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# SEX-DIFFERENCES OF THE HEALTHY INFRA-PATELLAR (HOFFA) FAT PAD IN RELATION TO INTERMUSCULAR AND SUBCUTANEOUS FAT CONTENT-DATA FROM THE OSTEOARTHRITIS INITIATIVE

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## SUMMARY

The infra-patellar fat pad (IPFP) is composed of intra-articular adipose tissue; it represents a potential source of pro-inflammatory cytokines and has been associated with osteoarthritis of the knee. Yet, to what extent the size of the IPFP differs between healthy men and women, and how sex differences compare to those in inter-muscular and subcutaneous fat tissue content is unknown. We studied healthy reference subjects from the Osteoarthritis Initiative, without knee pain, without radiographic signs or without risk factors of femorotibial osteoarthritis. Sagittal magnetic resonance images (MRIs) of 99 right knees were used to segment the IPFP; in a subset, axial images of the thigh were available to segment inter-muscular and subcutaneous fat. Healthy men (n=40) displayed a 41% greater ($p<0.001$) IPFP volume and a 9% greater ($p<0.01$) ratio of IPFP volume/body weight than women (n=59). Men (n=13) displayed 15% greater intermuscular fat content (not significant), and a 50% lesser ($p<0.01$) subcutaneous fat content than women (n=12); when related to total thigh cross-sectional areas, these sex differences were +2% (not significant) and −53% ($p<0.001$). This is the first study to explore quantitative measures of the IPFP in healthy men and women, and to relate these to sex differences of inter-muscular and subcutaneous fat tissue content. Men displayed a significantly greater ratio of IPFP volume/body weight than women, similar amounts of inter-muscular fat, and strikingly less subcutaneous fat. These data provide a basis for further systematic studies of the variability of the IPFP with the body mass index and its role in knee osteoarthritis.

### Keywords

Infra-patellar fat pad; Hoffa; Inter-muscular fat; Subcutaneous fat; Sex differences

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## 1. Introduction

Knee osteoarthritis (OA) represents the most common form of arthritis (Felson et. al., 1987; Felson et. al., 1997) and is a frequent cause of chronic disability (Peat et. al., 2001). Knee OA and obesity are responsible for a huge number of quality-adjusted life-years lost in older men and women (Losina et. al., 2011). At a structural level, knee OA has been traditionally characterized by the formation of osteophytes and loss of cartilage (i.e. joint space narrowing) on radiographs (Kellgren and Lawrence, 1957). However, with the advent of magnetic resonance imaging (MRI) evidence has emerged that knee OA involves all synovial joint tissues, including subchondral bone, capsule and synovium, ligaments and menisci, etc. (Guermazi et. al., 2013).

Although mechanical factors are known to play a crucial role in the degeneration of articular tissue, recent evidence suggests that these fail to fully explain the relationship between obesity and knee OA, and that "endocrine" pathways may be of similar importance (Eckstein and Kwoh, 2014; Issa and Griffin, 2012a). Adipocytes were shown to secrete pro-inflammatory mediators ("adipokines") that may cause articular tissue degradation by release of metalloproteinases (MMPs) und growth factors (Griffin et. al., 2012; Griffin and Guilak, 2008; Issa and Griffin, 2012b; Sokolove and Lepus, 2013). The most prominent adipokine, leptin, is thought to be a crucial player of obesity-associated OA, acting in concert with other cytokines (Hui et. al., 2012; Scotece et. al., 2013; Stannus et. al., 2010; Stannus et. al., 2013). Because obesity is amendable to therapeutic intervention, it represents a particularly interesting risk factor of knee OA. Results from a recent randomized controlled trial showed that diet and exercise intervention were effective in achieving weight loss, reduced knee pain, improved knee function, and reduced plasma levels of interleukin-6, a measure of inflammation (Messier et. al., 2013).

Only recently has the infra-patellar (Hoffa) fat pad (IPFP) become a subject of interest in knee OA research. The IPFP is unique in that its adipose tissue is located intra-articularly, more specifically within the capsule but extra-synovial (Saddik et. al., 2004), with the potential of its "endocrine" activity directly affecting joint structure (Conde et. al., 2013; Hui et. al., 2012; Klein-Wieringa et. al., 2011). The IPFP is suggested to be a source of intra-articular leptin, with leptin being unique in being present at higher concentrations in the synovial fluid than in serum (Gegout et. al., 2008). A small study in humans examined the volume of the IPFP with MRI in women with knee OA vs. controls, but was underpowered to identify structural differences (Chuckpaiwong et. al., 2010). More recently, maximal IPFP areas determined from sagittal MRIs were related to longitudinal changes in knee pain, cartilage volume, and cartilage lesion scores (Pan et. al., 2014) and with radiographic joint space narrowing (JSN) and bone marrow lesions (BMLs) (Han et. al., 2014). Interestingly, the findings indicated that maximal IPFP area may have a protective role for knee OA progression in older women, but the results were not fully consistent between various measures and measurement locations, and were not reproduced in older men (Pan et. al., 2014).

Radiographic and particularly symptomatic knee OA are more frequent in older women than men (Felson et. al., 1987). Women display greater rates of incident knee OA and

progression (Felson et. al., 1995), particularly when obese (Felson et. al., 1997), but these findings do not necessarily hold for other joints (Srikanth et. al., 2005). Women are known to display greater fat tissue mass at the thigh (Dannhauer et. al., 2014; Delmonico et. al., 2009; Tseng et. al., 2014; Van Pelt et. al., 2011), but it has not been studied to date whether intra-articular (IPFP) fat tissue content is also greater in healthy woman than men, and may represent a potential reason for women being more susceptible to knee OA than men.

The specific purpose of the current study was a) to provide normal values for quantitative measures of the IPFP in healthy subjects without knee pain, without radiographic signs of knee OA, and without risk factors of incident knee OA; b) to describe sex differences in these measures, and to relate these to sex differences in subcutaneous and inter-muscular and fat tissue content of the thigh; c) to determine the correlation of IPFP volume with body weight and age; and d) to test whether the IPFP volume/body weight ratio differs between both sexes.

## 2. Material and methods

### 2.1. Study population

The participants used for this analysis were selected from the Osteoarthritis Initiative (OAI) data base (Eckstein et. al., 2012; Eckstein et. al., 2014). The OAI is a multicenter, longitudinal, prospective observational study that provides public access to clinical datasets, radiographs, magnetic resonance images (MRI) and biospecimens. 4796 female and male participants, aged 45-79 years, were recruited at four clinical centers in the U.S.. The participants either had symptomatic knee OA (i.e. progression cohort), were at risk of developing symptomatic knee OA (i.e. incident cohort), or were part of a healthy reference cohort (n=122) without (risk factors) of incident knee OA (Bloecker et. al., 2011; Eckstein et. al., 2010). The OAI is registered under clinicaltrials.gov (NCT00080171). The OAI received ethical approval by the Institutional Review Boards (IRB), and all participants gave informed consent. This informed consent includes use of the publicly available image and clinical data that will be used in this study.

Participants of the healthy reference cohort had to fulfill the following criteria (Bloecker et. al., 2011; Eckstein et. al., 2010):

- No pain, aching or stiffness in either knee in the past year
- No radiographic signs of femorotibial OA (i.e. no osteophytes and no joint space narrowing) of either knee, using the site reading of the baseline bilateral fixed flexion radiographs (Peterfy et. al., 2003)..
- No risk factors for the onset of knee OA, including:
  - ○ Obesity
  - ○ History of knee injury, defined as having caused difficulty walking for at least a week
  - ○ History of knee surgery
  - ○ Family history of total knee replacement in a biological parent or sibling

- ○ Heberden's nodes, defined as self-reported bony enlargements of one or more distal interphalangeal joints in both hands
- ○ Repetitive knee bending

Recruitment of the above healthy reference cohort depended on the radiographic readings performed by trained and certified readers (one to three radiologists or rheumatologists) at the clinical OAI sites (Eckstein et. al., 2012; Eckstein et. al., 2014). (Altman and Gold, 2007). However, following recruitment, additional central radiographic readings were performed by three expert radiologists or rheumatologists at Boston University (https://oai.epiucsf.org/datarelease/SASDocs/kXR_ SQ_BU_descrip.pdf). KLGs were assigned pertinent to the original description (Kellgren and Lawrence, 1957), independent of OARSI atlas osteophyte and JSN grades (Eckstein et. al., 2012; Eckstein et. al., 2014). During the central readings, 23 of the 122 reference subjects were identified to display signs of radiographic knee osteoarthritis in at least one of both knees, and 99 showed no sign of femorotibial OA in either knee. The analysis of the IPFP in this study was performed on the right knees of these 99 participants (59 women, 40 men), of whom the demographics are reported in Table 1.

A subset of the OAI healthy reference cohort (13 women and 13 men) also had axial MRIs of both thighs, of which data from 12 women and 13 men were usable (for specific explanations please see below; demographics listed in Table 2). The rationale of including this subset was to provide a direct comparison of sex differences in IPFP, subcutaneous, and intermuscular adipose tissue content, and to provide a basis for linking the sex differences in the IPFP to those in thigh subcutaneous tissue content previously reported in the literature (Dannhauer et. al., 2014; Delmonico et. al., 2009; Tseng et. al., 2014; Van Pelt et. al., 2011).

### 2.2. Image acquisition using MRI

The MRI acquisition protocol of the knees has previously been described in detail (Eckstein et. al., 2012; Peterfy et. al., 2008), with the analyses in the present study relying on data set 0.E.1 (the baseline images). For the analysis of the IPFP, a sagittal intermediate-weighted fat-suppressed turbo spin-echo sequence (IW TSEwas used (time of repetition =3200ms, time of echo =30ms, slice thickness 3.0mm; in plane resolution 0.36mm × 0.36mm; Fig. 1a, b). These images were acquired using a 3 Tesla Magnetom Trio magnet (Siemens Healthcare Erlangen, Germany) and a quadrature knee coil. MRIs of both knees were available, but only the right one was used for the present analysis. For normalization purposes, we included analyses of the tibial subchondral surface size, which was obtained from a coronal fast low angle shot (FLASH) gradient echo sequence with water excitation, as described previously (Eckstein et. al., 2010).

The analysis of the thigh adipose tissue content relied on axial MRIs of the thigh acquired using a T1-weighted spin echo sequence (time of repetition 500ms, time of echo 10ms; slice thickness 5.0mm, in-plane resolution 0.98mm × 0.98mm; Fig. 2), using the same magnet and a body coil (Eckstein et. al., 2012; Eckstein et. al., 2014). Coronal localizer images were used to delineate the distal femoral epiphyses, with the acquisition of the axial images starting 10cm proximal to the distal femoral epiphysis and extending 7.5cm proximally (Sattler et. al., 2012). Details on this imaging protocol are available online

(www.oai.ucsf.edu/ datarelease/operationsmanuals.asp). Please note that due to the fixed distance (10cm) between the distal femoral epiphysis and the most distal MR image being acquired per OAI protocol, the position of the images varied relative to the femur, depending on bone length and body height (Eckstein et. al., 2014; Sattler et. al., 2012). In order to adjust for this variability, we selected a variable slice number depending on individual body height. This was estimated to be located at 33% of the femoral length (from distal to proximal), based on the relationship between body height, femoral length, and location of the distal femoral epiphysis previously determined in 48 OAI participants (Dannhauer et. al., 2010; Sattler et. al., 2012). One of the 26 muscle acquisitions (in a male participant) could not be analyzed, because the images were acquired starting 8cm (instead of 10cm) proximal from the knee joint space (rather than the distal epiphysis), so that the 33% femoral location was not covered by the 15 images.

### 2.3. Image analysis of the IPFP and the thigh adipose tissue content

All segmentations in this study were performed by the same reader (J.D.), who was trained using standardized test data sets. The imaging parameters (brightness, intensity, contrast, gray value limit) were adjusted manually in each image and the reader processed all slices that clearly depicted the IPFP. By applying different labels, the user marked the anterior border of the IPFP (the one facing the lig. patellae) and the posterior border (the one facing the knee joint; Fig.1a, b). When recesses, clefts or vessels were located in the periphery of the IPFP, these were excluded from the segmentation, and the same was done for all pathological alterations not originating from the IPFP. However, if small alterations were completely surrounded by adipose tissue, these had to be included in the volume segmentations; yet, no larger structures (cysts) were observed in these knees. All segmentations were quality controlled by a postdoc anatomist (A.R.) with ample experience in the analysis of thigh muscle cross sectional areas and adipose tissue. The IPFP volume, the size of the anterior and posterior surface area, and the mean thickness (depth) were computed using custom software without use of an interpolation algorithm (Fig. 1 c, d).

To analyze the adipose tissue content of the thigh, manual segmentation of the thigh muscle anatomical cross sectional areas (i.e. the quadriceps, hamstrings, adductors, and the sartorius) was performed as described previously (Dannhauer et. al., 2013; Ruhdorfer et. al., 2013; Sattler et. al., 2012); interstitial adipose tissue was being included in these segmentations. The outer circumference of the thigh was identified by an edge-detection algorithm applied to a “signal intensity threshold modified” image, and the femoral bone area was determined by an edge detection and shape identification algorithm (Dannhauer et. al., 2014). The area between these two contours included all non-muscular soft tissue and a semi-automated algorithm was then used to delineate a convex contour (“sling”) tightly enclosing the previously segmented muscle tissue, to separate inter-muscular tissue (IMT) and subcutaneous fat (SCF) cross sectional areas (in $cm^2$) (Fig. 2). Finally, inter-muscular fat (IMF) was identified from the IMT by applying a signal intensity threshold. The result was quality controlled with correction factors of the settings being applied until the result was approved visually (Dannhauer et. al., 2014).

### 2.4. Statistics

Demographics data and quantitative measures of IPFP and thigh fat tissue content were reported as means and standard deviations (SDs) for men and women. Since men are larger than women, several normalizations were performed to identify whether sex differences persisted after accounting for differences in body dimensions. Sex differences were evaluated using unpaired two-sided t-tests. P-values of <0.05 were considered significant. No adjustment for multiple comparisons was made in this exploratory study, but the primary analytic focus was set on IPFP volume divided by body weight, and the secondary focus on the anterior surface of the IPFP divided by the total tibial cartilage surface area. The latter had been derived in a previous study, from segmentation of the medial and lateral cartilage surface in the same participants (Eckstein et. al., 2010). However, measures of tibial surface area were not available in 7 of the participants studied here, because only participants with one year follow-up data had been included in the previous work (Eckstein et. al., 2010).

For comparative purposes, sex differences in thigh SCF and IMF areas were determined in the subsample of participants with thigh MRIs, with and without normalization to the total thigh cross sectional areas. All quantitative IPFP parameters were also determined for this subsample, to explore whether these were consistent between this and the larger sample.

Finally, Pearson correlation coefficients and their 95% confidence intervals (95% CI) were determined for IPFP volume vs. body weight and IPFP volume vs. age, in men and women, respectively.

## 3. Results

The 99 OAI healthy references subjects studied included 40 men (age 56±8.9 y [mean±SD]; weight 79.5±8.3 kg; height 1.75±65.6m, BMI 26.2±3.1) and 59 women (53.8 ±6.3 y; weight 61.6±8.5 kg; height 1.63±66.7m; BMI 23.2±2.52). The differences in age were not statistically significant (p=0.14), but men had a significantly greater BMI than women (p<0.001).

Men displayed a 41% greater IPFP volume than women as well as a 27% greater IPFP anterior surface area, a 31% greater posterior surface area, and a 12% greater thickness (p<0.001; for all comparisons). Men displayed a 9% greater IPFP volume than women, when normalized to body weight (p=0.008; primary analytic focus). When normalized to tibial cartilage surface area, men had a 2% smaller IPFP anterior surface than women (p=0.58; secondary analytic focus), with the tibial surface area being 30% larger in men (Table 1).

There was a weak to moderate correlation of IPFP volume with body weight in men (r=0.34 [95% CI 0.04; 0.59], p=0.03) and in women (r=0.50 [95% CI 0.28; 0.67]; p<0.001). However, no relevant or statistically significant correlation was observed between IPFP volume with age in men (r=0.03 [95% CI −0.29; 0.33], p=0.88) or women (r=0.18, [95% CI −0.08; 0.42]; p=0.17], p<0.001).

The 25 OAI healthy references subjects who had thigh MRI acquisitions included 13 men (age 61.1±10.6 y; BMI 26.2±2.86) and 12 women (mean age 52.1±5.6; BMI 23.3±3.34). The sex differences in IPFP parameters observed in this subsample were very similar to those in the larger sample (Table 2). The men displayed 50% smaller SCF areas (p=0.002), 21% greater IMT areas (p=0.07), 15% greater IMF areas (p=0.28), and 9.0% greater thigh total cross sectional areas (p=0.23) than women (Table 2). When normalized to thigh total area, sex differences in SCF, IMT and IMF amounted to −53% (p<0.001), +8% (p=0.44) and +2% (p=0.87) for men vs. women (Table 2).

## 4. Discussion

This is the first study to describe sex differences in quantitative anatomical measures of the IPFP (Hoffa) in healthy men and women, and to relate these to sex differences in subcutaneous (SCF) and inter-muscular adipose (IMF) tissue content. The current study was conducted using publically available clinical and imaging data from the Osteoarthritis Initiative (OAI) data base; image analysis software was used specifically for analysis of SCF and IMF tissue content of the thigh (Dannhauer et. al., 2014), and for quantitative analysis of anatomical measures of the IPFP. We find healthy men to display substantially greater IPFP volume then women, with the sex difference remaining significant when the IPFP was normalized to body weight. Men did not display a greater anterior surface area of the IPFP when normalized to tibial cartilage surface area, but a significantly greater IPFP depth than women. When related to total thigh cross sectional area, men displayed similar inter-muscular fat (IMF) tissue content, but only half of the subcutaneous fat tissue (SCF) content as women, despite their slightly greater BMI. Further, we observed a weak to moderate correlation of the IPFP volume with body weight in men and women, but no relevant correlation with age.

A limitation of the current study is the limited sample size of subjects with axial MRIs available for thigh tissue composition. However, the finding of substantially greater subcutaneous fat tissue content in this small subset is consistent with the literature (Dannhauer et. al., 2014; Delmonico et. al., 2009; Tseng et. al., 2014; Van Pelt et. al., 2011). Also, the sex differences of IPFP measures in this subset were very consistent with that in the larger set of almost 100 healthy participants. One of the strengths of our study is the rigor by which the OAI eliminated structural (radiographic) alterations and risk factors of femorotibial OA from participants of the healthy OAI reference cohort. A limitation here though is that no lateral radiographs were available, and that therefore radiographic alterations of the femoropatellar joint could not be excluded. Further, we did not exclude knees with potential structural pathology on MRI (i.e. meniscus-, cartilage-, and bone marrow lesions, synovitis, etc.) Yet, the participants had no knee pain, and most of the risk factors eliminated are not specific to femorotibial OA, but also apply to femoropatellar OA and structural pathology on MRI.

Another strength of the study is that the image analysis was not restricted to a central slice displaying the “maximal” area of the IPFP (Pan et. al., 2014), but that its’ distinguishable volumetric extent was analyzed entirely, permitting a comparison with individual body weight. Identification of the IPFP in its peripheral (medial-lateral) aspects can be

challenging; however, it may be important given that the IPFP is confined anatomically by the patella, the lig. patellae, the patellar surface of the femur (the trochlea), and the tibia. Therefore, extension of the IPFP with greater body weight and BMI may occur in medial-lateral dimension, and may not be appreciated in a single sagittal image. Yet, a limitation of our study is that quantitative anatomical measures were derived from fat-suppressed MR images without validation of the “ground truth” of these measurements based on an external reference standard. However, the reader (J.D.) was trained using standardized data sets produced by our group, and all segmentations were controlled by an experienced postdoc anatomist (A.R.). Further, even if systematic differences may theoretically exist between the anatomical imaging measures derived here and a “ground truth”, it is unlikely that these would affect men and women differently; hence the sex-differences reported here should be robust against potential systematic errors and should be accurate.

Both SCF and IMF have been suggested to be of relevance to physical function in knee OA (Maly et. al., 2013; Messier et. al., 2014). We find that the IMF content is similar between both sexes, when related to the total thigh cross sectional area, a finding that is in contrast to the much greater SCF content in women compared with men. Delmonico et al. previously reported in a 5-year longitudinal study that IMF increased with age in men and women, independent of who lost weight, gained weight, or remained weight-stable. Changes in SCF, in contrast, were associated with weight gain or loss, and were independent of the increase in IMF (Delmonico et. al., 2009). In our current study, healthy men appear to have greater IPFP volume than women, even after normalization to the individual body weight. Hence, the current findings do not support the hypothesis that the greater prevalence, incidence, and progression of symptomatic knee OA in women (Srikanth et. al., 2005) is due to a greater relative amount of intra-articular adipose tissue than in men, which may be responsible for a potentially greater amount of secretion of (pro-) inflammatory cytokines. However, it is of note that we did find a positive association of the IPFP volume with body weight across the BMI range of the sample included, suggesting that the amount of intra-articular adipose tissue may depend on the level of obesity in men and women. Future studies therefore will have to examine to what extent IPFP volumes vary across different BMI strata, and to what extent the IPFP volume correlates with intra-articular and serum levels of leptin and other (pro-) inflammatory cytokines. A recent study indicated that there may be an inverse relationship of IPFP maximal area to knee OA progression in women, and the authors suggested several potential endocrinological and biomechanical mechanisms by which a greater IPFP may play a protective role in knee OA. However, it is unclear why this “protective” mechanism should only apply in women and not in men. These findings therefore will have to be reproduced and extended in larger samples, in order to better understand the specific role of the IPFP in the pathogenesis of knee OA in men and women.

In conclusion, this is the first study to explore quantitative measures of the IPFP in healthy men and women and to relate these to sex differences of thigh subcutaneous and intermuscular fat. Men are shown to display a significantly greater ratio of IPFP volume/ body weight than women, similar amounts of inter-muscular fat, and strikingly less subcutaneous fat. These data provide a basis for further systematic studies of the variability of the IPFP with BMI, and its role in knee OA.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.


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## References


Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage. 2007; 15(Suppl A):1–56. [PubMed: 16891130]

Bloecker K, Englund M, Wirth W, Hudelmaier M, Burgkart R, Frobell RB, Eckstein F. Size and position of the healthy meniscus, and its correlation with sex, height, weight, and bone area- a cross-sectional study. BMC.Musculoskelet.Disord. 2011; 12:248. [PubMed: 22035074]

Chuckpaiwong B, Charles HC, Kraus VB, Guilak F, Nunley JA. Age-associated increases in the size of the infrapatellar fat pad in knee osteoarthritis as measured by 3T MRI. J.Orthop.Res. 2010; 28:1149–1154. [PubMed: 20225314]

Conde J, Scotece M, Lopez V, Abella V, Hermida M, Pino J, Lago F, Gomez-Reino JJ, Gualillo O. Differential expression of adipokines in infrapatellar fat pad (IPFP) and synovium of osteoarthritis patients and healthy individuals. Ann.Rheum Dis. 2013

Dannhauer T, Wirth W, Eckstein F. Selection of comparable anatomical locations of muscle cross-sectional images in the Osteoarthritis Initiative MRI data. Osteoarthritis Cartilage. 2010; 18:195. [abstract ].

Dannhauer T, Wirth W, Ruhdorfer A, Eckstein F. Quantitative relationship of thigh adipose tissue with pain, radiographic status, and progression of knee osteoarthritis - longitudinal findings from the Osteoarthritis Initiative. Invest Radiol. 2014 in press.

Dannhauer T, Sattler M, Wirth W, Hunter DJ, Kwoh CK, Eckstein F. Longitudinal sensitivity to change of MRI-based muscle cross-sectional area versus isometric strength analysis in osteoarthritic knees with and without structural progression: pilot data from the Osteoarthritis Initiative. MAGMA. 2013

Delmonico MJ, Harris TB, Visser M, Park SW, Conroy MB, Velasquez-Mieyer P, Boudreau R, Manini TM, Nevitt M, Newman AB, Goodpaster BH. Longitudinal study of muscle strength, quality, and adipose tissue infiltration. Am.J.Clin.Nutr. 2009; 90:1579–1585. [PubMed: 19864405]

Eckstein F, Kwoh CK. Imaging in rheumatology in 2013. From images to data to theory. Nat.Rev.Rheumatol. 2014; 10:69–70. [PubMed: 24366318]

Eckstein F, Kwoh CK, Link TM. Imaging research results from the Osteoarthritis Initiative (OAI): a review and lessons learned 10 years after start of enrolment. Ann.Rheum Dis. 2014

Eckstein F, Wirth W, Nevitt MC. Recent advances in osteoarthritis imaging-the Osteoarthritis Initiative. Nat.Rev.Rheumatol. 2012; 8:622–630. [PubMed: 22782003]

Eckstein F, Yang M, Guermazi A, Roemer FW, Hudelmaier M, Picha K, Baribaud F, Wirth W, Felson DT. Reference values and Z-scores for subregional femorotibial cartilage thickness--results from a large population-based sample (Framingham) and comparison with the non-exposed Osteoarthritis Initiative reference cohort. Osteoarthritis.Cartilage. 2010; 18:1275–1283. [PubMed: 20691798]

Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. Arthritis Rheum. 1987; 30:914–918. [PubMed: 3632732]

Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman B, Aliabadi P, Levy D. Risk factors for incident radiographic knee osteoarthritis in the elderly: the Framingham Study. Arthritis Rheum. 1997; 40:728–733. [PubMed: 9125257]

Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman BN, Aliabadi P, Levy D. The incidence and natural history of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. Arthritis Rheum. 1995; 38:1500–1505. [PubMed: 7575700]

Gegout PP, Francin PJ, Mainard D, Presle N. Adipokines in osteoarthritis: friends or foes of cartilage homeostasis? Joint Bone Spine. 2008; 75:669–671. [PubMed: 19028435]

Griffin TM, Guilak F. Why is obesity associated with osteoarthritis? Insights from mouse models of obesity. Biorheology. 2008; 45:387–398. [PubMed: 18836239]

Griffin TM, Huebner JL, Kraus VB, Yan Z, Guilak F. Induction of osteoarthritis and metabolic inflammation by a very high-fat diet in mice: effects of short-term exercise. Arthritis Rheum. 2012; 64:443–453. [PubMed: 21953366]

Guermazi A, Roemer FW, Haugen IK, Crema MD, Hayashi D. MRI-based semiquantitative scoring of joint pathology in osteoarthritis. Nat.Rev.Rheumatol. 2013; 9:236–251. [PubMed: 23321609]

Han W, Cai S, Liu Z, Jin X, Wang X, Antony B, Cao Y, Aitken D, Cicuttini F, Jones G, Ding C. Infrapatellar fat pad in the knee: is local fat good or bad for knee osteoarthritis? Arthritis Res.Ther. 2014; 16:R145. [PubMed: 25008048]

Hui W, Litherland GJ, Elias MS, Kitson GI, Cawston TE, Rowan AD, Young DA. Leptin produced by joint white adipose tissue induces cartilage degradation via upregulation and activation of matrix metalloproteinases. Ann.Rheum.Dis. 2012; 71:455–462. [PubMed: 22072016]

Issa RI, Griffin TM. Pathobiology of obesity and osteoarthritis: integrating biomechanics and inflammation. Pathobiol.Aging Age Relat Dis. 2012a; 2

Issa RI, Griffin TM. Pathobiology of obesity and osteoarthritis: integrating biomechanics and inflammation. Pathobiol.Aging Age Relat Dis. 2012b; 2

Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann.Rheum.Dis. 1957; 16:494–502. [PubMed: 13498604]

Klein-Wieringa IR, Kloppenburg M, Bastiaansen-Jenniskens YM, Yusuf E, Kwekkeboom JC, El-Bannoudi H, Nelissen RG, Zuurmond A, Stojanovic-Susulic V, Van Osch GJ, Toes RE, Ioan-Facsinay A. The infrapatellar fat pad of patients with osteoarthritis has an inflammatory phenotype. Ann.Rheum Dis. 2011; 70:851–857. [PubMed: 21242232]

Losina E, Walensky RP, Reichmann WM, Holt HL, Gerlovin H, Solomon DH, Jordan JM, Hunter DJ, Suter LG, Weinstein AM, Paltiel AD, Katz JN. Impact of obesity and knee osteoarthritis on morbidity and mortality in older Americans. Ann.Intern.Med. 2011; 154:217–226. [PubMed: 21320937]

Maly MR, Calder KM, Macintyre NJ, Beattie KA. Relationship of intermuscular fat volume in the thigh with knee extensor strength and physical performance in women at risk of or with knee osteoarthritis. Arthritis Care Res.(Hoboken.). 2013; 65:44–52. [PubMed: 23044710]

Messier SP, Beavers DP, Loeser RF, Carr JJ, Khajanchi S, Legault C, Nicklas BJ, Hunter DJ, Devita P. Knee joint loading in knee osteoarthritis: influence of abdominal and thigh fat. Med.Sci.Sports Exerc. 2014; 46:1677–1683. [PubMed: 25133996]

Messier SP, Mihalko SL, Legault C, Miller GD, Nicklas BJ, Devita P, Beavers DP, Hunter DJ, Lyles MF, Eckstein F, Williamson JD, Carr JJ, Guermazi A, Loeser RF. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. JAMA. 2013; 310:1263–1273. [PubMed: 24065013]

Pan F, Han W, Wang X, Liu Z, Jin X, Antony B, Cicuttini F, Jones G, Ding C. A longitudinal study of the association between infrapatellar fat pad maximal area and changes in knee symptoms and structure in older adults. Ann.Rheum.Dis. 2014

Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. Ann.Rheum.Dis. 2001; 60:91–97. [PubMed: 11156538]

Peterfy C, Li J, Zaim S, Duryea J, Lynch J, Miaux Y, Yu W, Genant HK. Comparison of fixed-flexion positioning with fluoroscopic semi-flexed positioning for quantifying radiographic joint-space width in the knee: test-retest reproducibility. Skeletal Radiol. 2003; 32:128–132. [PubMed: 12605275]

Peterfy CG, Schneider E, Nevitt M. The osteoarthritis initiative: report on the design rationale for the magnetic resonance imaging protocol for the knee. Osteoarthritis Cartilage. 2008; 16:1433–1441. [PubMed: 18786841]

Ruhdorfer A, Dannhauer T, Wirth W, Hitzl W, Kwoh CK, Guermazi A, Hunter DJ, Benichou O, Eckstein F. Thigh muscle cross-sectional areas and strength in advanced versus early painful osteoarthritis: an exploratory between-knee, within-person comparison in osteoarthritis initiative participants. Arthritis Care Res.(Hoboken.). 2013; 65:1034–1042. [PubMed: 23401316]

Saddik D, McNally EG, Richardson M. MRI of Hoffa's fat pad. Skeletal Radiol. 2004; 33:433–444. [PubMed: 15221217]

Sattler M, Dannhauer T, Hudelmaier M, Wirth W, Sanger AM, Kwoh CK, Hunter DJ, Eckstein F. Side differences of thigh muscle cross-sectional areas and maximal isometric muscle force in bilateral knees with the same radiographic disease stage, but unilateral frequent pain - data from the osteoarthritis initiative. Osteoarthritis.Cartilage. 2012; 20:532–540. [PubMed: 22395037]

Scotece M, Conde J, Lopez V, Lago F, Pino J, Gomez-Reino JJ, Gualillo O. Leptin in joint and bone diseases: new insights. Curr.Med.Chem. 2013; 20:3416–3425. [PubMed: 23746275]

Sokolove J, Lepus CM. Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations. Ther.Adv.Musculoskelet.Dis. 2013; 5:77–94. [PubMed: 23641259]

Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. Osteoarthritis Cartilage. 2005; 13:769–781. [PubMed: 15978850]

Stannus OP, Cao Y, Antony B, Blizzard L, Cicuttini F, Jones G, Ding C. Cross-sectional and longitudinal associations between circulating leptin and knee cartilage thickness in older adults. Ann.Rheum.Dis. 2013

Stannus OP, Jones G, Quinn SJ, Cicuttini FM, Dore D, Ding C. The association between leptin, interleukin-6, and hip radiographic osteoarthritis in older people: a cross-sectional study. Arthritis Res.Ther. 2010; 12:R95. [PubMed: 20482813]

Tseng LA, Delmonico MJ, Visser M, Boudreau RM, Goodpaster BH, Schwartz AV, Simonsick EM, Satterfield S, Harris T, Newman AB. Body composition explains sex differential in physical performance among older adults. J.Gerontol.A Biol.Sci.Med.Sci. 2014; 69:93–100. [PubMed: 23682159]

Van Pelt RE, Jankowski CM, Gozansky WS, Wolfe P, Schwartz RS, Kohrt WM. Sex differences in the association of thigh fat and metabolic risk in older adults. Obesity.(Silver.Spring). 2011; 19:422–428. [PubMed: 20559300]

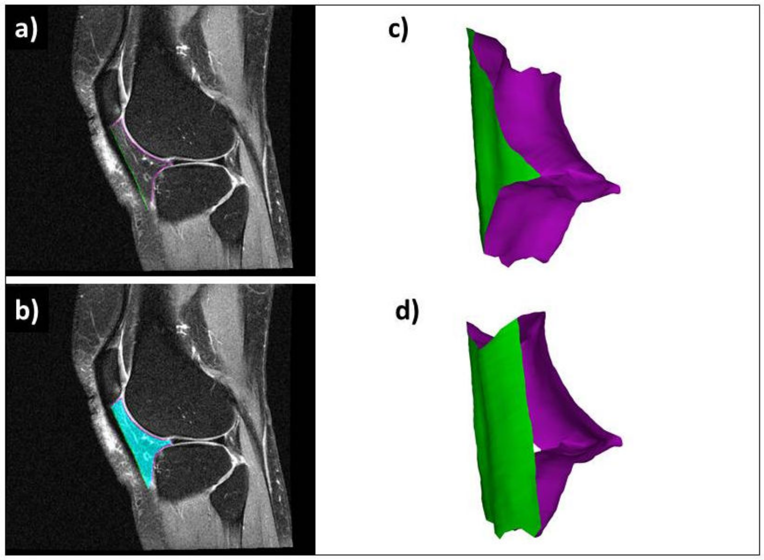


**Figure 1.**

a) Sagittal MRI of the knee joint; segmentation of the IPFP anterior surface (green, facing the lig. patellae) and posterior surface (magenta, facing the patellar surface of the distal femur.

b) IPFP area with filling

c) 3D reconstruction of the IPFP viewed from the posterior- lateral (the red area marks the anterior and the blue areas the posterior surface).

d) 3D reconstruction of the IPFP viewed from the anterior- lateral

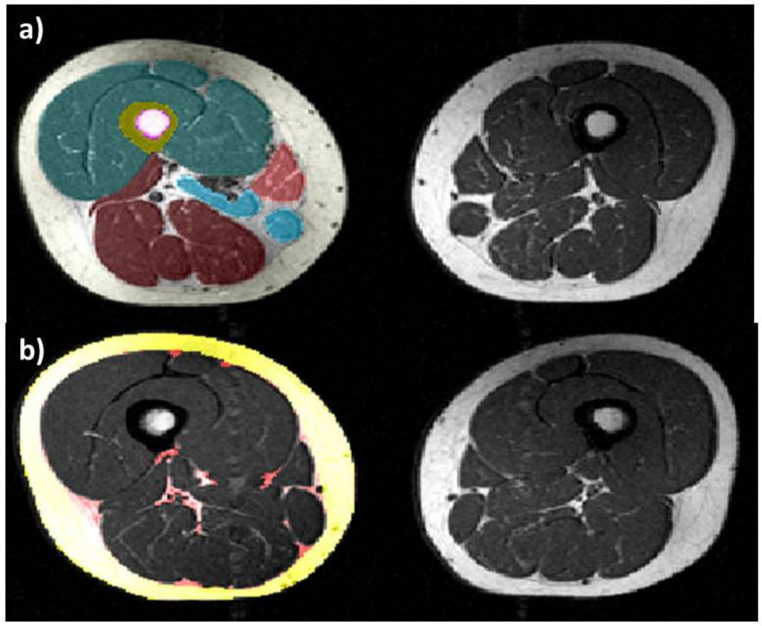


**Figure 2.**

Images showing bilateral acquisitions of the thigh at 33% of the femoral length (distal to proximal), with segmentation of the muscles and adipose tissue displayed on the right thigh:

a) Quadriceps is shown in green, hamstrings in dark red, adductors in turquoise, and sartorius in light red. The femoral cortical bone in marked yellow and the femoral medulla pink.

b) Subcutaneous fat (SCF) depicted yellow and intermuscular tissue and fat (IMF) magenta

## Table 1

Quantitative anatomical measures of the infrapatellar fat pad (IPFP) in healthy women and men, and sex differences of these measures

| | Woman (n=59) Mean±SD | Men (n=40) Mean±SD | Absolute difference | Percent difference | p value (unpaired t-test) |
|---|---|---|---|---|---|
| Body height (m) | 1.63± 66.7 | 1.75± 65.6 | +0.12 | +7 | <0.001 |
| Body weight (kg) | 61.6± 8.45 | 79.5± 8.28 | +17.9 | +29 | <0.001 |
| BMI (kg/m$^2$) | 23.2± 2.52 | 26.2± 3.06 | +3.00 | +13 | <0.001 |
| Age (years) | 53.8± 6.31 | 56.1± 8.9 | +2.28 | +4 | 0.14 |
| *Tib. S. (cm$^2$) | 18.5± 1.7 | 24.2± 2.2 | +5.64 | +30 | <0.001 |
| IPFP Ant. S.(cm$^2$) | 16.9± 2.7 | 21.4± 3.5 | +4.55 | +27 | <0.001 |
| IPFP Ant. S./Tib. S. | 0.90± 0.12 | 0.89± 0.13 | −0.01 | −2 | 0.58 |
| IPFP Thick (mm) | 12.5± 1.4 | 14.0± 1.4 | +1.46 | +12 | <0.001 |
| IPFP Vol. (cm$^3$) | 21.0± 3.4 | 29.7± 4.3 | +8.71 | +41 | <0.001 |
| IPFP Vol./weight | 0.34± 0.06 | 0.38± 0.06 | +0.03 | +9 | 0.008 |

SD = standard deviation; BMI = body mass index, Tib. S. = surface size of the medial and lateral tibial cartilages (* these were available in 92 participants only); IPFP = infra-patellar fat pad (Hoffa); Ant. S. = anterior surface (towards the lig. patellae); Thick = thickness; Vol. = Volume;

**Table 2**

Quantitative anatomical measures of subcutaneous (SCF) and intermuscular fat (IMF) of the thigh in women and men, and sex differences of these measures; anatomical measures of the IPFP in this subset are reported for comparison

| | Woman (n=12) Mean± SD | Men (n=13) Mean± SD | Absolute difference | Percent difference | p- value (unpaired t-test) |
|---|---|---|---|---|---|
| Body height (m) | 1.58± 54.4 | 1.73± 52.8 | +149.8 | +9 | <0.001 |
| Body weight (kg) | 58.3± 8.90 | 78.8± 8.89 | +20.5 | +35 | <0.001 |
| BMI (kg/m$^2$) | 23.3± 3.34 | 26.2± 2.86 | +3.00 | +13 | 0.024 |
| Age (years) | 52.1± 5.62 | 61.1± 10.6 | +8.99 | +17 | 0.015 |
| Thigh Total Area | 157.8± 34.6 | 172.1± 22.2 | +14.34 | +9 | 0.23 |
| SCF (cm$^2$) | 63.9± 31.8 | 31.7± 9.05 | −32.2 | −50 | 0.002 |
| SCF % | 38.6± 10.9 | 18.3± 3.86 | −20.32 | −53 | <0,001 |
| IMF (cm$^2$) | 7.80± 1.87 | 8.98± 3.22 | +1.18 | +15 | 0.28 |
| IMF % | 5.09± 1.49 | 5.20± 1.65 | +0.11 | +2 | 0.87 |
| IPFP Ant. S. (cm$^2$) | 14.9± 2.69 | 20.9± 3.15 | +6.05 | +40 | <0.001 |
| IPFP thick. (mm) | 12.5± 1.90 | 13.6± 1.49 | +1.08 | +8 | 0.13 |
| IPFP vol. (cm$^3$) | 18.4± 2.89 | 28.4± 4.48 | +9.99 | +54 | <0,001 |
| IPFP vol./BW | 0.32± 0.05 | 0.36± 0.05 | +0.04 | +13 | 0.051 |

SCF = subcutaneous fat tissue content; IMF = intermuscular fat tissue content; SCF/IMF% = proportion of the SCF and IMF on the thigh total cross sectional areas in percent; for other abbreviations, please see Table 1; Of these 25 subjects, 24 were part of the 99 participants without signs of radiographic femorotibial OA in the central readings, but one was part of the larger cohort. In this participant, the right knee (the one examined here) had a KL grade=0 (normal), but the left showed definite osteophytes. This knee was only included for the purpose to compare the sex differences in the IPFP directly with those in thigh adipose tissue (Table 2), but not in the comparison presented in Table 1.