Research Square

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# Quantitatively Measured Infrapatellar Fat Pad Signal Intensity Alteration is Associated with Joint Effusion-Synovitis in Knee Osteoarthritis

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# Abstract

Background: Abnormal infrapatellar fat pad (IPFP) plays a detrimental role in knee osteoarthritis (OA) by producing pro-inflammatory cytokines. IPFP may interact with synovium because of their adjacent anatomical positions; however, whether abnormal IPFP can contribute to effusion-synovitis in knee OA is unclear.

Methods: Among 255 knee OA patients, IPFP signal intensity alteration represented by four measurement parameters [standard deviation of IPFP signal intensity (IPFP sDev), upper quartile value of IPFP high signal intensity region (IPFP UQ (H)), ratio of IPFP high signal intensity region volume to whole IPFP volume (IPFP percentage (H)), and clustering factor of IPFP high signal intensity (IPFP clustering factor (H))] was measured quantitatively at baseline and two-year follow-up using magnetic resonance imaging (MRI). Effusion-synovitis of the suprapatellar pouch and other cavities were measured both quantitatively and semi-quantitatively as effusion-synovitis volume and effusion-synovitis score at baseline and two-year follow-up using MRI. Mixed-effects models were used to assess the associations between IPFP signal intensity alteration and effusion-synovitis over two years.

Results: In multivariable analyses, all four parameters of IPFP signal intensity alteration were positively associated with total effusion-synovitis volume and effusion-synovitis volumes of the suprapatellar pouch and of other cavities over two years (all $P$ 0.05). They were also associated with the semi-quantitative measure of effusion-synovitis except for IPFP percentage (H) with effusion-synovitis in other cavities.

Conclusion: Quantitatively measured IPFP signal intensity alteration is positively associated with joint effusion-synovitis in people with knee OA, suggesting that IPFP signal intensity alteration may contribute to effusion-synovitis and a coexistent pattern of these two imaging biomarkers could exist in knee OA patients.


# Introduction

Osteoarthritis (OA) is the most common form of joint disease, and is most frequently seen in knee [1]. Knee OA is characterized by articular cartilage loss and osteophyte formation as well as other joint structure abnormal changes, such as synovitis, menisci injury, ligament tears, and infrapatellar fat pad (IPFP) alteration [2]. It is the leading cause of joint pain and physical disability, which causes a large socioeconomic burden [1]. Although the pathogenesis of OA is unclear, low grade chronic inflammation is thought to play a central role in OA [1].

Synovial inflammation is common in all stages of OA, and its influence on articular cartilage is thought to play an important role in the pathophysiology of OA [3, 4]. Joint effusion volume has been shown to correlate with synovial inflammation [5]. A combined assessment of synovial effusion and synovitis by using non-contrast-enhanced magnetic resonance imaging (MRI) has been proposed, termed as

“effusion-synovitis” [6]. Effusion-synovitis can predict the incidence and progression of knee OA [3, 7–9], suggesting that this could be a risk factor and a prognostic biomarker of knee OA.

The IPFP is a local fat pad situated inferior to the patella and filling the anterior knee compartment intra-articularly and extra-synovial [2, 10]. Despite a buffering and lubricating function in the knee joint, abnormal IPFP appears to play a detrimental role in the initiation and progression of knee OA [2, 11]. It is believed that abnormal IPFP produces various pro-inflammatory cytokines, and thus promotes the pathological process of knee OA [10, 12]. Inflammation within the IPFP can be assessed using non-contrast-enhanced MRI [11] and is an imaging biomarker that can predict knee OA progression [13, 14].

As an extra-synovial tissue, the IPFP does not directly interact with the articular cartilage but closely contacts with the synovial membrane [15]. Therefore, abnormal IPFP may play roles in knee OA by affecting the synovial membrane. However, currently no study has explored the interaction between IPFP and synovium, and whether abnormal IPFP assessed by MRI has an influence on synovitis in knee OA remains to be determined.

Recently, we developed a semi-automatic, quantitative method to measure IPFP high signal intensity alteration on MRI images [14]. This method is reproducible and has predictive validity in knee OA [2, 11, 13, 14]. The objective of this study, therefore, was to investigate whether quantitatively assessed IPFP signal intensity alteration was associated with effusion-synovitis in patients with knee OA.

# Methods

Study design and participants

The data of this study was from Vitamin D Effect on Osteoarthritis (VIDEO) study, a multicenter, randomized, double-blind and placebo-controlled clinical trial for evaluating the effects of vitamin D supplementation on knee pain and structural changes in knee OA patients with vitamin D deficiency [16]. The inclusion and exclusion criteria were the same as the VIDEO study [16]. Briefly, participants were aged between 50 and 79 years, met the American College of Rheumatology (ACR) criteria for clinical knee OA [17], and had a pain score of more than 20 mm on a 100 mm visual analog scale (VAS). They also had an ACR function class rating of I, II and III [18], and relatively good health, with a score of 0–2 on a 5 point Likert scale (from 0 indicating very good health to 4 indicating very poor health). Participants were excluded if they had grade 3 knee radiographic OA (ROA) according to the Osteoarthritis Research Society International (OARSI) atlas [19], contraindication to magnetic resonance imaging (MRI), rheumatic diseases, and other severe diseases. Our current study consisted of 255 participants of the VIDEO study in Tasmania who had received sagittal T2-weighted MRI scans. In this study, treatment and placebo groups were combined and set as a cohort for analyses.

Knee MRI protocol

MRI of the study knees was obtained at baseline and 24-month follow-up on a non-contrast 1.5-Tesla whole-body MRI unit (Picker, Cleveland, OH, USA) using a commercial transmit-receive extremity coil. Fat-suppressed T2-weighted fast spin-echo sequence were used as following: sagittal T2-weighted fat-saturated fast spin-echo with flip angle 90, repetition time 3060 ms, echo time 94 ms, FOV 160 mm, 46 slices, 256×224-pixel matrix slice thickness of 2 mm with no gap.

IPFP signal intensity measurement

High signal intensity in IPFP was assessed on T2-weighted MRI, using MATLAB software (MATLAB 8.4, The MathWorks Inc) based on our newly developed program [14]. The segmentation of IPFP was performed at 10 intermediate slices in the whole IPFP to avoid the interference from other tissues (i.e., synovium, ligaments, and subcutaneous fat) and effusion, which were hard to distinguish in the beginning and ending slices. This measurement is a semi-automated procedure. The reader manually chose a set of points in sequence near the outer contour of IPFP and created an initial lasso around IPFP, then the initial lasso contracted inward and approximated to the boundary of IPFP automatically until the actual edge was approached. High signal-intensity alterations of IPFP were calculated based on the algorithm of the newly developed program and the data were output automatically.

The measurement parameters of IPFP signal intensity can be classified into four categories: the signal intensity of IPFP, the high signal intensity of IPFP, the volume of high signal intensity, and clustering effect of high signal intensity. We selected one measurement parameter to represent each of these four categories based on the concurrent validity and the clinical construct validity we reported [14]. The measurement parameters were standard deviation of IPFP signal intensity (IPFP sDev), upper quartile value of IPFP high signal intensity region (IPFP UQ (H)), ratio of IPFP high signal intensity region volume to whole IPFP volume (IPFP percentage (H)), and clustering factor of IPFP high signal intensity (IPFP clustering factor (H)) to represent the four categories, respectively. Intraobserver and interobserver reliabilities for these quantitative measurements were high (all intraclass correlation coefficients and interclass correlation coefficients > 0.90).

Effusion-synovitis measurement

Effusion-synovitis was assessed both quantitatively and semi-quantitatively on T2-weighted MRI. Effusion-synovitis was distinguished in the following subregions according to the anatomy of the knee joint synovial cavity: (1) suprapatellar pouch and (2) other cavities which includes central portion, posterior femoral recess, and sub popliteal recess.

Quantitative measurement of effusion-synovitis was by effusion-synovitis volume. The effusion synovitis volume was isolated by selecting a region of interest with an intra-articular fluid-equivalent signal on a section-by-section basis. The final three-dimensional volume rendering was generated using commercial in-house OsiriX Lite imaging software (32-bit version 5.9, Pixmeo SARL). Intraobserver and interobserver reliabilities for effusion-synovitis in both subregions were high (all intraclass correlation coefficients and

interclass correlation coefficients > 0.90). Total effusion-synovitis volume of the whole joint was obtained by summing effusion-synovitis volume of the suprapatellar pouch and other cavities.

Semi-quantitative measurement of effusion-synovitis was by effusion-synovitis score. The effusion-synovitis score was evaluated based on a modified Whole-Organ Magnetic Resonance Imaging Score (WORMS) method. This method was scored from 0 to 3 in terms of the estimated maximal distention of the synovial cavity: 0, normal; 1, no more than 33% of maximum potential distention; 2, 33–66% of maximum potential distention; 3, more than 66% of maximum potential distention. The interrater reliabilities and intrareader reliabilities of effusion-synovitis score in different subregions were 0.63–0.75 and 0.60–0.75 (weighted κ), respectively. Total effusion-synovitis score of the whole joint was obtained by summing effusion-synovitis score of the suprapatellar pouch and other cavities.

Anthropometrics

Height and weight were measured at baseline by using stadiometer (Invicta Plastics Ltd) and electronic scales (Heine S-7307), respectively. Body mass index (BMI) was calculated as weight (kg) divided by square of height ($m^2$).

Serum vitamin D measurement

Serum 25-hydroxyvitamin D was measured at baseline using direct competitive chemiluminescent immunoassays (DiaSorin Inc).

# Statistical analysis

Baseline characteristics were summarized using descriptive statistics. Associations between IPFP signal intensity and effusion-synovitis over 24 months were estimated using mixed-effects model (multilevel mixed-effects linear regression model or multilevel mixed-effects ordered logistic regression model), which allows for more appropriate adjustments for repeated measures and protection against bias for missing data [20]. In these models, IPFP signal intensity parameters, age, sex, BMI, intervention (vitamin D supplementation), and baseline serum vitamin D level were used as fixed effects, and individual participant identification was used as random intercepts. The normality of model residuals was routinely checked.

All statistical analyses were performed on Stata (version 15.0, StataCorp). A *P* value less than 0.05 (two tailed) was regarded as statistically significant.

# Results

A total of 255 participants (49.41% females) with a mean age of 63.0 years were included in this study. Participants' baseline median level of total effusion-synovitis volume was 6.74 ml, and the median volume of effusion-synovitis in suprapatellar pouch and other cavities were 4.23 ml and 2.45 ml,

respectively (Table 1). Other baseline characteristics including anthropometrics and IPFP signal intensity parameters are also shown in Table 1.

All the IPFP signal intensity parameters including IPFP sDev, IPFP percentage (H), IPFP UQ (H), and IPFP clustering factor (H) were positively and significantly associated with total effusion-synovitis volume and effusion-synovitis volumes of suprapatellar pouch and other cavities over two years after adjustment for age, sex, BMI, intervention, and baseline serum vitamin D level (Table 2).

Similarly, all these four IPFP signal intensity parameters had positively significant associations with total effusion-synovitis score and effusion-synovitis scores of suprapatellar pouch and other cavities over two years after adjustment for potential confounders, except for the association of IPFP percentage (H) with other cavities effusion-synovitis score which did not reach statistical significance (Table 3).

# Discussion

To the best of our knowledge, this is the first study to investigate the associations between MRI assessed IPFP signal intensity alteration and effusion-synovitis in knee OA patients. We found that quantitative measurements of IPFP signal intensity alteration were positively associated with effusion-synovitis measured both quantitatively and semi-quantitatively, suggesting that a coexistent pattern of IPFP signal intensity alteration and effusion-synovitis may appear in knee OA patients and a combination of these two imaging biomarkers could be considered in future knee OA research.

IPFP is the biggest adipose tissue structure within the knee, with an abundance of adipocytes, immune cells, vessels, and nerve fibers [11]. It is a potential source of pro-inflammatory cytokines [12]. Abnormal IPFP could produce various cytokines such as IL-1β, TNF-α, IL-6, IL-8, leptin and resistin, and thus might play a detrimental role in knee OA through stimulating the inflammatory process [2, 12]. In epidemiological studies, IPFP signal intensity alteration is associated with knee structural abnormalities and knee symptoms, and can predict the deterioration of knee structure and symptoms, as well as the occurrence of radiographic OA and knee replacement [2, 13, 21–25]. However, as IPFP and articular cartilage are separated by synovium, so much so that the pro-inflammatory factors secreted by IPFP may not act directly on cartilage; therefore, how abnormal IPFP plays a damaging role in OA remains unclear.

Owing to having adjacent anatomical positions, IPFP and the synovium may affect each other mutually by the pro-inflammatory factors they secrete. Previous studies have indicated that abnormal IPFP may be related to synovitis [26–28]. One study showed that IPFP opacity grading based on lateral knee radiography was well correlated with synovitis grades observed at contrast-enhanced MRI [26]. In another study in young adults following anterior cruciate ligament tear, IPFP hyperintense signal alteration was associated with higher inflammatory cytokine levels in synovia [27]. An in vitro study has proved that the conditioned medium of IPFP from end-stage knee OA patients can induce an inflammatory and pro-degradative phenotype in autologous fibroblast-like synoviocytes [28]. In our current study, IPFP signal intensity alteration was positively associated with effusion-synovitis, suggesting that abnormal IPFP reflected by signal intensity alteration could accelerate effusion-synovitis. As effusion-synovitis plays a

detrimental role in OA, the damaging effect of abnormal IPFP in OA could be mediated by effusion-synovitis. Moreover, this study suggested a coexistent pattern of IPFP signal intensity alteration and effusion-synovitis in knee OA patients. Considering both two imaging biomarkers are surrogates of the local inflammation, studying the two biomarkers simultaneously could be suggested in future knee OA research.

There are some strengths of this study. First, our semi-automatic quantitative method for IPFP signal intensity alteration measurement has certain advantages. Before we developed this novel method, almost all studies determined IPFP signal intensity alteration by manual semi-quantitative methods. The reproducibility of the manual semi-quantitative method is not high as it depends on a subjective evaluation. It may be less sensitive than quantitative measurements for changes over time and the cost of the manual assessment can be high due to the expense for radiology expertise [14]. Second, the feature of IPFP signal intensity alteration was comprehensively displayed as four parameters were selected to represent the different aspects of IPFP signal intensity alteration. Last, effusion-synovitis was measured both qualitatively and semi-quantitatively; therefore, measurement reliability of the outcome was relatively high.

There are some potential limitations of this study. First, it was a post hoc analysis using data from the randomized controlled trial; therefore, results could be affected by the intervention (vitamin D supplementation). However, adjustment for the intervention was performed in all analyses. Second, the inclusion and exclusion criteria were designed for the original randomized controlled trial; therefore, generalizability to the general knee OA population needs to be further confirmed. Last, our newly developed method mainly focuses on hyperintense signal alteration in IPFP. Hypointense signal alteration may represent different pathological changes of IPFP and also could be associated with effusion-synovitis. Further studies focusing on the hypointense signal alteration of IPFP are needed.

# Conclusion

Quantitatively measured IPFP signal intensity alteration is positively associated with joint effusion-synovitis in patients with knee OA, suggesting that IPFP signal intensity alteration may contribute to effusion-synovitis and a coexistent pattern of these two imaging biomarkers could exist in knee OA patients.

# Abbreviations

Infrapatellar fat pad: IPFP; Osteoarthritis: OA; Standard deviation of IPFP signal intensity: IPFP sDev; Upper quartile value of IPFP high signal intensity region: IPFP UQ (H); Ratio of IPFP high signal intensity region volume to whole IPFP volume: IPFP percentage (H); Clustering factor of IPFP high signal intensity: IPFP clustering factor (H); magnetic resonance imaging: MRI; Vitamin D Effect on Osteoarthritis: VIDEO; American College of Rheumatology: ACR; Visual analog scale: VAS; radiographic OA: ROA; Osteoarthritis Research Society International: OARSI; Whole-Organ Magnetic Resonance Imaging Score: WORMS.

# Declarations

Ethics approval and consent to participate

This study was approved by the Tasmania Health and Human Medical Research Ethics Committee (reference number H1040). Written informed consent was obtained from all participants.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Acquisition of data: XW, JL, ST, and TC. Analysis and interpretation of data: all authors. Drafting of the article: GR and CD. Revising and final approval of the article: All authors.

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# Tables

Table 1. Baseline characteristics of participants (N = 255)

| Characteristic | Value |
|---|---|
| Age (years)[a] | 63.00 (7.27) |
| Female, N (%) | 126 (49.41) |
| Height (cm)[a] | 168.85 (9.78) |
| Weight (kg)[a] | 84.62 (15.23) |
| BMI (kg/m$^2$)[a] | 29.69 (4.94) |
| Total effusion-synovitis volume (ml)[b] | 6.74 (3.15, 14.23) |
| Suprapatellar pouch effusion-synovitis volume (ml)[b] | 4.23 (1.65, 10.43) |
| Other cavity effusion-synovitis volume (ml)[b] | 2.45 (1.42, 4.02) |
| IPFP sDev[a] | 8.41 (2.95) |
| IPFP percentage (H)[a] | 6.90 (1.33) |
| IPFP UQ (H)[a] | 4.17 (1.42) |
| IPFP clustering factor (H)[a] | 6.34 (0.90) |

[a]Means (standard deviation); [b]Medians (interquartile range).

IPFP sDev: standard deviation of IPFP signal intensity; IPFP UQ (H): upper quartile value of IPFP high signal intensity region; IPFP percentage (H): ratio of IPFP high signal intensity region volume to whole IPFP volume; IPFP clustering factor (H): clustering factor of IPFP high signal intensity.

Table 2. Mixed-effects model for associations between IPFP signal intensity parameters and joint effusion synovitis volume over 2 years

| | IPFP sDev* | | IPFP percentage (H)* | | IPFP UQ (H)* | | IPFP clustering factor (H)* | |
|---|---|---|---|---|---|---|---|---|
| | β (95% CI) | *P* Value | β (95% CI) | *P* Value | β (95% CI) | *P* Value | β (95% CI) | *P* Value |
| Effusion synovitis volume (total) | 0.66 (0.36, 0.96) | < 0.001 | 1.56 (0.88, 2.23) | < 0.001 | 0.91 (0.31, 1.50) | 0.003 | 2.57 (1.64, 3.49) | < 0.001 |
| Effusion synovitis volume (SP) | 0.51 (0.24, 0.78) | < 0.001 | 1.39 (0.78, 1.99) | < 0.001 | 0.66 (0.13, 1.20) | 0.016 | 2.10 (1.26, 2.94) | < 0.001 |
| Effusion synovitis volume (OC) | 0.15 (0.10, 0.19) | < 0.001 | 0.17 (0.06, 0.28) | 0.002 | 0.24 (0.15, 0.33) | < 0.001 | 0.46 (0.32, 0.61) | < 0.001 |

Dependent variable: effusion synovitis volume (ml).

Multilevel mixed-effects linear regression was used, results were expressed as coefficients (β).

IPFP sDev: standard deviation of IPFP signal intensity; IPFP UQ (H): upper quartile value of IPFP high signal intensity region; IPFP percentage (H): ratio of IPFP high signal intensity region volume to whole IPFP volume; IPFP clustering factor (H): clustering factor of IPFP high signal intensity; SP: suprapatellar pouch; OC: other cavities.

* Adjusted for age, sex, BMI, intervention, and baseline serum vitamin D level.

Table 3. Mixed-effects model for associations between IPFP high signal intensity parameters and joint effusion synovitis score over 2 years

| | IPFP sDev* | | IPFP percentage (H)* | | IPFP UQ (H)* | | IPFP clustering factor (H)* | |
|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) | *P* Value | OR (95% CI) | *P* Value | OR (95% CI) | *P* Value | OR (95% CI) | *P* Value |
| Effusion synovitis score (total) | 1.44 (1.27, 1.62) | < 0.001 | 1.44 (1.09, 1.89) | 0.010 | 1.73 (1.37, 2.17) | < 0.001 | 2.77 (1.90, 4.05) | < 0.001 |
| Effusion synovitis score (SP) | 1.33 (1.18, 1.50) | < 0.001 | 1.71 (1.28, 2.27) | < 0.001 | 1.50 (1.18, 1.89) | 0.001 | 2.86 (1.93, 4.24) | < 0.001 |
| Effusion synovitis score (OC) | 1.39 (1.23, 1.56) | < 0.001 | 1.23 (0.94, 1.60) | 0.124 | 1.67 (1.33, 2.10) | < 0.001 | 2.33 (1.62, 3.34) | < 0.001 |

Dependent variable: effusion synovitis score.

Multilevel mixed-effects ordered logistic regression was used, results were expressed as odds ratio (OR).

IPFP sDev: standard deviation of IPFP signal intensity; IPFP UQ (H): upper quartile value of IPFP high signal intensity region; IPFP percentage (H): ratio of IPFP high signal intensity region volume to whole IPFP volume; IPFP clustering factor (H): clustering factor of IPFP high signal intensity; SP: suprapatellar pouch; OC: other cavities.

* Adjusted for age, sex, BMI, intervention, and baseline serum vitamin D level.