defined as a knee without RKOA at baseline (i.e., Kellgren–Lawrence grade (KLG) 0/1 from fixed-flexion posteroanterior radiographs) that developed both an osteophyte and joint space narrowing (JSN) (Osteoarthritis Research Society International atlas JSN grade $\geq$1) by 48-month follow-up[7], were frequency-matched by baseline KLG 0/1 to 186 control knees without incident RKOA. The left knees of 25 participants with bilateral incident RKOA were excluded from analyses, resulting in 161 incident case knees (161 participants) and 186 frequency-matched control knees (186 participants). The OAI was approved by each study site's institutional review board, and participants gave informed consent.

Local and central adiposity

From baseline T1-weighted axial-spin-echo thigh MRI acquisitions (imaging dataset 0.E.1), SCF and IMF anatomical cross-sectional areas (ACSAs) were segmented at an anatomically consistent location (33% femoral length; distal-proximal), using custom software[8]. Briefly, a semi-automated algorithm applied a convex 'sling' around the outer circumference and the thigh muscle tissue, separating SCF. Using a signal intensity threshold, IMF was separated from other intermuscular tissue (i.e., vessels, nerves etc.), with the method having shown to display reasonable test-retest precision[8]. To account for body size differences, SCF and IMF ACSAs were normalized to femoral bone ACSA (Supplementary File).

Central adiposity was estimated using the waist circumference-to-height ratio (WHtR), a well-accepted proxy measure of central obesity[9]. Waist circumference was measured at the level of the umbilicus between the lower rib and iliac crest manually with a tape measure to the nearest millimeter. To calculate BMI (kg/m^2), height was measured barefoot using a stadiometer to the nearest millimeter and weight with lightweight clothing only using a balance beam scale to the nearest 0.1 kg.

Statistical analysis

Generalised linear models with logistic regression were used to evaluate the contribution of BMI and each of the three adiposity measures (WHtR, SCF and IMF) to incident RKOA, both unadjusted and adjusted for age (continuous), sex, race (dichotomized as self-reported white vs other), and knee extensor muscle specific-strength (force ÷ anatomical cross-sectional area [Newtons/cm^2]) as previously described in this cohort[7]. To allow for a direct comparison of the effect of BMI and each adiposity measure on incident RKOA, we report odds ratios (ORs) and 95% confidence intervals (CIs) per standard deviation of each of these. The area under receiver operating characteristic curves (AUC) for each of the adiposity measures association with incident RKOA was compared with that for BMI, and amongst each other, using a chi-squared test (DeLong method). To determine which of central or peripheral adiposity measures conferred greater odds of incident KOA, independent of BMI, logistic regression models for each of the three adiposity measures were adjusted for BMI, similar to our previous analysis of highly correlated metabolic variables in knee OA[10]. Finally, we constructed a single model with all adiposity measures included and performed a backward stepwise logistic regression analysis (with BMI and demographic covariates forced in and adiposity measures added when $P < 0.2$) to determine whether any of the central or peripheral adiposity measures contributed significantly to the odds of incident RKOA, independent of BMI, and when adjusting for one another. We carefully assessed multicollinearity and goodness-of-fit by computing a variance inflation factor (VIF), and by performing a Pearson goodness-of-fit test for each model. When VIFs were >3.3 (a conservative indication of multicollinearity)[11], additional regression models were created using the residuals of the respective adiposity measures to control for weight-related confounding, as done previously[10]. The sex-specific residuals of the adiposity measures were the difference between the observed and expected values from separate linear regression models, with each adiposity measure as the dependent variable and BMI as the independent variable. We present whole cohort results and evaluate the interaction term between sex and each adiposity measure. Although the interaction term showed that no significant differences in the relationship between each adiposity measure and incident RKOA existed between men and women ($P > 0.5$), as we previously observed potentially different mechanisms by which BMI increases risk of incident RKOA in men and women[7], we also present sex-specific results for completeness. Statistical analyses were completed using Stata v14.2.

Results

Of the 161 incident cases and 186 controls, 100 (62%) and 108 (58%) were female, respectively (Table I). In the whole cohort, BMI, WHtR, SCF and IMF were all significantly associated with incident RKOA when analysed separately, with similar effect sizes, before and after adjustment for age, race and knee extensor specific-strength (OR range 1.30–1.53) (Table II). No central or peripheral adiposity measure continued to be associated with incident RKOA after adjustment for BMI (Table II). Direct comparison of AUCs showed that no measure of central or peripheral adiposity was more strongly associated with incident RKOA than BMI, nor was there any significant difference between various central and peripheral adiposity measures (AUC ranged from 0.62 to 0.63,

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