Association Between Infrapatellar Fat Pad Volume and Knee Structural Changes in Patients with Knee Osteoarthritis

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ABSTRACT. ***Objective.*** 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. The study included 174 patients with clinical knee OA (mean age, 55.5 yrs). Fat-suppressed 3-D T1-weighted spoiled gradient recall magnetic resonance imaging (MRI) was used to measure the IPFP and cartilage volume. T2-weighted fast spin echo MRI was used to assess cartilage defects and bone marrow lesions (BML). 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 (OR 0.88–0.91, all $p < 0.05$). IPFP volume was associated with presence of BML at lateral tibial and medial femoral sites (OR 0.88–0.91, 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. (J Rheumatol First Release August 15 2015; doi:10.3899/jrheum.150175)

Key Indexing Terms:

INFRAPATELLAR FAT PAD	OSTEOARTHRITIS	CARTILAGE VOLUME
CARTILAGE DEFECT	BONE MARROW LESION	OSTEOPHYTE

Osteoarthritis (OA) is the most common form of arthritis, characterized by cartilage damage, osteophyte formation, and other joint structural changes[1]. OA can affect 1 or more joints, but is most common in the knees[2]. Although the pathogenesis of knee OA is still unclear, well-known risk factors are sex[3], age[4], and body mass index (BMI)[5], 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]. Because 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 limit the progression of knee OA. So far, there have been few studies examining the relationship between IPFP and 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 (BML) are usually used to assess progression of knee OA. The aim of our study was to assess cross-sectional associations between IPFP volume and these structural measures in patients with knee OA.

MATERIALS AND METHODS

Subjects. This study was carried out as part of the Anhui Osteoarthritis (AHOA) Study, a clinical and epidemiological study of 206 patients aged

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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 the American College of Rheumatology[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 contraindications to magnetic resonance imaging (MRI; including metal sutures, presence of shrapnel, iron filings in eyes, and claustrophobia), those living in an institution, those who had been diagnosed with rheumatoid arthritis or other inflammatory diseases, or anyone with severe OA who was planning to have knee arthroplasty within the next 2 years. Thirty-two patients met the exclusion criteria and therefore were excluded from our study. The remaining 174 patients participated in assessments including radiography and MRI measurements. The study was approved by the Human Medical Research Ethics Committee, and written informed consent was obtained from all participants.

Anthropometrics. Height was measured to the nearest 0.1 cm (with shoes, socks, and headgear removed) using a stadiometer. Weight was measured to the nearest 0.1 kg (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 one, if both), with 15° 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 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-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 (ROA) 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.

MRI assessment. MRI scans of the diseased knees (the more affected one, if both) were performed. Knees were imaged in the sagittal plane on a 1.5T whole-body magnetic resonance unit with a commercial transmit-receive extremity coil. The following image sequences were used: (1) a T1-weighted fat saturation 3-D spoiled gradient recall (SPGR) acquisition in the steady state with flip angle 30°, repetition time 31 ms, echo time 6.71 ms, field of view 16 cm, 60 partitions, 512 × 512 matrix, acquisition time 11 min 56 ms, 1 acquisition, and sagittal images 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 2-dimensional fast spin echo, flip angle 90°, repetition time 3067 ms, echo time 112 ms, field of view 16 cm, 15 partitions, 256 × 256 pixel matrix, and sagittal images obtained at a slice thickness of 4 mm with an interslice gap of 1.0 mm. IPFP volume, cartilage volume, cartilage defects, and BML were scored independently.

IPFP volume (Figure 1A) was measured by manually drawing disarticulation contours around the IPFP boundaries on 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 (Figures 1B, 1C) was determined on T1-weighted MRI with image processing on an independent work station as 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 3-D rendering. One observer measured cartilage volume. The coefficients of variation (CV) for this method 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 1 site. Two observers estimated cartilage defects at all sites. ICC in our hands was 0.89-0.94 for intraobserver reliability and interobserver reliability was 0.85-0.93[12].

Subchondral BML 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 = BML area < 25%; grade 2 = BML area ≥ 25% but < 50%; grade 3 = BML area ≥ 50%. The presence of BML was defined as a BML score ≥ 1 at 1 site. One observer assessed BML. The intraobserver reliabilities ranged between 0.89 and 1.00, as described[14].

Data analysis. Data were entered into a computerized database. All statistical analyses were performed using SPSS version 10.0 for Windows. A p value < 0.05 (2-tailed) or 95% CI not including the null point (for linear regression) or 1 (for logistic regression) was considered statistically significant. T-tests or chi-squared 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 this 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 ROA) 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 and 74 years of age (mean, 55.5 yrs) participated in our 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 12.39–42.90). The mean total cartilage defect score in this sample was 22.67 (SD 6.37). Characteristics of the subjects are presented in Table 1. Subjects with low and high IPFP volume (divided by median value) were similar in age, BMI, prevalence of ROA, cartilage defects, and BML; 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

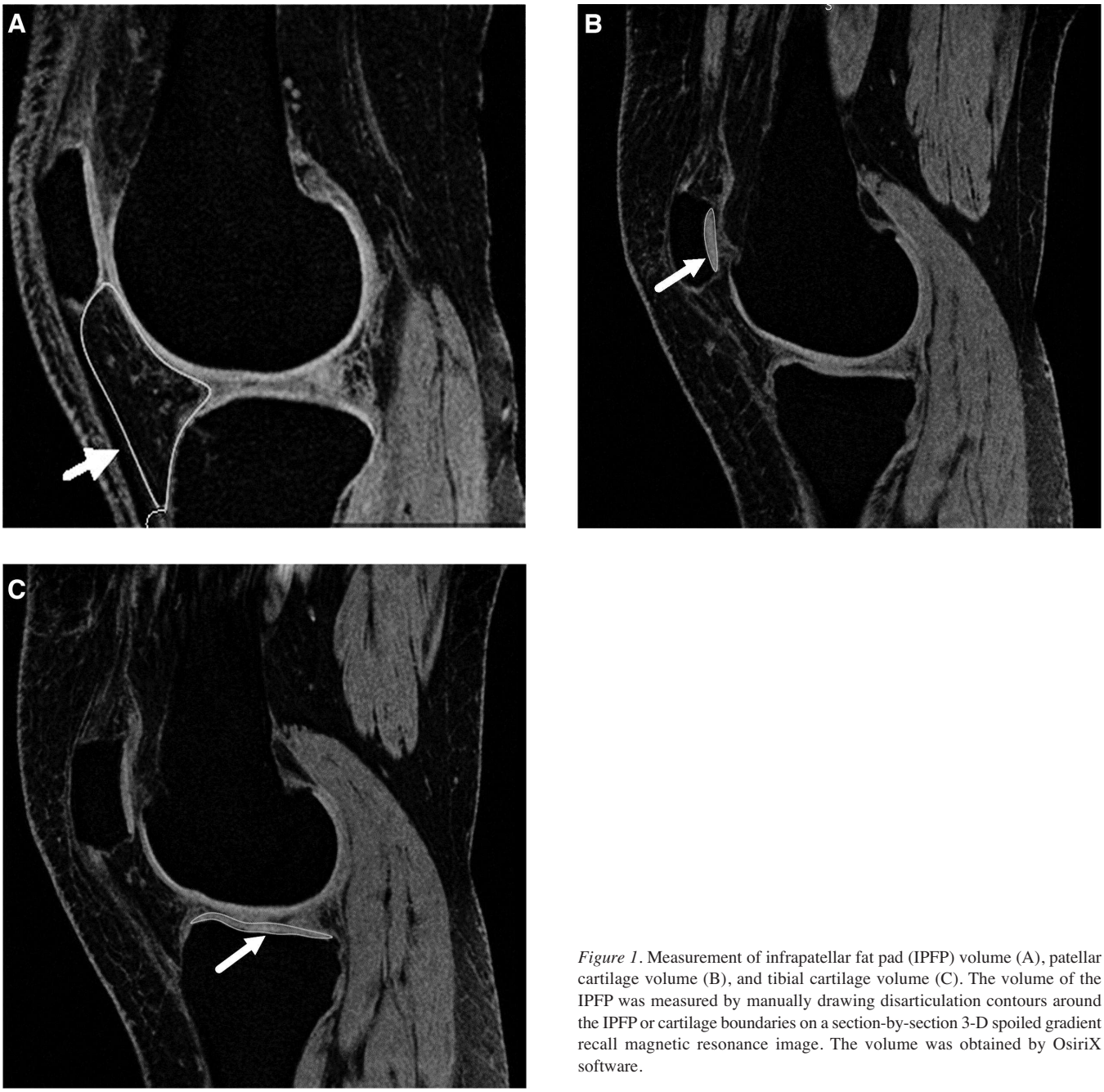

Figure 1. Measurement of infrapatellar fat pad (IPFP) volume (A), patellar cartilage volume (B), and tibial cartilage volume (C). The volume of the IPFP was measured by manually drawing disarticulation contours around the IPFP or cartilage boundaries on a section-by-section 3-D spoiled gradient recall magnetic resonance image. The volume was obtained by OsiriX software.

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 BML 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 BML (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 ROA on the outcomes (cartilage volume, cartilage defects, BML, and osteophytes; data not shown); therefore, males and females or subjects with and without ROA were combined for analyses.

Table 1. Characteristics of the participants. Participants were grouped by the median of the IPFP volume (19.1 cm^3), and results were shown as mean (95% CI) or frequency (%).

	Low IPFP volume, n = 88	High IPFP volume, n = 86	p*
Age, yrs	54.35 (52.64–56.06)	56.31 (54.50–58.13)	0.104
Males/females	1 (1.1)/87 (98.9)	24 (27.9)/62 (72.1)	< 0.001
Height, cm	155.21 (154.26–156.16)	163.15 (161.59–164.70)	< 0.001
Weight, kg	60.39 (58.57–62.20)	69.31 (66.95–71.68)	< 0.001
BMI (kg/m^2)	25.12 (24.26–25.97)	26.04 (25.20–26.89)	0.114
MT cartilage volume	1.10 (1.06–1.14)	1.34 (1.26–1.41)	< 0.001
LT cartilage volume	1.04 (1.00–1.09)	1.26 (1.18–1.34)	< 0.001
Patellar cartilage volume	1.61 (1.52–1.70)	2.26 (2.12–2.39)	< 0.001
Knee ROA	79 (89.8)	76 (88.3)	0.931
KL grade 1	9 (10.2)	10 (11.6)	0.326
KL grade 2	40 (45.5)	38 (44.2)	0.370
KL grade 3	34 (38.6)	28 (32.6)	0.769
KL grade 4	5 (5.7)	10 (11.6)	0.465
MTF cartilage defect	87 (98.9)	81 (94.2)	0.427
LTF cartilage defect	87 (98.9)	84 (97.6)	0.299
Patellar cartilage defect	75 (85.2)	68 (79.1)	0.066
MTF BML	32 (36.4)	26 (30.2)	0.477
LTF BML	29 (33.0)	26 (30.2)	0.987
Patellar BML	49 (55.6)	42 (48.8)	0.586

*t test, or chi-square test. IPFP: infrapatellar fat pad; BMI: body mass index; ROA: radiographic osteoarthritis; MT: medial tibial; LT: lateral tibial; MTF: medial tibiofemoral; LTF: lateral tibiofemoral; KL: Kellgren-Lawrence arthritis grading scale; BML: bone marrow lesions.

Table 2. Associations between IPFP volume and knee cartilage volume.

	Univariable β (95% CI)	Multivariable* β (95% CI)
Medial tibial, ml/cm^3	**0.03 (0.02, 0.04)**	**0.03 (0.02, 0.04)**
Lateral tibial, ml/cm^3	**0.03 (0.03, 0.04)**	**0.03 (0.02, 0.04)**
Patellar, ml/cm^3	**0.09 (0.08, 0.10)**	**0.08 (0.07, 0.10)**

Statistically significant numbers are in bold face. *Adjusted for age, sex, height, and weight. Linear regression analyses were used. IPFP: infrapatellar fat pad.

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 fewer BML 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 an important risk factor for OA, the role of local fat deposits such as the IPFP remains unclear. IPFP can produce inflammatory cytokines and adipokines including interleukin 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 by enlarging the synovial area[18], and has buffering and lubricating functions in the knee joint. IPFP may share some 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.

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] studied 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 2 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 these data, in the current study we found that higher IPFP volume was associated with increased cartilage volume

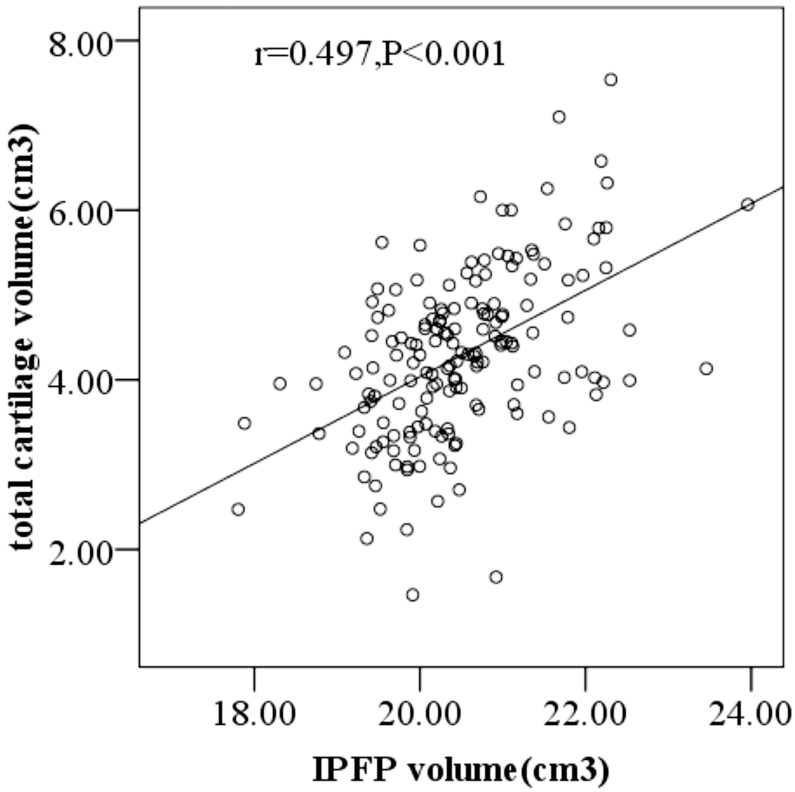

Figure 2. Scatter plot showing results of multivariable analyses, in which greater infrapatellar fat pad volume was associated with greater total cartilage volume, which is the sum of medial and lateral tibial cartilage volume, and patellar cartilage volume.

Table 3. Associations between IPFP volume and knee cartilage defects.

	Univariable, OR (95% CI)	Multivariable*, OR (95% CI)
Tibial cartilage defects		
Medial	0.94 (0.88, 1.00)	**0.91 (0.84, 0.98)**
Lateral	0.96 (0.90, 1.02)	**0.90 (0.83, 0.97)**
Femoral cartilage defects		
Medial	**0.93 (0.87, 0.99)**	**0.88 (0.81, 0.95)**
Lateral	0.95 (0.89, 1.01)	**0.89 (0.82, 0.97)**
Patellar cartilage defects	**0.91 (0.85, 0.97)**	**0.90 (0.83, 0.97)**

Statistically significant numbers are in bold face. *Adjusted for age, sex, height and weight. Ordinal logistic regression analyses were used. IPFP: infrapatellar fat pad.

at medial and lateral tibial and patellar sites; higher IPFP volume was also 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 may have a protective effect against cartilage damage and loss in the whole joint in persons with knee OA.

Osteophytes and BML 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 our study, we reported that greater IPFP volume was associated with reduced osteophytes and BML. 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 centimeter greater IPFP volume was associated with 30 to 80 cm^3 (0.03 to 0.08 ml) greater knee cartilage volume, 10% to 12% reduced odds of knee cartilage defects, 9% to 12% reduced odds of medial femoral and lateral tibial BML, 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], supporting these findings. 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, because IPFP-conditioned medium could inhibit catabolic

Table 4. Associations between IPFP volume, knee bone marrow lesions, and osteophytes.

	Univariable, OR (95% CI)	Multivariable*, OR (95% CI)
Tibial bone marrow lesions		
Medial	0.96 (0.89, 1.03)	0.93 (0.85, 1.02)
Lateral	0.92 (0.85, 1.00)	**0.88 (0.80, 0.98)**
Femoral bone marrow lesions		
Medial	0.95 (0.88, 1.02)	**0.91 (0.83, 0.99)**
Lateral	1.01 (0.95, 1.08)	0.99 (0.91, 1.07)
Patellar bone marrow lesions	0.95 (0.89, 1.01)	0.97 (0.89, 1.05)
TF osteophytes		
Medial	0.98 (0.92, 1.04)	0.95 (0.87, 1.04)
Lateral	0.97 (0.91, 1.03)	**0.88 (0.80, 0.97)**
Tibial osteophytes		
Medial	1.02 (0.96, 1.08)	0.99 (0.91, 1.07)
Lateral	0.99 (0.93, 1.05)	0.91 (0.83, 1.01)
Femoral osteophytes		
Medial	0.95 (0.88, 1.01)	0.92 (0.84, 1.02)
Lateral	**0.92 (0.85, 0.99)**	**0.78 (0.69, 0.89)**

Statistically significant numbers are in bold face. *Adjusted for sex, age, height, and weight. Ordinal logistic regression analyses were used. TF: tibiofemoral; IPFP: infrapatellar fat pad.

processes in cartilage[17]. Biomechanical factors, especially abnormal mechanical loading, play important roles in the initiation and development of knee OA. IPFP could dissipate knee joint loads, thus reducing stress on the joint. Additionally, the IPFP is situated in close proximity to the 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 strengths of our study are that we measured IPFP volume in 3-D T1-weighted MRI that would more accurately reflect IPFP size than IPFP maximal area, and the highly reproducible measures of assessment used to measure study factors.

Limitations of our 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 with reduced cartilage loss and cartilage defect development in older adults[24].

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

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