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RESEARCH ARTICLE

Quantitative MRI analysis of infrapatellar and suprapatellar fat pads in normal controls, moderate and end-stage osteoarthritis

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ABSTRACT

The aim of this study was to analyze the magnetic resonance imaging (MRI) volumetric and morphometric characteristics of the infrapatellar fat pad (IFP) and the suprapatellar fat pad (SFP) in normal controls, moderate and end-stage osteoarthritis (OA) patients. Forty-four MRI images of the three groups were collected: a) 17 patients undergoing meniscectomy with Outerbridge score 0 (control group); b) 15 patients undergoing meniscectomy with Outerbridge score 3/4 (moderate OA group); and c) 12 patients undergoing total knee replacement (end-stage OA group). Volume, depth, femoral and tibial arch lengths of IFP were quantified. The hypointense IFP signals were also scored. The SFP volume, oblique, antero-posterior and cranio-caudal lengths were determined. IFP and SFP characteristics were compared between groups. A decrease of IFP volume, depth, femoral, and tibial arch lengths in moderate and end-stage OA compared to controls were observed. A difference in IFP hypointense signal was found between groups. No differences were found in SFP characteristics between the groups. In controls and moderate OA patients, correlations were found among the different MRI characteristics of both IFP and SFP, while in the end-stage OA group correlations were found only in SFP. We evidenced differences of the IFP MRI morphometric characteristics between the groups analyzed, supporting an important role of IFP in OA pathology and progression. On the contrary, no differences were highlighted in SFP analysis suggesting that this fat pad is not clearly involved in OA, probably due to its peculiar localization and different function.

1. Introduction

Osteoarthritis (OA) is the most frequent joint disease which leads to pain, joint dysfunction and disability. Recent concept of OA considers this pathology as a whole joint disease in which all articular tissues (subchondral bone, synovial membrane, ligaments, and meniscus) might contribute to OA pathogenesis (Favero et al., 2015).

Recently, the role of infrapatellar fat pad (IFP), which is a small adipose tissue localized within the knee joint, has been evidenced in the onset and development of OA (Belluzzi et al., 2017; Clockaerts et al., 2010; Ioan-Facsinay and Kloppenburg, 2013). IFP is located anteriorly underneath the patella and it is bordered by the following anatomical structures: the patellar tendon and retinacula, the

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anterior part of the tibia, the anterior horns of the menisci, and the femur condyles. IFP is an extra-synovial but intra-capsular adipose depot attached to the intercondylar notch of the femur by the IFP synovial plica (Macchi et al., 2016), even if proximal projections wrapping around the patella have been recently described (Stephen et al., 2018). It has been shown that IFP is a source of adipocytokines possibly contributing to the low-grading inflammation exhibited by OA joints (Distel et al., 2009; Eymard et al., 2017; Ushiyama et al., 2003). In addition, IFP has been demonstrated to be more inflamed, vascularized and fibrous in OA patients compared to non-OA controls (Favero et al., 2017). Interestingly, imaging studies, other than molecular and histological examinations, have been carried out on IFP of patients affected by OA. IFP maximal area, measured on magnetic resonance imaging (MRI) has been associated with joint space narrowing, medial osteophytes, knee tibial and patellar cartilage volume, tibial cartilage defects, bone marrow lesions and knee pain (Han et al., 2014; Pan et al., 2015). Recently, Steidle-Kloc et al reported no differences in IFP size related to knee pain in OA (Steidle-Kloc et al., 2018). However, the relationship between IFP MRI characteristics and the onset and progression of OA remains still to be elucidated.

Furthermore, another small fat pad within the knee has recently focused the attention in OA studies: the suprapatellar fat pad (SFP), which is located above the patella and behind the suprapatellar joint recess with the function of increasing the congruency of the extensor mechanism (Eymard et al., 2017). OA SFP has been demonstrated to also produce high amount of inflammatory molecules and to be more fibrous than subcutaneous adipose tissue in OA patients (Eymard et al., 2017). Nevertheless, the role of SFP on anterior knee pain and joint OA has not been clearly elucidated so far. As matter of fact, the evidence based on MRI studies is contradictory. A large MRI study carried on 843 patients has not found correlations between SFP swelling and patellofemoral malalignment, patellofemoral joint OA, fat thickness in the medial compartment of the knee and anterior knee pain (Tsavalas and Karantanas, 2013). On the contrary, other MRI studies demonstrated an association between SFP mass effect and/or signal intensity alterations and knee pain, radiographic OA and BMLs suggesting that SFP abnormalities may contribute to pain and structural abnormalities in the knee (Schwaiger et al., 2018; Wang et al., 2014).

The aim of the present study was to evaluate the IFP e SFP MRI volumetric and morphometric characteristics in normal controls (without evidence of cartilage defects) and patients with moderate and end-stage OA. We hypothesized a progressive reduction of both IFP and SFP MRI measures with the progression of the disease.

2. Material and methods

2.1. Study population

The data used in the present study were obtained in the framework of a multicenter prospective cohort study, entitled 'The role of the meniscus in OA pathology and symptoms', funded by the Italian Ministry of Health between 2012 and 2016 (Project code: GR-2010-2317593) (Trisolino et al., 2017). The study obtained extensive records of preclinical, intra-operative and post-operative data from patients undergoing meniscectomy or meniscal repair for degenerative or traumatic meniscal tears. During arthroscopy, cartilage damage was assessed using the Outerbridge scoring system: Grade 0 = normal cartilage; Grade 1 = cartilage with softening and swelling; Grade 2 = a partial-thickness defect with fissures on the surface that do not reach subchondral bone or exceed 1.5 cm in diameter; Grade 3 = fissuring to the level of subchondral bone in an area with a diameter of 1.5 cm and; Grade 4 = exposed subchondral bone (Outerbridge, 1961). The cartilage tears were assessed intra-operatively for each knee at the following six different sites: medial and lateral femoral condyles; medial and lateral tibial plateau; and trochlear and patellar surfaces. The most severe lesion detected at each site was taken into account for scoring. In addition, the study collected clinical and imaging data from patients undergoing total knee replacement as control of end-stage OA disease.

The study was approved by the Local Ethical Committee and patients were enrolled after providing written informed consent.

For the current study, we analyzed the following three groups of patients: a) 17 patients undergoing meniscectomy for meniscal tears with Outerbridge score 0, who were considered as non-osteoarthritic control subjects; b) 15 patients undergoing meniscectomy for meniscal tears with Outerbridge score 3 or 4, who were considered affected by moderate OA; and c) 12 patients undergoing total knee replacements for knee OA, who were considered affected by end-stage OA.

2.2. MR image acquisition and IFP hypointense scoring

We retrospectively analyzed MRI images of forty-four knees from forty-four patients enrolled at the Orthopedic and Traumatological Clinic of the University-Hospital of Padova. Images were obtained by different magnetic resonance imaging sequences, but all had at least T2-weighted sequence, one sequence with fat suppression and a sequence for each scanning plane (sagittal, coronal and axial). Since our group recently reported that IFP is more fibrous in OA patients compared to controls, we decided to analyze the IFP hypointense signals which have been described to be an MRI marker of fibrosis (Han et al., 2016).

According to Han et al. hypointense signals within the IFP were scored on T2-weighted MRI images by counting imaging slices with this abnormality as follows: grade 0 = none; grade 1 = 1–2 slices, grade 2 = 3–5 slices, grade 3 = $\geq$ 6 slices (Han et al., 2016). This measurement was conducted by an experienced radiologist (VM).

The hypointense scoring was not assessed within the SFP since this MRI grading system was not validated at this site.

2.3. Volumetric analysis

The DICOM images were processed by using an imaging density segmentation software. The reconstruction of the soft tissues requires the elaboration of MRI images that makes possible to distinguish the different soft tissues with different grey levels (Fontanella et al., 2012; Natali et al., 2012). During segmentation of the knees, the imaging parameters, as brightness, intensity and contrast, were adjusted manually. For all slices the IFP and the SFP were depicted with different masks (Fig. 1A-B). The same reader (CGF) defined all segmentations, with a quality control performed by an experienced reader (VM) to ensure reliable measurements (Steidle-Kloc et al., 2016).

The IFP volume and the depth, the femoral arch and the tibial lengths of the sagittal slice located in the centre of the segmented IFP (central sagittal slice) were determined (Fig. 1C). The depth was calculated as the length of the perpendicular segment to the patellar tendon passing through the point of the IFP more internally to the joint. The femoral and tibial arch lengths were calculated as the profile of the IFP adjacent to the corresponding bone head.

In the same way, the SFP volume was determined together with the antero-posterior (A-P), cranio-caudal (C-C) and oblique lengths (OBL) of the sagittal slice located in the centre of the segmented IFP (central sagittal slice) (Fig. 1D) (Tsavalas and Karantanas, 2013). The A-P length was defined as the distance between the posterior point of the pad and the dorsal contour of the distal quadriceps tendon along a line parallel to the patient axial plane. The C-C length was defined as the distance between the most superior and inferior points of the pad along a line vertical to the patient's axial plane.

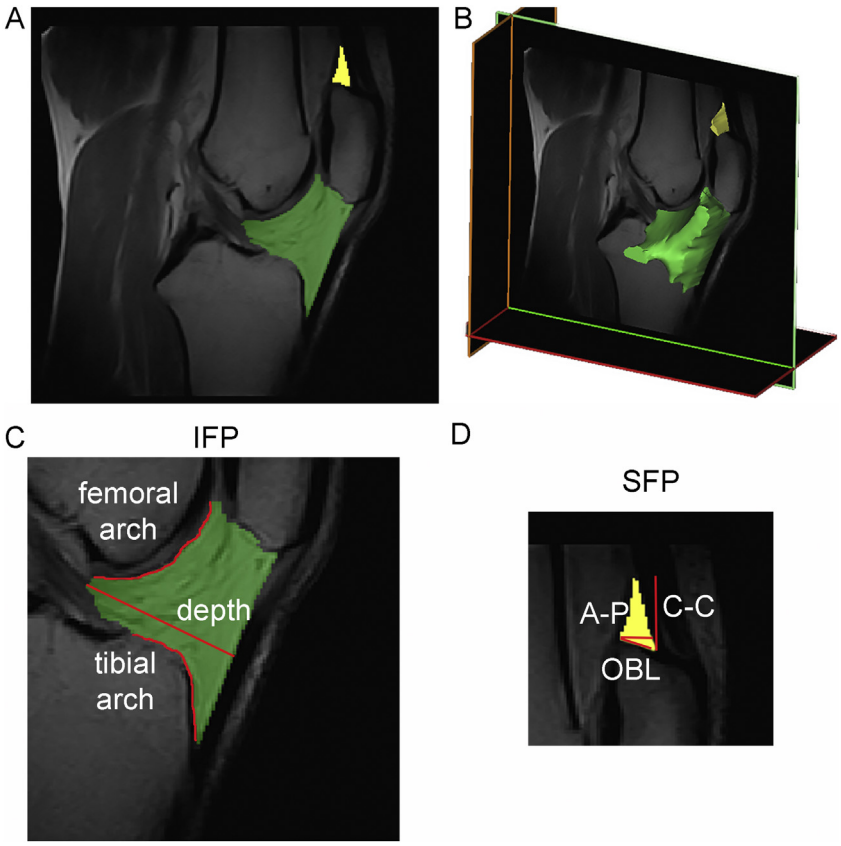

Fig. 1. IFP (marked ared under the patella) and SFP (marked area over the patella) masks (A) and volume identification (B) on MRI. Definition of depth, femoral and tibial arch lengths for the IFP (C) and of antero-posterior (A-P), cranio-caudal (C-C) and oblique (OBL) lengths for the SFP in the central slice (D).

The OBL length was defined as the distance between the most posterior and anterior points of the pad along an obliquely oriented measurement tangent running parallel to the superior aspect of the base of the osseous contour of the patella (Fig. 1D).

2.4. Statistical analysis

The Shapiro–Wilk test was used to assess normality of the different variables. Results were reported as mean (±SD) or median (interquartile range [IQR] Q3-Q1) according to the data distribution. Differences between groups were measured using ANOVA with Tukey's post-hoc tests. Spearman's or Pearson's correlations were performed depending on non-parametric or parametric variables. The chi-square test or Fisher's exact test was performed to compare categorical and dichotomous data. All analyses were performed with SPSS version 22.0. A $p < 0.05$ was considered significant.

3. Results

3.1. Patients demographic and clinical characteristics

Patients' characteristics are summarized in Table 1.

Patients without arthroscopic evidence of cartilage defects were predominantly male (88.2%), while patients affected by OA were predominantly female (moderate OA 66.7%, end-stage OA 75%). Patients with end-stage OA were older than patients with moderate OA ($p = 0.0252$) and non-osteoarthritic controls ($p < 0.0001$). Control group patients were younger than moderate OA subjects ($p < 0.0001$). End-stage OA patients had a higher BMI compared to non-osteoarthritic controls ($p = 0.0170$).

3.2. IFP and SFP MRI characteristics

The volume, depth, femoral and tibial arch lengths of IFP were evaluated and compared between the three groups (Fig. 2, Table 2). We have observed a progressive decrease of IFP volume in moderate and end-stage OA compared to non-osteoarthritic controls, even if the difference was not statistically significant (Fig. 3A). IFP depth was smaller in end-stage OA compared to moderate OA group ($p = 0.00312$) and controls ($p = 0.0006$), respectively (Fig. 3B). IFP femoral arch length was smaller in end-stage OA compared to moderate OA group ($p = 0.0104$) and controls ($p = 0.0004$), respectively (Fig. 3C). Similarly, IFP tibial arch length was smaller in end-stage OA compared to moderate OA patients ($p = 0.0447$) and controls ($p = 0.0073$), respectively (Fig. 3D).

Importantly, no correlations were observed between IFP volume and BMI or age in the three groups analyzed. Only fair negative correlations were found in the whole study population between age and IFP depth or femoral length ($p = 0.012$, $r = -0.376$; $p = 0.005$, $r = -0.416$, respectively).

The hypointense signals were graded as 0 or 1 in 100% of patients of both control and moderate OA groups and in 8.3% of patients with end-stage OA. 50% of patients with end-stage OA had an IFP hypointense signal scored as 2 and 41.7% as 3. The difference scoring distribution among the groups was statistically significant ($p < 0.0001$) (Table 3).

SFP volume, A-P, C-C and OBL lengths were evaluated in all patients enrolled showing no differences between the three groups analyzed, even excluding outlier values (Supplementary materials) (Table 2).

In the non-osteoarthritic control group as well as in the cohort of moderate OA patients, correlations were found among the different MRI morphometric characteristics of both IFP and SFP (supple-

Table 1
Demographic and clinical data of controls, moderate OA, and end-stage OA patients.

	Controls	Moderate OA	End-stage OA	P
Number of patients	17	15	12	N/A
Sex, male, n (%)	15 (88.2%)	5 (33.3%)	3 (25%)	0.0007
Age, years, median (IQR)	35.0 (44.0–32.0)	57.0 (62.5-51.0)	67.5 (74.0-58.5)	[a]**p < 0.0001** b**p < 0.0001** [c]**p = 0.0252**
BMI, Kg/m^2, median (IQR)	24.7 (29.5–22.7)	25.1 (32.2-24.7)	29.8 (33.5-26.4)	[a]p = 0.2038 [b]**p = 0.0170** [c]p = 0.4514

Data are expressed as median (IQR). P-values less than 0.05 were considered statistically significant and bolded.
OA = osteoarthritis, IQR = interquartile range, BMI = body mass index, C = controls, MOA = moderate OA, ESOA = end-stage OA. N/A = not applicable.
[a] C vs MOA = comparison control vs moderate OA.
[b] C vs EOA = comparison control vs end-stage OA
[c] MOA vs ESOA = comparison moderate OA vs end-stage OA

Table 2
IFP and SFP MRI morphometric characteristics.

	Controls	Moderate OA	End stage OA	P
IFP volume (mm^3), median (IQR)	33054 (41319–27702)	25541 (36371–15895)	23108 (28651–21467)	[a]p = 0.2580 [b]p = 0.0554 [c]p = 0.6676
IFP depth (mm), median (IQR)	31.2 (35.5–37.4)	27.6 (31.7–24.3)	24.6 (26.6–20.9)	[a]p = 0.3179 [b]**p = 0.0006** [c]**p = 0.0312**
IFP Femoral arch length (mm), median (IQR)	31.7 (34.9–29.3)	29.85 (35.1–28.3)	22.5 (26.3-18)	[a]p = 0.5182 [b]**p = 0.0004** [c]**p = 0.0104**
IFP Tibial arch length (mm), median (IQR)	32.7 (37.6–29.1)	30.2 (35.1–28.3)	29 (29.9–24.3)	[a]p = 0.7667 [b]**p = 0.0073** [c]**p = 0.0447**
SFP volume (mm^3), median (IQR)	959.2 (1332–834.2)	1287 (1538–978)	1350 (1752–990)	[a]p = 0.4466 [b]p = 0.1193 [c]p = 0.6737
SFP OBL (mm), median (IQR)	10.3 (12.1–9.4)	9.9 (11.9–9.2)	10.8 (11.7–9.3)	[a]p = 0.8066 [b]p = 0.8607 [c]p = 0.9968
SFP C–C (mm), median (IQR)	14.7 (18.1–13.7)	16.4 (18.6–14)	15.5 (19.9–14.2)	[a]p = 0.9479 [b]p = 0.7048 [c]p = 0.8745
SFP A–P (mm), median (IQR)	8 (9.1–6.7)	8.7 (9.8–6.9)	8.6 (9.3–7.6)	[a]p = 0.4601 [b]p = 0.6097 [c]p = 0.9845

IFP = infrapatellar fat pad, SFP = suprapatellar fat pad, MRI = magnetic resonance imaging, OA = osteoarthritis, IQR = interquartile range. C = controls, MOA = moderate OA, ESOA = end-stage OA. Data are expressed as median (IQR). P-values less than 0.05 were considered statistically significant and bolded.
[a] C vs MOA = comparison control vs moderate OA.
[b] C vs EOA = comparison control vs end-stage OA
[c] MOA vs ESOA = comparison moderate OA vs end-stage OA

Table 3
MRI hypotense signal grading in non-osteoarthritic controls, moderate OA, and end-stage OA patients.

	Controls	Moderate OA	End-stage OA	P
Grade 0	11 (64.7%)	8 (53.3%)	0 (0%)	p < 0.0001
Grade 1	5 (29.4%)	7 (46.7%)	1 (8.3%)	
Grade 2	0 (0%)	0 (0%)	6 (50%)	
Grade 3	0 (0%)	0 (0%)	5 (41.7%)	

OA = osteoarthritis. Data are reported as number of patients (%).

mentary materials). Interestingly, no correlations were found in the group of OA patients among IFP characteristics, while positive correlations were observed between the SFP A–P and OBL lengths (r = 0.893, p < 0.0001), the A-P and C-C lengths (r = 0.622, p = 0.035) and, finally between the C-C and the OBL lengths (r = 0.608, p = 0.040) (Supplementary materials).

4. Discussion

To the best of our knowledge this is the first study analyzing the MRI volumetric and morphometric characteristics of both IFP and SFP in non-OA subjects and patients with different grade of OA severity. The selection of patients undergoing meniscectomy represented a unique opportunity to accurately group subjects according to different grade of cartilage defects based on the Outerbridge scoring system performed during arthroscopy (Trisolino et al., 2017).

Interestingly, in our study we have observed a progressive statistical significance reduction of IFP MRI morphometric measures as depth, femoral and tibial lengths and a trend in IFP volume decreasing with the progression of OA. Several studies have been published comparing IFP volume between OA patients and healthy subjects with contradictory results. Cowan et al. found an increase of the IFP volume in individuals with patellofemoral joint OA compared

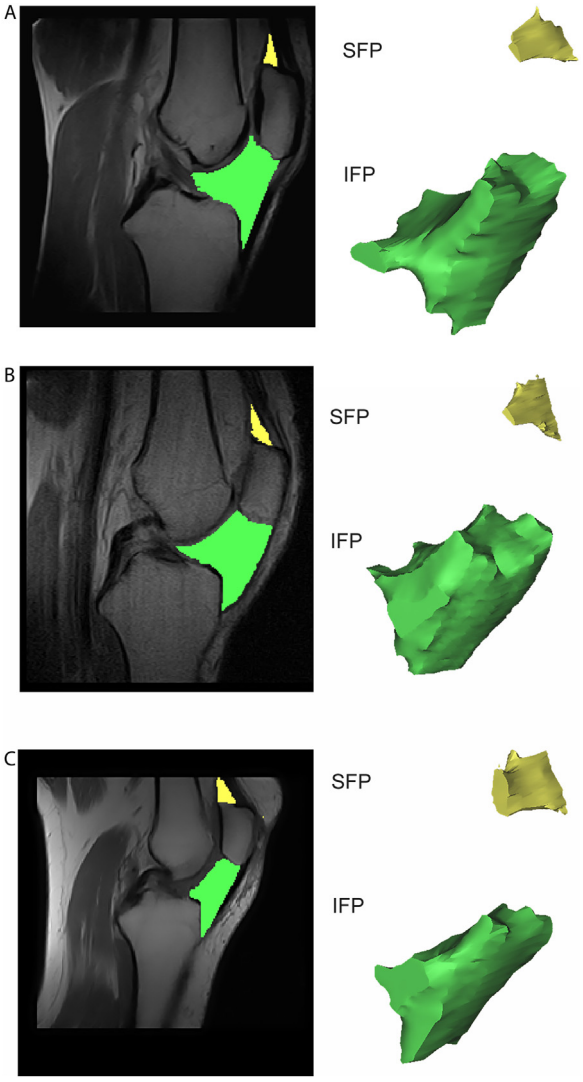

Fig. 2. IFP (marked ared under the patella) and SFP (marked area over the patella) masks and volume in normal controls (A), moderate OA (B) and end stage OA patients (C). The figure represents an example of progressive decrease of IFP volumetric and morphometric characteristics in moderate (B) and end-stage OA (C) compared to controls. No differences were observed in SFP.

to controls (Cowan et al., 2015). Instead, different authors have previously analyzed the IFP volume of participants with and without knee OA and no statistical differences were observed between the two groups (Chuckpaiwong et al., 2010; Ruhdorfer et al., 2017; von Drygalski et al., 2017). Interestingly, Cai et al. studied the IFP volume in a large cohort of patients with OA and showed that a greater volume was associated with greater cartilage volume and fewer structural abnormalities, suggesting a protective role of the IFP size in OA (Cai et al., 2015). Moreover, Teichtahl et al. showed that a larger IFP protects against knee pain and lateral tibial cartilage volume loss (Teichtahl et al., 2015). Our study demonstrated a significant reduction in morphological MRI features and a decrease of the IFP volume related to the progression of OA. This appears a quite interesting observation that has to be deepen in the future. In particular, there is a need to carry out prospective studies in order to correlate the IFP volume with OA progression.

In addition, we have found an increase in the MRI hypointense signal scoring system, which is considered a marker of fibrosis, in the end-stage OA patients compared to the moderate OA and non-osteoarthritis control groups. These findings agree with the results of our previous histological study on IFP collected from patients with OA undergoing TKR, which demonstrated an increasing of the interlobular septa thickness in OA IFP compared to controls (Favero et al., 2017). An increased fibrosis of OA IFP was also confirmed by other groups. Eymard et al. recently showed an higher extent of fibrosis and vascularization in OA IFP compared to subcutaneous adipose tissue (Eymard et al., 2017). Barboza et al. observed an increase of volume and expression of genes associated with fibrosis and extracellular matrix production in the IFP of obesity induced OA mice fed with high-fat diet (Barboza et al., 2017). A recent study has clearly shown a close correlation between the fibrosis and inflammation of the OA IFP (Ioan-Facsinay and Kloppenburg, 2017). As a matter of fact, we have previosuly found that IFP of OA patients is more inflamed and vascularized, with smaller adipose lobuli compared to controls, supporting the relationship between inflammation and fibrosis (Favero et al., 2017). To this regard, Henegar et al. demonstrated that in the white adipose tissue of obese subjects there is an increase of extracellular matrix components, suggesting that an inflammatory stimulus may be responsable for an excessive synthesis of extracellular matrix components and subsequent interstitial deposition of fibrotic material (Henegar et al., 2008).

In our study, we did not find any difference on MRI SFP parameters in moderate and end-stage OA compared to non-OA controls. Previous authors analyzed SFP volume of healthy and OA patients without finding any difference in accordance with our data (von Drygalski et al., 2017). Morevover, our findings partially match the study of Eymard and al. which demonstrated that SFP was less fibrotic than IFP but more fibrotic than subcutaneous adipose tissue (Eymard et al., 2017). To explain the differences with our study, we should consider that: 1) the SFP in Eymard et al. study included both the quadriceps fat pad and the pre-femoral fat pad, while in our study only the first one was analyzed; 2) SFP is a fat pad 20 times smaller than IFP (SFP median volume overall population 12640.20 mm^3 (IQR [1510.30-877.20]) versus IFP median volume overall population 27701.84 mm^3 (IQR [34699.16-22730.21]) and possibly microscopic changes do not induce any macroscopic modification; 3) IFP and SFP are located in different anatomical site and exposed to different mechanical load.

The three patient groups analyzed in the present study were statistically different in age, sex and BMI. The controls group represented by patients undergoing meniscectomy were predominantly composed by young lean males, while the moderate and end-stage OA group were mainly composed by older females with a higher BMI compared to controls. It has been demostrated that sex, age and BMI might effect the volume of IFP (Burda et al., 2017; Chuckpaiwong et al., 2010; Diepold et al., 2015). In a recent study evaluating patients without symptoms or signs of knee disease, IFP volume has been showed to increase in obese subjects compared to controls (Burda et al., 2017). Furthermore, in a study analyzing 15 knee OA patients and 15 controls IFP volume measured by MRI has been positively correlated with age but not with BMI in the OA group (Chuckpaiwong et al., 2010). All OA subjects enrolled were obese females, with a Kellgren-Lawrence grade 2 or 3; while female patients of the controls group did not show any symptoms or radiographic evidence of OA and were lean. No differences in IFP volume were found between OA and controls group suggesting that BMI does not influence the IFP volume (Chuckpaiwong et al., 2010). The correlations between IFP volume and age, but not BMI, were successively confirmed in a larger study including 977 patients aged between 50 and 80 years aimed to identyfing factors associated with the development and progression of OA (Han et al., 2014). In addition, IFP area was negatively associated with female sex (Han et al., 2014). In Han et al. study population the prevalence of diagnosed knee OA was 14% and IFP was negatively associated with prevalence of radiographic OA. In addition IFP was found to be associated with cartilage volume and with decreased presence of

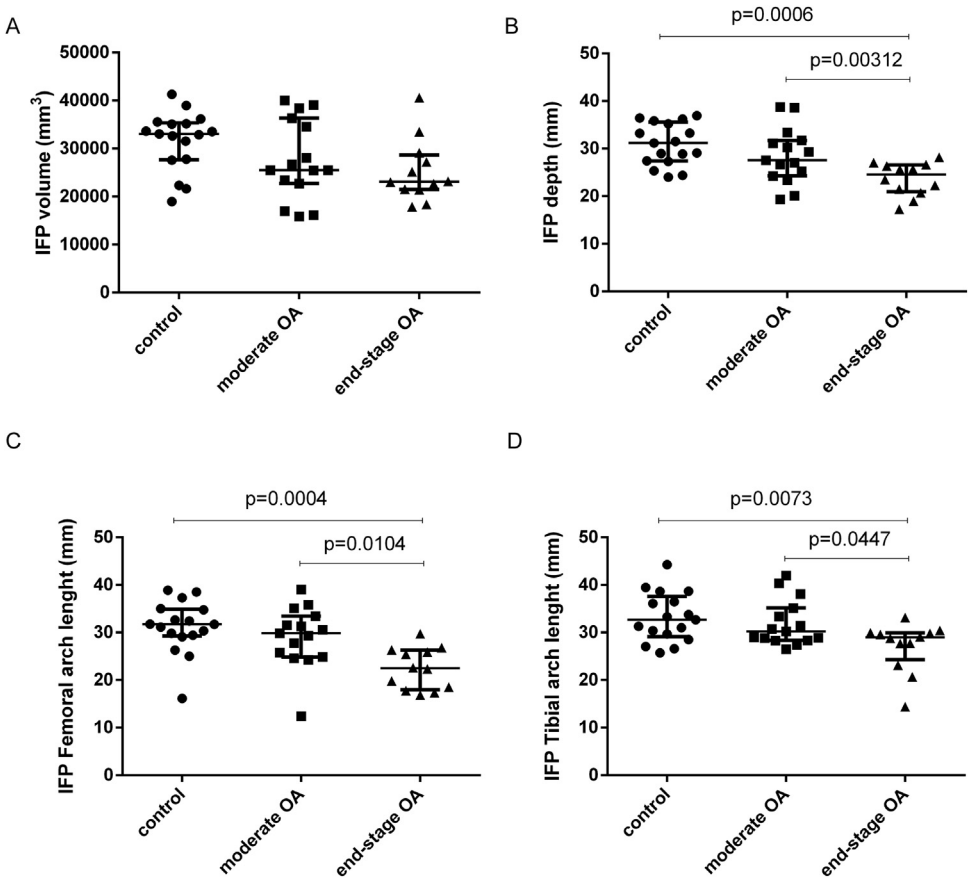

Fig. 3. IFP MRI morphometric characteristics evaluated in normal controls, moderate OA and end-stage OA patients.
IFP volume (A), IFP depth (B), IFP femoral arch (C), and IFP tibial arch (D) were evaluated in the three patient groups showing that all parameters decrease with the progression of the pathology. Data are expressed as median (IQR). OA = osteoarthritis, IFP = infrapatellar fat pad

joint space narrowing, which is a marker of cartilage loss (Han et al., 2014). The present study confirmed those observations, nevertheless while Han et al. highlighted a potential protective role of IFP, we hypothesize that this fat pad is influenced by the local inflammation of the OA joint and undergoes fibrotic structural changes. As a matter of fact, OA IFP seems to be different from the other adipose tissue depots of the body since its volume is not influenced by the BMI and its adipocytes do not become hyperthrophic as the body weight increases. Moreover, recent evidence suggests that IFP forms a unique functional unit with synovial membrane and these two tissues undergo similar changes during the OA process (Macchi et al., 2018). Even if different age and BMI can represent a bias of this study, we did not find any correlation between the IFP and SFP volume and age or BMI. Only fair correlations were identified between age or BMI and some MRI morphometric parameters of IFP or SFP. It would be interesting to carry out studies comparing patients with different grade of OA severity matched for age, sex and BMI.

The present study has some limitations. First, the analysis has been conducted in a small sample size and it would be interesting to confirm our observations in a larger population. Second, because of the small sample size, we did not grouped patients according to gender even if it has been reported that men show a significantly higher ratio of IFP volume/body weight than women (Diepold et al., 2015). Nevertheless, the study population was well characterized allowing the evaluation of patient groups with different OA severity comparing them with patients without cartilage defects.

In conclusion, a progressive decrease of IFP depth, femoral and tibial length and an increase of hypointense signal were observed in MRI of moderate and end-stage OA compared to non-osteoarthritic controls suggesting an important role of inflammation derived fibrosis and dimensions in OA pathology. No differences were observed in SFP MRI characteristics between different grade of OA patients and controls suggesting that this fat pad might be not involved in OA at least in terms of volume and 2D dimensions.

Author contributions

The conception and design of the study, or acquisition of data, or analysis and interpretation of data: CGF, EB, MR, GT, EO, VM and MF. Drafting the article or revising it critically for important intellectual content: CGF, EB, MR, EO, GT, PR, AR, AP, AN, RDC, RV, RR, VM and MF. Final approval of the version to be submitted: all authors approved the final version of the manuscript.

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Conflicts of interest

The authors declare no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.aanat.2018.09.007.

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