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BETWEEN-GROUP DIFFERENCES IN INFRA-PATELLAR FAT PAD SIZE AND SIGNAL IN SYMPTOMATIC AND RADIOGRAPHIC PROGRESSION OF KNEE OSTEOARTHRITIS VS NON-PROGRESSIVE CONTROLS AND HEALTHY KNEES - DATA FROM THE FNIH BIOMARKERS CONSORTIUM STUDY AND THE OSTEOARTHRITIS INITIATIVE

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Abstract

Objective—To examine cross-sectional and longitudinal between-group differences of infra-patellar fat pad (IPFP) size and magnetic resonance imaging (MRI) signal from fat-suppressed intermediate-weighted images with clinically relevant symptomatic and radiographic progression of knee osteoarthritis (OA), versus healthy references.

Methods—We studied 110 case knees (KLG1-3) with radiographic (≥0.7mm loss in joint space width) and symptomatic progression (≥+9/100units on the WOMAC knee pain subscale) vs. 118 control knees without progression from the FNIH Biomarkers Consortium cohort. We further studied 88 knees from the Osteoarthritis Initiative healthy reference cohort without (risk factors) of knee OA. The IPFP was manually segmented using baseline and year-2 sagittal fat-suppressed

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Author's Contribution

All authors have made substantial contributions to: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Disclosure of interest

Felix Eckstein is CEO and is co-owner of Chondrometrics GmbH, a company providing MR image analysis services. He provides consulting services to MerckSerono, Samumed and Bioclinica. Wolfgang Wirth and Torben Dannhauer are part-time employed and Wolfgang Wirth is co-owner of Chondrometrics GmbH. David Hunter is a consultant for Flexion therapeutics and Merck Serono. Anja Ruhdorfer, Franziska Haniel, Tobias Petersohn and Jan Dorrenberg have no conflicts of interest.

intermediate-weighted spin-echo 3 Tesla MRIs. Baseline measures and longitudinal change in IPFP volume and 3D MRI signal (mean, standard deviation [SD]) were compared between groups.

Results—No statistically significant baseline differences in IPFP volume, 3D MRI signal mean or signal heterogeneity (SD) were observed between progressor and non-progressor OA knees. Yet, the IPFP 3D MRI signal SD, but not its volume, was statistically significantly greater in OA versus healthy knees. No statistically significant 2-year changes in IPFP volume were observed in either group, but the increase in 3D MRI signal heterogeneity (SD) was greater in progressor versus non-progressor knees, and was greater in OA versus healthy knees.

Conclusion—Whereas IPFP-related morphometric measures did not statistically significantly differ between groups, a stronger increase in 3D IPFP MRI signal and signal heterogeneity may be associated with radiographic/symptomatic progression of OA, when compared to non-progressive OA or healthy knees.

Keywords

infra-patellar fat pad; knee osteoarthritis; progression; knee pain; healthy; intermediate-weighted MRI

INTRODUCTION

Obesity is one of the leading risk factors of knee osteoarthritis (OA) and reduced quality of life[1], albeit being potentially preventable. There is emerging evidence that endocrine, and not exclusively biomechanical, pathways mediate the increased risk of knee OA incidence and progression with an increased body mass index (BMI)[2,3]. Pro-inflammatory cytokines are known to be secreted by adipose tissue[4], and the intra-articular location of the infra-patellar fat pad (IPFP) renders it a potential source of joint pathology by releasing "adipokines" directly into the joint[5].

A previous study found an increase in subcutaneous fat content of the thigh to be associated with chronic pain in knee OA[6]. While the IPFP has been reported to display higher levels of adipokines than subcutaneous fat[7], cross-sectional studies that examined the relationship between the IPFP size and pain have reported inconsistent results[8–12]. Although inflammation of the IPFP tissue, i.e. Hoffa synovitis, has been linked to knee pain[8] and advanced radiographic knee OA[9], the role of the size of the IPFP in the osteoarthritic knee remains controversial[11,13,14].

Apart from the size of the IPFP, the magnetic resonance imaging (MRI) signal of the IPFP has gained recent interest as a marker for structural pathology of the IPFP. Alterations in the IPFP MRI signal have been related to Hoffa synovitis[9,15], but are also known to potentially represent other pathological alterations of the IPFP, such as Hoffa's ganglion or para-meniscal cysts[16], or even non-pathologic findings such as vessels, septa or bursae[16,17]. Yet, an increased IPFP MRI signal standard deviation (heterogeneity) has been associated with knee pain worsening and greater cartilage loss after two years of follow-up[18]. However, these longitudinal studies[13,18] did not use a definition of clinically relevant progression of knee pain[19] with generally accepted thresholds for symptomatic or radiographic worsening, and they did not analyze the size or MRI signal of the IPFP throughout its entire volume but

confined analysis to a single sagittal slice, i.e. the maximal cross-sectional IPFP area. Whereas IPFP volume has been shown to be more sensitive to longitudinal change than 2D analysis of single slices in an exercise and diet intervention[20], no previous studies have analyzed longitudinal changes of the IPFP volume and volumetric MRI signal in knee OA.

The aim of the current longitudinal study was therefore to investigate, for the first time, baseline between-group differences in IPFP volume and 3D IPFP MRI signal in participants with subsequent relevant radiographic and symptomatic progression of knee OA, in order to test, whether longitudinal changes in the IPFP occur concurrent with progression, and whether quantitative IPFP measures differ between OA and healthy knees from reference subjects without risk factors.

METHODS

Participants

Foundation for the National Institutes of Health Osteoarthritis Biomarkers Consortium—All Osteoarthritis Initiative (OAI) participants provided written informed consent, and the study was carried out in accordance with the IRB-approved OAI data user agreement, approved by the Committee on Human Research of the Institutional Review Board for the University of California, San Francisco (UCSF). Participants were selected from the database of the Osteoarthritis Initiative (OAI) by the Foundation for the National Institutes of Health (FNIH) Osteoarthritis Biomarkers Consortium[21,22]. The inclusion criteria have been thoroughly described in previous work[21,22]; in brief: participants needed to have baseline and 2-year follow-up knee radiographs, knee MRIs, serum and urine specimens, and clinical data available[22]. Kellgren-Lawrence (KLG) and semi-quantitative joint space narrowing (JSN grades) were assessed by the central reading site using non-fluoroscopic fixed-flexion knee radiographs[21,22]. Participants with KLG=1, 2, or 3 in at least one knee, and without total hip or knee joint replacement over the baseline to 2-year follow-up period were included[21,22]. Radiographic disease progression implied worsening (reduction in JSW) in the medial femorotibial compartment. A lateral OARSI atlas JSN score of 2 or 3[23] at baseline was an exclusion criterion[21,22], because of the risk of subsequent loss of lateral JSW, with the risk of masking change in medial JSW[24]. The minimum joint space width (JSW) in the medial femorotibial compartment was measured using automated software[21,25]; participants with a tibial plateau rim distance of ≥6.5mm at baseline, or with a change in the rim distance of >2.0mm between baseline and follow-up were excluded, because of radiographic mal-positioning [21] potentially rendering the longitudinal JSW measurements unreliable.

Progressor case knees—For the current study, we examined a sample of the case knees defined as “primary progression cases” of the FNIH Osteoarthritis Biomarkers Consortium (n=194)[21,22]; these knees encompassed knees from the Osteoarthritis Initiative (OAI) that displayed both radiographic and “persistent” symptomatic progression of knee OA from baseline to the 2-, 3- or 4-year follow-up time point[21,22]. Radiographic progression was defined by a longitudinal loss in the minimum JSW of ≥0.7mm from baseline to 2- and 4-year follow-up[21,22], to ensure a ≤10% probability of this change being due to measurement

error[21,22]. Symptomatic progression was defined as a "persistent" worsening of knee pain using the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) knee pain score subscale[21,22,26]. A relevant worsening was considered an increase of ≥9 units (on a 0–100 scale), as previously identified to be a "clinically relevant" change greater than the minimally clinically important difference (MCID)[19]. To exclude participants with only a transient increase, the increase in knee pain ≥ the MCID needed to persist at ≥2 time points between the 2- and 5-year follow-up visit[21,22]. A total of 194 knees from the OAI fulfilled the above conditions.

Non-Progressor control knees—As (primary) non-progressor controls, the FNIH OA Biomarkers Consortium studied knees without radiographic or symptomatic progression of knee OA as defined above, or with only radiographic (but not symptomatic), or only symptomatic (but not radiographic) progression (n=406). These participants did not display disease progression in the contralateral knee[21,22], as defined above. For the current analysis, non-progressor controls were selected from the 200 FNIH knees that did not display either radiographic or symptomatic progression from baseline through 2, 3, or 4- year follow-up. These knees were frequency matched with the progressor cases by baseline KLG 1, 2, or 3 and BMI (<25, 25–27.5, 27.5–30, 30–35, and ≥35kg/m^2 strata)[21,22].

OAI healthy reference knees—Participants of the OAI healthy reference cohort had no knee pain, and no signs of radiographic knee OA, i.e. osteophytes and/or joint space narrowing[23] on fixed-flexion radiographs in either knee at baseline according to the readings at the three sites recruiting OAI participants[25]. Further, the participants had no risk factors for knee OA, including obesity, history of knee injury or surgery, family history of total knee replacement (parent or sibling), Heberden's nodes, and repetitive knee bending. Of the 122 participants originally selected by the sites, 23 were later excluded because central radiographic readings performed by three expert readers at Boston University (https://oai.epi-ucsf.org/datarelease/SASDocs/kXR_SQ_BU_descrip.pdf) indicated that these were not free of radiographic signs of knee OA in at least one knee.

For the current study a convenience subsample of 110 progressor cases (68 women/42 men) of the FNIH progressor case cohort, and 118 non-pgrogressor controls (75 women/43 men) of the FNIH non-progressor control cohort (n=194 and 200, respectively) was selected in random manner. Further, all 88 participants of the healthy reference cohort without radiographic sign of knee OA in the central readings were included in the analysis. If both knees were eligible as progressor or as non-progressor control knee, one of both was selected randomly[21,22]. Because the progressor case and non-progressor control knees of the FNIH Osteoarthritis Biomarkers Consortium included right and left knees, we included 50% right and 50% left knees of the healthy reference cohort. For all groups, only one knee per participant was included[21,22].

Measurement of the IPFP on MRI

For analysis of IPFP volume and 3D IPFP MRI signal (mean, standard deviation [SD]), the anatomical outlines of the IPFP were manually segmented using sagittal, intermediate-weighted, fat-suppressed turbo spin echo 3 Tesla MRIs (Siemens Magnetom Trio, Erlangen,

Germany) (Figure 1A) and custom software (Chondrometrics GmbH, Ainring, Germany). To that end, all slices displaying the IPFP from medial to lateral were included (10 to 25 3mm slices per participant). Visible cysts, effusions, etc. were excluded from the segmentation, when possible, i.e. when they were in the periphery of the IPFP, but not when they were located centrally (Figure 1B). The area of the IPFP facing towards the Lig. patellae was considered the anterior surface, whereas the area facing the femur, tibia, and patella, was considered the posterior surface (Figure 1B&C). The maximal extension of the IPFP from anterior to posterior was calculated as the IPFP depth (Figure 1B). In addition to these 3D parameters, the central slice and cross-sectional area were determined from the middle slice for each IPFP, and the same parameters for the slice with the maximum cross-sectional area (which not necessarily was identical with the central slice). The 3D IPFP MRI signal mean was calculated as the mean grey value within the IPFP segmentation, and the 3D IPFP MRI signal SD (heterogeneity) as the variability, i.e. heterogeneity, of the grey values within the IPFP.

Segmentation was performed by four readers who were trained previously by a standardized training subset of datasets selected from the OAI healthy reference cohort[27]. All readers performed segmentations for all three groups in a balanced way, i.e. similar proportions of the progressor cases, non-progressor controls and healthy reference knees, and were blinded to group status and order of acquisition (baseline vs. 2-year follow-up). Quality control (QC) of all segmentations was performed by a postdoc anatomist with experience in IPFP analyses. A previous analysis of the inter-/intra-reader reliability on the manual segmentation method of the IPFP used in the current study was performed by five readers using randomly selected baseline fat-suppressed, intermediate-weighted MRIs of the OAI healthy reference cohort[27], whereas one reader segmented baseline ad 1-year follow-up MRIs to assess the intra-reader reliability and stability of the measurements for up to 1 year[27]. Applying the same QC procedures as in the current study, the inter-reader root mean square coefficient of variation was 2.0% for the IPFP volume, 1.8% for the anterior/posterior surface, and 2.1% for the maximal sagittal cross-sectional area, and the intra-reader variability 3.1%, 2.3%/2.8%, and 3.3%[27].

Statistical Analysis

All analyses were performed using Microsoft Excel 2010 (Redmond, WA) and SPSS (IBM Corp. Version 22.0. Armonk, NY). In a first step, we compared FNIH progressor cases versus non-progressor controls. We then combined progressor cases and non-progressor controls to one group with knee OA and compared these with the OAI healthy reference cohort. As to the best of our knowledge, this is the first study analyzing IPFP volume and volumetric MRI signal longitudinally in progressor versus non-progressor (and healthy) knees, we did not perform a power calculation to determine a set sample size. The primary analytic focus was the cross-sectional comparison of the IPFP volume between groups at baseline. The crosssectional comparison of the 3D MRI signal mean and SD (heterogeneity) of the IPFP was considered the co-primary focus. The secondary analytic focus was considered the longitudinal comparison of the 2-year changes in the IPFP volume, and the co-secondary focus the comparison of the 2-year changes in 3D MRI signal mean and SD (heterogeneity) of the IPFP between groups. Cross-sectional and longitudinal comparisons

and 2-year changes of the anterior and posterior surfaces, depth, and maximum and central slice cross-sectional areas of the IPFP were considered exploratory. Given previously reported differences in IPFP volume between men and women[28], sensitivity analyses were performed with stratification by sex.

2-year changes were tested for statistical significance using paired t-tests. Percent changes (for morphometric IPFP parameters) were computed for each participant individually and then averaged. Differences between groups were first analyzed using independent t-tests. To adjust for potential differences in covariates between the groups, analyses of progressor cases versus non-progressor controls were repeated with adjustment for baseline age, sex, BMI, KLG, and WOMAC knee pain score using ANCOVA models. To adjust for potential differences in the group-characteristics for the comparisons between (combined) OA versus healthy reference knees, which were not frequency matched, we repeated the analyses using ANCOVA models with adjustment for age, sex, and body mass index (BMI).

We performed one test for the primary and two tests for the co-primary focus; one test for the secondary and two tests for the co-secondary focus for either between-group comparison. For all six exploratory variables cross-sectional and longitudinal between-group comparisons were performed. For all nine variables the 2-year changes were tested for statistical significance. All nine variables were analyzed using ANCOVA models and with stratification by sex.

RESULTS

Demographics

The demographics of the participants included in the present analysis (110 progressor cases vs. 118 non-progressor controls) showed only very minor deviations from the full FNIH Osteoarthritis Biomarkers Consortium sample (194 progressor cases vs. 200 non-progressor controls; Table 1). Progressor cases tended to gain and non-progressor controls tended to lose body weight over the two years (+1.0%; 95% confidence interval [CI] [−0.1, 2.0] and − 0.7%; 95%CI [−1.8, 0.4], respectively).

Progressor versus non-progressor knees

At baseline, no statistically significant difference in the IPFP volume ($p=0.66$), in the 3D IPFP MRI signal mean ($p=0.22$) or in the 3D IPFP signal SD (heterogeneity) ($p=0.25$) was observed between progressor cases versus non-progressor controls (Table 2). We also did not observe a statistically significant difference in other morphometric IPFP parameters ($p\geq0.18$) (Table 2). Similar results were observed for men and women (Online Tables 1&2). These results remained unchanged after adjustment for baseline age, sex, BMI, KLG, and WOMAC knee pain scores (data not shown).

Only very small longitudinal changes in the IPFP volume were observed over the 2 year observation interval in either the progressor or non-progressor knees (−0.3% and −0.6%, respectively); and these were not statistically significantly different from zero ($p\leq0.10$) and also did not statistically significantly differ between both groups ($p=0.24$) (Table 2). In contrast, we observed a statistically significant longitudinal increase in the 3D IPFP MRI

signal mean and SD (heterogeneity) in the progressor cases (+42.7 units and 25.5 units, respectively; both p<0.0001) and also in non-progressor controls (+39.0 units and 18.9 units, respectively; both p<0.0001), with the progressor cases exhibiting a statistically significantly greater increase in the 3D IPFP MRI signal SD (p=0.04) (Table 2). The longitudinal increase in 3D IPFP MRI signal mean, in contrast, did not differ statistically significantly (p=0.54) between progressor and non-progressor knees. No statistically significant 2-year changes (or differences between the absolute changes) were observed for other exploratory parameters, except for a small reduction in the maximal slice cross-sectional area in progressor cases compared with a small increase in the non-progressor controls (p=0.03) (Table 1). As for the cross-sectional findings, the longitudinal observations were similar between men and women (Online Tables 1&2) and remained unchanged after adjustment for baseline age, sex, BMI, KLG, and WOMAC knee pain scores (data not shown).

Knee OA versus healthy reference knees

Based on the above results, progressor cases and non-progressor controls were combined to one group with knee OA, and then compared with knees without (risk factors of) knee OA. In this analysis, the IPFP volume did not differ statistically significantly between OA and healthy reference knees at baseline without (p=0.14) (Table 3) or after adjustment for age, sex, and BMI (p=0.35). However, the 3D IPFP MRI signal SD (heterogeneity) and the 3D IPFP signal mean were statistically significantly greater in those with knee OA than in the healthy reference cohort (p≤0.01) (Table 3). There was no statistically significant difference in the other exploratory parameters (p≥0.06), except for a greater maximum and central slice cross-sectional area in osteoarthritic vs healthy reference knees (p=0.04 for both) (Table 3). After stratification for sex, this difference was also observed in women, but not in men (Online Tables 3&4).

There were no statistically significant 2-year changes (or differences in the absolute changes) in the IPFP volume or other morphometric parameters in or between knee OA vs healthy reference knees (p≥0.21) (Table 3). The 3D IPFP MRI signal mean and SD (heterogeneity) increased statistically significantly in both groups, and the longitudinal increase was substantially greater in those with knee OA than in the healthy reference knees (+41; 95%CI [35, 47] vs. +26; 95%CI [16, 35]; p = 0.01 for the 3D MRI signal mean and +22; 95%CI [19, 25] vs. +14; 95%CI [10, 18]; p = 0.004 for the 3D MRI signal SD) (Table 3). Results were similar for men and women (Online Tables 3&4) and after adjustment for age, sex, and BMI (data not shown).

DISCUSSION

This is the first study to investigate, whether IPFP volume and a 3D analysis of the IPFP MRI signal and their longitudinal changes differ in the presence/absence of clinically relevant radiographic and symptomatic progression of knee OA, and further to explore whether longitudinal change in these parameters differ between subjects with versus those without (risk factors of) knee OA. Progressor cases displayed a statistically significantly greater longitudinal increase of 3D IPFP MRI signal SD (heterogeneity) than non-progressor controls, but we observed no relevant or statistically significant cross-sectional or

longitudinal differences in IPFP volume or other morphometric measures between both groups. Further, the 3D IPFP MRI signal SD (heterogeneity) in knee OA participants displayed greater baseline values and, both the MRI signal mean and signal SD, showed a stronger 2-year increase than in the healthy reference cohort. Similar results were observed in men and women.

A limitation of the current study is that for the current study design including right and left knees only fat-suppressed MIRs were available. However, a previous study reported only a small systematic offset and high correlation between IPFP analysis from fat-suppressed and non-fat-suppressed MRIs as well as similar inter-observer reproducibility for both image acquisition protocols[27]. Although four readers were involved in the analysis of the current study, they were all trained using a standard set of images[27], with all segmentations undergoing quality control by a post-doc anatomist and the inter-observer precision having been reported to be satisfactory under these conditions[27]. Although the vast majority of the knees in the progressor and non-progressor group had radiographic OA at baseline, it must be taken into account that a small fraction (11%) was KLG1, which represents doubtful ROA only. A strength of the current study is the analysis of the entire volume of the IPFP rather than just its maximal (sagittal) cross-sectional area[11,12,18] was measured, with the advantage of being sensitive also to potential changes in the medial or lateral IPFP periphery. Another limitation of the study is the number of IPFP parameters and groups that were compared in parallel, but the study is exploratory in nature and the primary and secondary analytic outcomes were defined a priori, in order to provide some hierarchy to the relative importance of the number of comparisons. In view of the current study design of an analysis of between-group differences, conclusions on the potential prognostic value of IPFP parameters on disease progression cannot be inferred. Observations of differences, however, may give an indirect hint on potential associations between the biomarker and disease progression and disease burden. Yet, further studies are needed to confirm, whether the observed increase in MRI signal SD (heterogeneity) is related to natural disease history and/or clinically relevant progression.

In previous work, the IPFP has been suggested to play a protective role as shock absorber for the knee joint and a greater IPFP was found to be associated with greater cartilage volume[11,29] and less knee pain[11] cross-sectionally, and with a reduced risk of prospective cartilage volume loss and progression to higher levels of knee pain at 2.3 year follow-up[12,13]. For exploratory and comparative purposes, we also analyzed the maximum sagittal area and the central slice of the IPFP as done by most previous studies[11–13]; however, we did not find consistent cross-sectional or longitudinal differences between groups using this type of 2D analysis. In the above studies[11–13], knee pain progression was defined as an increase of at least 1 unit on a 0–45 unit WOMAC knee pain scale[11,12], or as a WOMAC knee pain score at follow-up that was higher than the median WOMAC knee pain score of the study cohort, using a 0–500 unit WOMAC scale[13]. Our current study, in contrast, relied on established thresholds of clinically relevant increases in pain (MCID)[19] and on a reliable reduction in radiographic JSW well above the test-retest error[21,22]. Our findings extend previous cross-sectional reports that used a within-person, between-knee study design[9,10]. These studies also analyzed IPFP volume rather than only one sagittal slice[11–13] and did not find differences in the IPFP volume between painless versus contralateral painful knees[10] or

between knees with and without radiographic joint space narrowing[9]. Thus, the findings of the current study do not support the hypothesis that differences in the IPFP volume are found between combined radiographic and symptomatic progression versus non-progressive knee OA.

As outlined in a recent review, changes in 3D IPFP MRI signal can have multiple sources and are not specific to a given pathologic entity[30]. Yet, a pilot study showed an association between the 3D IPFP MRI signal (in particular the SD as a measure of signal heterogeneity) with semi-quantitative scores of Hoffa synovitis[9]. Although the current findings on longitudinal 3D IPFP MRI signal differences between progressor knees and non-progressor controls have to be interpreted with some caution, another study reported increased odds to be a progressor case in the FNIH Osteoarthritis Biomarkers Consortium cohort when Hoffa synovitis was present[31]. In other studies, Hoffa synovitis has been linked to knee pain[18,32] and incident knee OA[8] and advanced[9,33] radiographic knee OA status, this being consistent with our finding of a greater 3D IPFP MRI signal SD (heterogeneity) in OA versus healthy reference knees and a greater increase over time. It is surprising to see that there was a significant longitudinal increase in the 3D IPFP MRI signal (heterogeneity) even in healthy reference subjects. Yet, the same type of scanner (Siemens Trio) was used for all participants and no drift in MRI signal has been observed over up to 8 years in the OAI MRI acquisitions[34]. Even if scanner drift had occurred, this would have affected all cohorts equally. Also, importantly, the longitudinal increase in 3D IPFP MRI signal SD (heterogeneity) and signal mean were statistically significantly greater in knee OA participants than in healthy reference knees, and 3D IPFP MRI signal SD (heterogeneity) was statistically significantly greater in progressor cases than in non-progressor controls.

Given, that a greater increase in the 3D IPFP MRI signal SD (heterogeneity) was observed in participants with concurrent radiographic and symptomatic progression of knee OA, this between-group difference is of potential clinical significance, but should be confirmed in an independent analysis. Yet, it has to be taken into account that we also observed an increase in the 3D IPFP MRI signal SD (heterogeneity) in healthy knees so that the observed finding should not be overemphasized. The longitudinal findings suggest that an increase in signal heterogeneity may occur concurrent with symptomatic and radiographic progression of knee OA, and that it may represent a biomarker of structural alterations of disease progression that could be potentially helpful in diagnosing and in better evaluating disease burden. Although 3D IPFP MRI signal SD (heterogeneity) may be part of the natural history of the disease, based on our findings it appears to play a more consistent role than the 3D IPFP MRI signal mean in differentiating knee OA progressors from non-progressive controls and from healthy reference subjects. Future work should compare semi-quantitative readings of Hoffa synovitis, best with MRI contrast agents applied[32,35], vs. quantitative signal heterogeneity in longitudinal intervention studies, for instance testing anti-inflammatory treatment.

In conclusion, IPFP volume and 3D IPFP MRI signal baseline values do not appear to differ between participants with and without symptomatic and radiographic progression of knee OA. However, the longitudinal increase in 3D IPFP MRI signal SD (heterogeneity) appears to be greater in knees undergoing symptomatic and radiographic progression during the

same period than in those without, and is also greater than in healthy reference knees. The results thus suggest that a stronger increase in 3D IPFP MRI signal and signal heterogeneity may be associated with radiographic/symptomatic progression of OA, when compared to non-progressive OA or healthy knees.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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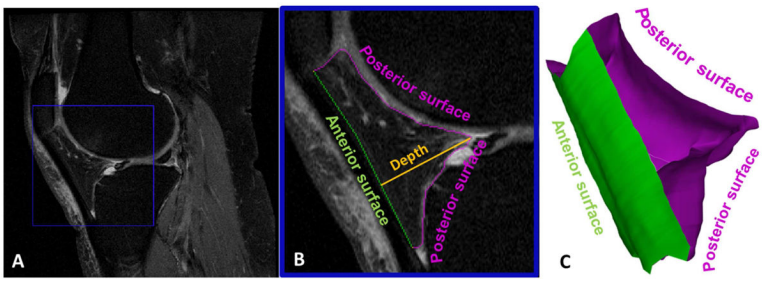

Figure 1.

A) Manual segmentation of the infra-patellar fat pad (IPFP) in sagittal fat-suppressed intermediate-weighted magnetic resonance images. **B)** One slice with the segmentation of the IPFP volume with different labels for the anterior surface (green) and the posterior surface (pink) and exclusion of peripheral cysts etc. **C)** 3-dimensional reconstruction of a completely segmented IPFP with anterior and posterior surfaces.

Table 1

Demographics of the analyzed subsamples of progressor cases and the non-progressor controls versus the entire progressor case and non-progressor control cohorts of the FNIH Osteoarthritis Biomarkers Consortium (All) and the healthy reference cohort of the Osteoarthritis Initiative.

	Cases		Controls		Healthy
	Subsample	**All**	**Subsample**	**All**	**References**
Participant number	110	194	118	200	88
Age[#]	60.8±8.3	62.0±8.8	61.4±9.1	61.5±9.1	54.5±7.5
BMI (kg/m^2)[#]	31.2±4.9	30.7±4.8	30.4±4.6	30.5±4.8	24.3±3.0
Body Weight (kg)[#]	88.6±15.9	87.1±15.8	85.1±16.3	85.8±16.4	68.8±12.1
Body Height (cm)[#]	168.4±9.9	168.3±9.9	167.2±10.0	167.4±10.3	167.7±8.8
WOMAC knee pain[#]	2.7±3.3	2.0±2.6	2.4±3.3	2.6±3.2	0.1±0.3
KLG 0 n (%)	0 (0)	0 (0)	0 (0)	0 (0)	100
KLG 1 n (%)	11 (10)	24 (12)	15 (13)	24 (12)	0 (0)
KLG 2 n (%)	50 (45)	84 (43)	62 (52)	114 (57)	0 (0)
KLG 3 n (%)	49 (45)	86 (45)	41 (35)	62 (31)	0 (0)

BMI=Body mass index; kg = kilogram; m=meter; cm=centimeter; WOMAC knee pain score = Western Ontario & McMaster Universities Osteoarthritis Index on 0–20 unit scale; n = Participant number; (%) = Percentage of participants

[#]mean ± standard deviation

Table 2

Infrapatellar fat pad (IPFP) size and magnetic resonance imaging signal at baseline and absolute and percent changes with between-group differences and effect sizes in FNIH Osteoarthritis Biomarkers Consortium participants with (progressor cases [PROG.]) and without (non-progressor controls [NON-PROG.]) symptomatic and radiographic progression in knee osteoarthritis.

	BASELINE					2-YEAR CHANGE						
	PROG.	NON-PROG.	PROG. vs NON-PROG.			PROG.		NON-PROG.		PROG. vs NON-PROG.		
			Difference at baseline	p□	Cohen d	2-year change Absolute	%	2-year change Absolute	%	Difference in changes	p◆	Cohen d
	mean±SD	mean±SD	mean (95% CI)			mean (95%CI)	mean	mean (95% CI)	mean	mean (95% CI)		
IPFP volume *(cm³)*	29.0±7.97	28.5±8.00	−0.47 (−2.55, 1.62)	0.66	0.06	−0.003 (−0.24, 0.24)	−0.3	−0.21 (−0.47, 0.04)	−0.6	−0.21 (−0.56, 0.14)	0.24	0.16
3D IPFP sign. mean	155±30.8	149±32.7	−5.25 (−13.6, 3.06)	0.22	0.16	+42.7 (34.1, 51.4) *	-	+39.0 (30.4, 47.5) *	-	−3.75 (−15.9, 8.35)	0.54	0.08
3D IPFP sign. SD	75.5±14.5	73.1±17.2	−2.42 (−6.59, 1.74)	0.25	0.15	+25.5 (20.7, 30.3) *	-	+18.9 (14.6, 23.2) *	-	−6.58 (−13.0, −18)	0.04	0.27
IPFP ant. *surface (cm²)*	24.8±6.11	23.7±5.55	−1.05 (−2.57, 0.47)	0.18	0.18	+0.09 (−0.16, 0.35)	+0.5	−0.13 (−0.43, 0.17)	−0.3	−0.23 (−0.62, 0.17)	0.26	0.15
IPFP post. surface *(cm²)*	39.6±8.83	38.5±8.54	−1.16 (−3.43, 1.11)	0.32	0.13	−0.11 (−0.48, 0.26)	−0.3	−0.04 (−0.41, 0.32)	−0.02	+0.07 (−0.45, 0.58)	0.80	0.03
IPFP depth *(cm)*	1.17±0.16	1.20±0.17	+0.03 (−0.02, 0.07)	0.20	0.17	−0.01 (−0.02, 0.002)	−0.6	−0.002 (−0.01, 0.01)	−0.1	+0.01 (−0.01, 0.02)	0.46	0.10
IPFP max. slice *(cm²)*	7.27±1.30	7.38±1.48	+0.11 (−0.25, 0.47)	0.55	0.08	−0.09 (−0.17, −0.01) #	−1.3	+0.02 (−0.05, 0.09)	+0.3	+0.11 (0.01, 0.22)	0.03	0.29
IPFP central slice *(cm²)*	6.89±1.31	7.05±1.41	+0.16 (−0.20, 0.51)	0.38	0.12	−0.11 (−0.20, −0.02) #	−1.5	−0.04 (−0.12, 0.05)	−0.3	+0.07 (−0.05, 0.20)	0.24	0.16

Diff=difference; Absolute=absolute change; %=percent change; SD=standard deviation; CI=confidence interval; cm=centimeter; sign.=signal; ant.=anterior; post.=posterior; max.=maximal;

□ t-test for progressor cases versus non-progressor controls at baseline;

◆ t-test for change in progressor cases versus change in non-progressor controls;

* p baseline vs 2-year FU <0.0001;

p baseline vs 2-year FU =0.02

Table 3

Infrapatellar fat pad (IPFP) size and magnetic resonance imaging signal at baseline and absolute and percent changes with between-group differences and effect sizes in FNIH Osteoarthritis Biomarkers Consortium participants (±progression in knee osteoarthritis [KNEE OA]) versus the Osteoarthritis Initiative healthy reference cohort (HEALTHY).

	BASELINE					2-YEAR CHANGE						
	KNEE OA	HEALTHY	KNEE OA vs. HEALTHY			KNEE OA		HEALTHY		KNEE OA vs. HEALTHY		
			Difference at baseline	p□	Cohen d	2-year change Absolute	%	2-year change Absolute	%	Difference in changes	p⬩	Cohen d
	mean±SD	mean±SD	mean (95% CI)			mean (95%CI)		mean mean (95% CI)		mean mean (95% CI)		
IPFP volume *(cm³)*	28.7±7.97	27.4±6.31	+1.40 (−0.47, 3.26)	0.14	0.18	−0.11 (−0.29, 0.06)	−0.5	−0.12 (−0.33, 0.09)	−0.4	+0.01 (−0.30, 0.32)	0.96	0.01
3D IPFP sign. mean	152±31.9	145±29.5	+7.33 (−0.38, 15.1)	0.06	0.23	+40.8 (34.7, 46.8)*	-	+25.6 (15.9, 35.4)*	-	+15.1 (3.73, 26.6)	0.01	0.33
3D IPFP sign. SD	74.3±16.0	60.4±9.86	+13.9 (10.3, 17.5)	<0.001	0.95	+22.1 (18.9, 25.3)*	-	+13.6 (9.5, 17.7)*	-	+8.50 (2.74, 14.3)	0.04	0.36
IPFP ant. surface *(cm²)*	24.3±5.84	23.7±4.64	+0.57 (−0.80, −0.67)	0.41	0.10	−0.02 (−0.22, 0.17)	+0.1	+0.01 (−0.22, 0.24)	0.00	−0.03 (−0.38, 0.32)	0.86	0.02
IPFP post. surface *(cm²)*	39.0±8.68	39.7±7.65	−0.69 (−2.76, 1.39)	0.52	0.08	−0.08 (−0.34, 0.18)	−0.2	+0.24 (−0.21, 0.68)	+0.5	−0.31 (−0.81, 0.19)	0.22	0.15
IPFP depth *(cm)*	1.19±0.17	1.16±0.14	+0.32 (−0.01, 0.07)	0.11	0.20	−0.005 (−0.01, 0.003)	−0.3	−0.004 (−0.01, 0.01)	−0.2	0.00 (−0.01, 0.01)	0.94	0.01
IPFP max. slice *(cm²)*	7.33±1.39	6.99±1.17	+0.34 (0.01, 0.67)	0.04	0.26	−0.03 (−0.08, 0.02)	−0.5	−0.03 (−0.13, 0.08)	−0.3	−0.005 (−0.11, 0.10)	0.93	0.01
IPFP central slice *(cm²)*	6.97±1.36	6.64±1.08	+0.33 (0.01, 0.65)	0.04	0.26	−0.07 (−0.13, −0.01)#	−0.9	−0.07 (−0.16, 0.03)	−0.8	+0.006 (−0.12, 0.11)	0.91	0.01

Diff=difference; Absolute=absolute change; %=percent change; SD=standard deviation; CI=confidence interval; cm=centimeter; sign.=signal; ant.=anterior; post.=posterior; max.=maximal;

□ t-test for progressor cases versus non-progressor controls at baseline;

⬩ t-test for change in those with knee osteoarthritis versus change in healthy references;

* p baseline vs 2-year FU <0.0001;

p baseline vs 2-year FU =0.02