Association between infrapatellar fat pad volume and knee structural changes in patients with knee osteoarthritis

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Abstract

Introduction: The function of the infrapatellar fat pad (IPFP) in knee osteoarthritis (OA) remains uncertain. This study aimed to examine cross-sectional associations between IPFP volume and knee structures in patients with knee OA.

Methods: 174 patients with clinical knee OA (mean age, 55.5 years) participated in the study. The fat-suppressed 3- dimensional T1-weighted spoiled gradient recall (SPGR) magnetic resonance imaging (MRI) was used to measure the IPFP and cartilage volume. T2-weighted fast spin echo MRI was utilized to assess cartilage defects and bone marrow lesions (BMLs). Radiographic knee osteophytes and joint space narrowing (JSN) were assessed using the Osteoarthritis Research Society International atlas.

Results: After adjustment for potential confounders, greater IPFP volume was associated with greater tibial and patellar cartilage volume (all $p<0.05$), and fewer cartilage defects at all sites [odds ratio (OR): 0.88 to 0.91, all $P<0.05$]. IPFP volume was associated with presence of BMLs at lateral tibial and medial femoral sites (OR: 0.88 and 0.91, all $P<0.05$) and osteophytes at lateral tibiofemoral compartment (OR: 0.88, $P<0.05$). IPFP volume was not significantly associated with JSN.

Conclusion: Greater IPFP volume was associated with greater knee cartilage volume and fewer structural abnormalities, suggesting a

protective role of IPFP size in knee OA.

Keywords: infrapatellar fat pad, osteoarthritis, cartilage volume, cartilage defect, bone marrow lesion, osteophyte

A short running title: Infrapatellar fat pad in OA

Introduction

Osteoarthritis (OA) is the most common form of arthritis, characterised by cartilage damage, osteophyte formation and other joint structural changes [1]. OA can affect one or more joints, but is most common in the knees [2]. Although the pathogenesis of knee OA is still unclear, sex [3], age [4] and body mass index (BMI) [5] are well-known risk factors, and mechanical and metabolic factors are important in the development and progression of knee OA [1,2].

The infrapatellar fat pad (IPFP) is an irregularly shaped intracapsular structure [6] that is situated in the knee under the patella, and between the patellar tendon, femoral condyle and tibial plateau [7]. It is structurally similar to subcutaneous adipose tissue [8]. As the IPFP is located close to cartilage and bone surfaces, the normal role of this structure may be to reduce loading on the joint, and it may play a beneficial role in the progression of knee OA. So far, there have been few studies examining the relationship between IPFP and knee structural changes in knee OA; therefore, the specific function of the IPFP in the development and progression of knee OA is not known.

Joint structural abnormalities such as reduced cartilage volume, cartilage defects, osteophytes and bone marrow lesions (BMLs) are usually used to assess progression of knee OA. The aim of this study was to assess cross-sectional associations between IPFP volume and these structural measures in patients with knee OA.

Methods

Subjects

This study was carried out as part of Anhui Osteoarthritis (AHOA) Study, a clinical and epidemiological study of 206 patients aged 34-74 years, aimed at identifying environmental and biochemical factors associated with progression of knee OA. Patients with clinical knee OA, diagnosed using criteria of American College of Rheumatology (ACR) [9], were consecutively recruited from the Department of Rheumatology and Immunology in the First Affiliated Hospital of Anhui Medical University, from January 2012 to November 2013. We excluded persons with contraindication to MRI (including metal sutures, presence of shrapnel, iron filings in eyes, and claustrophobia), if they were living in an institution, had been diagnosed with rheumatoid arthritis or other inflammatory diseases, or if they had severe OA and were planning to have knee arthroplasty within the next two years. 32 patients fulfilled the exclusion criteria and therefore were excluded from this study. The

remaining 174 patients participated in assessments including x-ray and MRI measurements. The study was approved by Human Medical Research Ethics Committee and written informed consent was obtained from all participants.

Anthropometrics

Height was measured to the nearest 0.1cm (with shoes, socks and headgear removed) using a stadiometer. Weight was measured to the nearest 0.1kg (with shoes, socks and bulky clothing removed) by using a single pair of electronic scales that were calibrated using a known weight at the beginning of each clinic. BMI was calculated ((weight (kg) /height (m^2)).

Knee radiographic assessment

A standing anteroposterior radiograph of the diseased knee (the more affected if both), with 15 degrees of fixed knee flexion was performed in all participants. Radiographs were assessed for osteophytes and joint space narrowing（JSN）on a scale of 0 to 3 using the Osteoarthritis Research Society International (OARSI) atlas developed by Altman et al [10] as follows: grade 0 = normal; grade 1 = mild change; grade 2 = moderate change; grade 3 = severe change. The radiographic severity of OA was assessed by Kellgren and Lawrence (KL) grades: grade 0 = normal; grade 1 = no JSN, suspicious osteophytes; grade 2 = suspicious JSN, mild osteophytes; grade 3 = definite JSN, moderate osteophytes,

and/or subchondral bone sclerosis; grade 4 = marked JSN, large osteophytes, and/or severe subchondral bone sclerosis. Radiographic OA was defined as KL grade of > =2. Two investigators evaluated the grade of JSN and osteophytes. Intraclass correlation coefficient (ICC) was 0.95 for osteophytes and 0.93 for JSN. Interclass correlation coefficient was 0.90 for osteophytes and 0.88 for JSN.

Magnetic resonance imaging assessment

MRI scans of the diseased knees (the more affected if both) were performed. Knees were imaged in the sagittal plane on a 1.5T whole body magnetic resonance unit with the use of a commercial transmit-receive extremity coil. The following image sequences were used: (1) a T1-weighted fat saturation three-dimensional spoiled gradient recall (SPGR) acquisition in the steady state; flip angle 30 degrees; repetition time 31 millisecond (ms); echo time 6.71 ms; field of view 16 cm; 60 partitions; 512 × 512 matrix; acquisition time 11 minutes 56 ms; one acquisition. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31 × 0.31 (512 × 512 pixels). (2) a T2-weighted fat saturation two-dimensional fast spin echo, flip angle 90 degrees, repetition time 3067 ms, echo time 112 ms, field of view 16 cm, 15 partitions, 256 × 256 - pixel matrix; sagittal images were obtained at a slice thickness of 4 mm with a interslice gap of 1.0 mm. IPFP volume, cartilage volume, cartilage defects and BMLs were scored independently.

IPFP volume (**Figure 1a**)was measured by manually drawing disarticulation contours around the IPFP boundaries (Figure 1) on a section-by-section SPGR images, using the software program OsiriX. IPFP volume was computed by the software program. One observer graded the IPFP volume on all MRI scans. ICC was 0.95 for intraobserver reliability (measured in 30 images).

Knee cartilage volume(**Figure 1b,1c**) was determined on T1-weighted MRI with image processing on an independent work station as previously described [11,12]. The total cartilage volume was divided into patellar, medial and lateral tibial cartilage volume by manually drawing disarticulation contours around the cartilage boundaries section-by-section, which were then re-sampled for final three-dimensional rendering. One observer measured cartilage volume. The coefficients of variation (CVs) for this method in our hands were 2.1% to 2.6% [11,12].

Cartilage defects (0 to 4 scale) were assessed at the medial femoral, lateral femoral, medial tibial, lateral tibial and patellar sites using T2-weighted images as follows: grade 0 = normal cartilage, grade 1 = focal blistering and intracartilaginous increased-signal intensity area with intact surface; grade 2 = irregularities on the surface or bottom and loss of thickness <50%; grade 3 = deep ulceration with loss of thickness >50%; grade 4 = full-thickness chondral wear with exposure of subchondral

bone. The presence of cartilage defect was defined as cartilage defect score ≥ 2 at one site. Two observer estimated cartilage defects at all sites respectively. ICCs in our hands was 0.89-0.94 for intraobserver reliability and interobserver reliability was 0.85 -0.93 [12].

Subchondral BMLs were defined as discrete area of increased signal adjacent to subcortical bone at the tibia and femur on T2-weight MRI using a semiquantitative (0 to 3) scoring system [13]: Grade 0 = normal; grade 1 = BMLs area < 25%; grade 2 = BMLs area >25%, but <50%; grade 3 = BMLs area >50%. The presence of BMLs was defined as a BML score ≥ 1 at one site. One observer assessed BMLs. The intraobserver reliabilities ranged between 0.89 to 1.00, as previously described [14].

Data analysis

Data were entered into a computerised database. All statistical analyses were performed using SPSS version 10.0 for windows. A p value < 0.05 (two-tailed) or 95% confidence interval (CI) not including the null point (for linear regression) or one (for logistic regression) was considered as statistically significant. T-tests or Chi square tests were used to test differences in participants' characteristics. Univariable and multivariable linear regression analyses were used to examine the associations between IPFP volume (the independent variable) and knee cartilage volume (the dependent variable) before and after adjustment for age, sex, height and

weight. Scatter plots were used to assess linear relationship between IPFP volume and total knee cartilage volume. Residuals from the regression of IPFP volume or total cartilage volume on age, sex, height and weight represent the component of IPFP volume or cartilage volume not explained by these factors. We added to these residuals the mean IPFP volume or mean total cartilage volume and plotted these adjusted IPFP volume against the adjusted total cartilage volume. Univariable and multivariable ordinal logistic regression analyses were used to assess the associations between IPFP volume (the independent variable) and cartilage defects, bone marrow lesions, osteophytes and JSN (the dependent variables) before and after adjustment for age, sex, height and weight. Interactions between sex (or radiographic OA) and IPFP volume on cartilage volume were investigated by testing the statistical significance of the coefficient of a product term (IPFP volume × age, or ROA) after adjustment for confounders.

Results

A total of 174 subjects between 34 to 74 years of age (mean, 55.5 years) participated in the study. There were no significant differences in demographic factors (age, sex and BMI) between these participants and those excluded (n=32) (data not shown). The mean IPFP volume was 20.46 cm^3 (SD 5.02, range 12.39 to 42.90). The total cartilage defect

score in this sample was 22.67 (SD 6.37). Characteristics of the subjects were presented in **Table 1**. Subjects with low and high IPFP volume (divided by median value) were similar in the terms of age, BMI, and prevalence of radiographic OA, cartilage defects and BMLs; however, those with high IPFP volume had greater height, weight, and knee cartilage volume than those with low IPFP volume. There was also a difference in the proportion of males and females between those with high and low IPFP.

Associations between IPFP volume and cartilage volume are described in **Table 2**. In multivariable analyses, greater IPFP volume was associated with greater medial and lateral tibial cartilage volume, and patellar cartilage volume (**Figure 2**).

In univariable analyses, IPFP volume was associated with cartilage defects at the medial femur (OR 0.93 (95% CI 0.87; 0.99), but associations between tibial and lateral femoral cartilage defects and IPFP volume did not reach statistical significance. After adjustment for age, sex, height and weight, greater IPFP volume was associated with reduced severity of cartilage defects at all sites (**Table 3**).

In univariable analyses, associations between IPFP volume and BMLs did not reach statistical significance at any site. After adjustment for age, sex, height and weight, greater IPFP volume was associated with reduced lateral tibial and medial femoral BMLs (**Table 4**).

In multivariable analyses, greater IPFP volume was associated with decreased grades of lateral tibiofemoral and lateral femoral osteophytes ($p<0.05$), but associations between IPFP volume and tibial and medial femoral osteophytes did not reach statistical significance (**Table 4**). There were no significant associations between IPFP volume and JSN (data not shown).

There were no interactions between IPFP volume and sex or between IPFP volume and radiographic OA on the outcomes (cartilage volume, cartilage defects, BMLs and osteophytes) (data not shown); therefore, males and females or subjects with and without radiographic OA were combined for analyses.

Discussion

To the best of our knowledge, this is the first comprehensive study to examine cross-sectional association between IPFP volume and structural abnormalities in patients with knee OA. We found consistent evidence that IPFP volume was beneficially associated with knee structural changes, such as increased cartilage volume, reduced cartilage defects, and less BMLs and osteophytes. Although IPFP volume was not significantly associated with JSN, our findings suggest that IPFP may play a protective role in knee OA.

IPFP is a major adipose tissue in the knee joint as a part of body fat,

in close proximity to the patella. Although fat in the body as a whole is considered as an important risk factor for OA, the role of local fat deposits such as the IPFP remain unclear. IPFP can produce inflammatory cytokines and adipokines including interleukin 6 (IL-6) and leptin [15], and secrete more inflammatory cytokines than subcutaneous fat in patients with OA [16]; therefore, it may play a detrimental role in knee OA.

In contrast, IPFP inhibited cartilage catabolism by restraining the production of matrix metalloproteinase (MMP-1), MMP-3 and collagen type II gene expression [17]. It can contribute to improving the distribution of lubricant through enlarging the synovial area [18], and has buffering and lubricating functions in knee joint. IPFP may share some of functions of the meniscus, in reducing mechanical shocks and friction between the patellar tendon and tibia [19]. Thus, the IPFP would have a protective effect in knee OA progression.

In a previous study, Han et al [19] measured IPFP maximal area using MRI, and reported that age, height and weight were significantly associated with IPFP area, but BMI was not. These findings were consistent with the findings of our study with regard to height, weight and BMI, but we did not find associations between age and IPFP volume. Chuckpaiwong et al [20] carried out a study of 15 control subjects and 15 knee OA participants and reported that there was no difference between

control and OA groups in IPFP volume. Cowan et al [21] reported that individuals with patellofemoral joint OA (n=35) had a larger IPFP volume than controls (n=11), and IPFP volume was directly related to patellofemoral joint OA pain suggesting that IPFP volume may be detrimental. However, these two studies were limited by small sample size. Han et al [19] reported that IPFP maximal area was associated with increased cartilage volume at medial and lateral tibial and patellar sites, and decreased medial and lateral tibial cartilage defects, but not with cartilage defects at medial and lateral femoral and patellar sites. Consistent with this data, in the current study, we found that higher IPFP volume was associated with increased cartilage volume at medial and lateral tibial and patellar sites; higher IPFP volume was associated with reduced cartilage defects at medial and lateral femoral and patellar sites, as well as medial and lateral tibial sites in patients with knee OA. These findings indicate that IPFP size may have a protective effect against cartilage damage and loss in the whole joint in persons with knee OA.

Osteophytes and BMLs are the most common subchondral bone abnormalities in knee OA, and are closely associated with knee pain, cartilage loss and cartilage defects [22-23]. In this study, we reported that greater IPFP volume was associated with reduced osteophytes and BMLs. Although the associations did not all reach statistical significance, they were consistent in direction, with deleterious associations. These results

were consistent with findings in older adults [19], further supporting that IPFP is protective against knee subchondral bone changes in knee OA.

Inconsistent with the previous study using IPFP maximal area measurement [19], associations between IPFP volume and JSN did not reach statistical significance. This may be related to lower power for this outcome; further studies with larger sample sizes will be required to confirm this.

A cubic centimetre (cm^3) greater IPFP volume was associated with 30 to 80 cm^3 (0.03 to 0.08 ml) greater in knee cartilage volume, 10% to 12% reduced odds of knee cartilage defects, 9% to 12% reduced odds of medial femoral and lateral tibial BMLs, and 12% reduced odds of lateral tibiofemoral osteophytes. The magnitude of these associations was similar to what we observed for increasing per cm^2 IPFP maximal area in an older cohort with larger sample size [19], suggesting these findings are real. The reasons underlying the protective effects of IPFP on joint structures are unclear. It may be related to some protective biochemical factors secreted from the IPFP, as IPFP conditioned medium could inhibit catabolic processes in cartilage [17]. It is well known that biomechanical factors, especially abnormal mechanical loading, play important roles in the initiation and development of knee OA. IPFP could dissipate knee joint loads, thus reduce stress on the joint. Additionally, the IPFP is situated in close proximity to the as patellar ligament around the joint and

it may reduce the instability and injury to the joint. Based on these findings, we conclude that IPFP volume has a beneficial rather than a detrimental role in knee OA. Further longitudinal studies are required to confirm these findings.

The strength of this study that we measured IPFP volume in 3-dimensional T1-weighted MRI that would be more accurately reflect IPFP size than IPFP maximal area, and the highly reproducible measures of assessment used to measure study factors.

Limitations of this study include the cross-sectional study design, rendering us unable to speculate on causal relationships, and the modest sample size, which hindered our ability to rule out associations between IPFP volume and JSN. However, these results were consistent with data from a recent longitudinal study, which reported that IPFP maximal area was associated reduced cartilage loss and cartilage defect development in older adults [24].

Conclusion

Greater IPFP volume was associated with reduced knee cartilage volume and more advanced structural abnormalities suggesting a protective role of IPFP size in knee OA.

Authors' Contributions

CD had full access to all of the data in the study and takes

responsibility for the integrity of the data and the accuracy of the data analysis. CD carried out the study design, participated in the acquisition, analysis and interpretation of data, manuscript preparation, and statistical analysis. JC participated in the acquisition, analysis and interpretation of data, manuscript preparation, and statistical analysis. JX participated in the study design, acquisition of data, manuscript preparation, and statistical analysis. KW participated in the analysis and interpretation of data, manuscript preparation, and statistical analysis. SZ participated in the acquisition, analysis and interpretation of data, and manuscript preparation. FH participated in the acquisition of data, manuscript preparation, and statistical analysis. SH participated in the acquisition, analysis and interpretation of data, and manuscript preparation. SX participated in the acquisition of data, manuscript preparation, and statistical analysis. HZ participated in the data acquisition, and assessment of radiographs and MRI images. LL participated in the interpretation of data and manuscript preparation. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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