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SYSTEMATIC REVIEW

Fatty infiltration in the thigh muscles in knee osteoarthritis: a systematic review and meta-analysis

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Abstract

Knee osteoarthritis is a chronic degenerative joint disease, influenced by inflammatory, mechanical and metabolic processes. Current literature shows that thigh muscles of people with knee osteoarthritis can have increased infiltration of fat, both between and within the muscles (inter- and intramuscular fat). The fatty infiltration in the thigh in this population is correlated to systemic inflammation, poor physical function, and muscle impairment and leads to metabolic impairments and muscle disfunction. The objective of this study is to systematically review the literature comparing the amount of fatty infiltration between people with knee osteoarthritis and healthy controls. A literature search on the databases MEDLINE, Embase, CINAHL SPORTDiscuss, Web of Science and Scopus from insertion to December 2018, resulted in 1035 articles, from which 7 met inclusion/exclusion criteria and were included in the review. All included studies analyzed the difference in intermuscular fat and only one study analyzed intramuscular fat. A meta-analysis (random effects model) transforming data into standardized mean difference was performed for intermuscular fat (six studies). The meta-analysis showed a standardized mean difference of 0.39 (95% confidence interval from 0.25 to 0.53), showing that people with knee osteoarthritis have more intermuscular fat than healthy controls. The single study analyzing intramuscular fat shows that people with knee osteoarthritis have more intramuscular fat fraction than healthy controls. People with knee osteoarthritis have more fatty infiltration around the thigh than people with no knee osteoarthritis. That conclusion is stronger for intermuscular fat than intramuscular fat, based on the quality and number of studies analyzed.

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Introduction

Osteoarthritis (OA) is a chronic degenerative joint disease that affects the cartilage and surrounding tissues leading to impairment in physical function during daily activities [1]. Aging, obesity, muscle weakness, sex and trauma are important risk factors for knee OA [2]. Obesity is considered a mechanical and biochemical risk factor for the knee OA; it is also a condition usually seen in people with metabolic syndrome [3, 4]. The metabolic syndrome is characterized by visceral obesity, elevated fasting glucose, hypertension, and dyslipidemia, and has been shown to increase the risk not only of OA but many musculoskeletal diseases [5, 6]. The metabolic syndrome can lead to low-grade systemic inflammation [7, 8], increased joint load due to excessive weight, ultimately having a negative impact in knee OA [9].

Previous researches have focused on obesity due to different explanations on how fat tissue could influence the

development of knee OA [5, 10]. The joint overload due to obesity and overweight is positively associated with knee OA, however, previous studies have shown the association between obesity and hand OA, which leads to the assumption that factors other than mechanical load are linked to OA [11, 12]. It is known that adipose tissue releases systemic factors, adipokines, that can reach and activate joint cells, thus participating in the inflammatory process in OA [3, 13]. In addition, the adipose tissue is a source of systemic inflammatory cytokines with high levels of interleukin-6, tumor necrosis factor-α and C-reactive protein [14–16]. Thus, current literature suggest that fat infiltration in different body tissues could lead to metabolic and functional impairment [17, 18].

Increasingly, studies have shown that the amount of fat tissue and its location in the body can lead to different outcomes [17, 18]. In the skeletal muscle, fatty infiltration can be divided into two major groups: adipose tissue stored within the muscle fibers (intraMAT), and adipose tissue found between muscles and beneath fascia (interMAT) [19, 20]. Both seem to act similarly to abdominal adipose tissue, contributing to the inflammation process [14, 16]. High levels of proinflammatory cytokines in fatty infiltrated muscles are associated with poor muscle function, thus being one of the reasons for the decrease in muscle strength and muscle activation [16, 21].

The inflammatory process also has a negative effect in joint degeneration. The release of cytokines and the increase in the inflammatory process in the muscle tissue could influence the homeostasis of the knee joint cartilage, leading to joint damage and increasing the severity of knee OA [18, 22].

Previous studies have shown that loss of muscle strength in people with knee OA is not proportional to loss of lean mass [23, 24], suggesting that tissues other than muscle are likely to be going through changes when weakness is present. Therefore, the structural composition of the skeletal muscle is an important factor underlying muscle strength and the physical function suggesting that fatty infiltration into skeletal muscle might be related to loss of strength [25, 26].

Despite emerging evidence of the important role that fatty infiltration plays in thigh muscles and its influence in knee OA, the number and quality of studies investigating the association between muscle fatty infiltration and knee OA has not been systematically investigated. Therefore, the aim of this study was to systematically review the evidence comparing fatty infiltration in thigh muscles, that is, inter- and intra-MAT, between healthy people and people with knee OA.

Methods

Registration

This systematic review was registered in the PROSPERO—International prospective register of systematic reviews, under the registration number CRD42016043231 (http://www.crd.york.ac.uk/PROSPERO/).

Eligibility criteria

For the purpose of this review, fatty infiltration was defined as interMAT and intraMAT. To be included in the review, studies had to present data on thigh inter- and/or intraMAT, collected via computed tomography (CT) or magnetic resonance image (MRI) in patients with radiographic and/or symptomatic knee OA and compare it to those of healthy controls. The search had no language or date restrictions. We only included full text papers published in peer-reviewed journals and excluded conference abstracts.
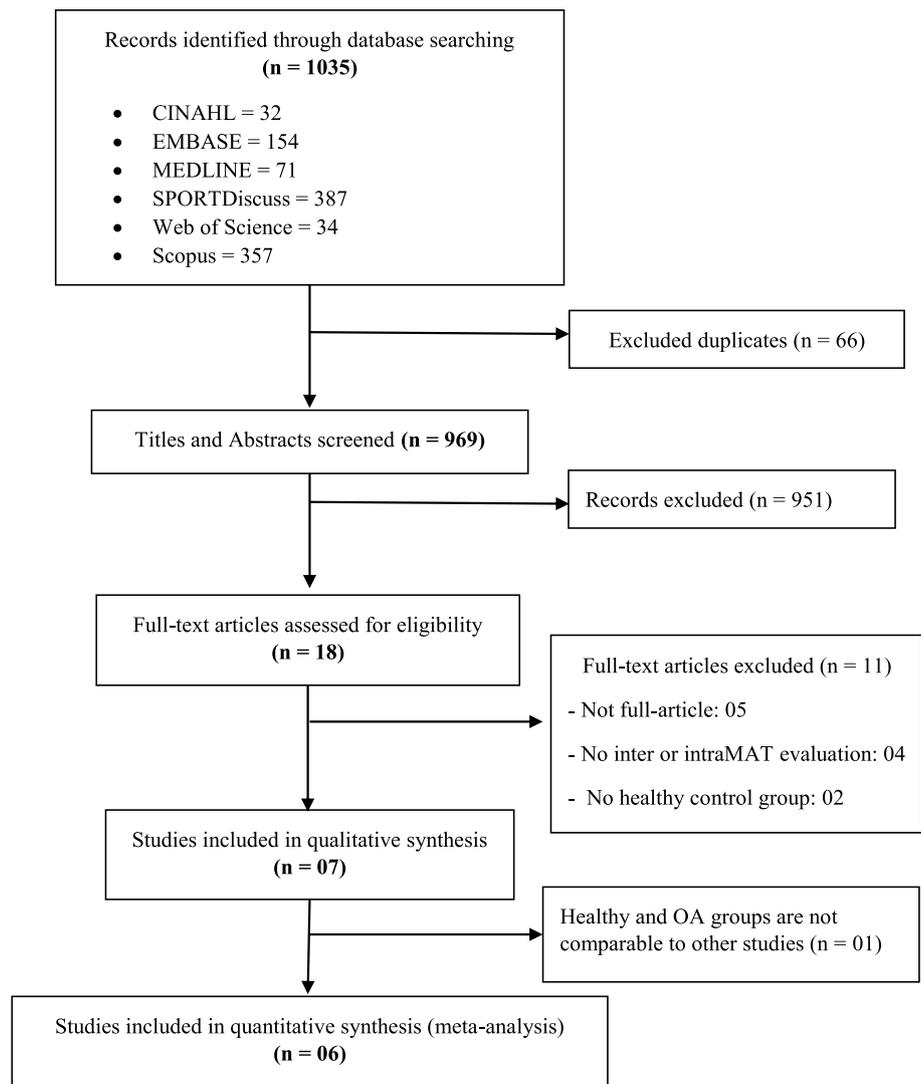
Search strategy

The selected studies for this systematic review were identified from six databases: MEDLINE, Embase, CINAHL, SPORTDiscuss, Web of Science, and Scopus. We also inserted all included studies in Google Scholar and used the tool "cited by". All studies that cited the initially included papers were also screened for potential inclusion. Searches covered studies from the earliest records available until December 2018.

The terms and keywords used for the search were set to identify interMAT and intraMAT in knee OA. The search strategy was adjusted for each database as necessary (Online Appendix A). Four reviewers (MGP, ACA, JBA, and MdN) working in pairs, independently assessed study eligibility and consensus was used to solve disagreements. Articles were first selected based on titles, followed by abstracts and full text. Figure 1 shows the flow chart for selection of studies and describes the reasons for exclusion.

Quality assessment

The eligible studies were assessed for methodological quality using a modified version of the Downs and Black quality assessment tool for randomized and non-randomized studies (Online Appendix B) [27, 28]. Quality assessment was performed by two independent reviewers (MGP and ACA) and any disagreements were resolved by a third reviewer (MDN). The original 27 item scale has a test–retest reliability of $r = 0.88$ and inter-rater reliability of $r = 0.75$. For this

Fig. 1 Flow diagram for search and selection of studies

Records identified through database searching
(n = 1035)

- CINAHL = 32
- EMBASE = 154
- MEDLINE = 71
- SPORTDiscuss = 387
- Web of Science = 34
- Scopus = 357

Excluded duplicates (n = 66)

Titles and Abstracts screened **(n = 969)**

Records excluded (n = 951)

Full-text articles assessed for eligibility
(n = 18)

Full-text articles excluded (n = 11)

- Not full-article: 05

- No inter or intraMAT evaluation: 04

- No healthy control group: 02

Studies included in qualitative synthesis
(n = 07)

Healthy and OA groups are not comparable to other studies (n = 01)

Studies included in quantitative synthesis (meta-analysis)
(n = 06)

systematic review, 7 items were retained for the modified version of the scale, with each item receiving either a "no" (0) or "yes" (1), therefore 7 being the best possible score (Table 1).

Synthesis and data analysis

Demographic and anthropometric data including body mass index (BMI), age, gender, and OA grade were

Table 1 Methodological quality assessment for included studies

Study	1	2	3	4	5	6	7
Ikeda et al. [35]	✓	✓	✓	✓	✓	✓	✗
Beattie et al. [31]	✓	✓	✓	✓	✓	✓	✓
Conroy et al. [29]	✗	✓	✓	✓	✗	✗	✓
Maly et al. [26]	✓	✓	✓	✓	✓	✗	✓
Kumar et al. [20]	✓	✓	✓	✓	✓	✗	✓
Ruhdorfer et al. [33]	✓	✓	✓	✓	✓	✗	✗
Dannhauer et al. [32]	✓	✓	✗	✓	✓	✓	✗

1—description of outcome; 2—description of participants; 3—appropriateness of participants; 4—appropriate statistical analysis; 5—valid and reliable outcome; 6—blinded assessment; 7—sufficient statistical power; ✓ = yes; ✗ = no

collected from all studies. Data related to inter- and intra-MAT were also extracted from all included studies. Only one study presented data for intraMAT [20], therefore it was only possible to conduct a meta-analysis for inter-MAT concentration. For that, data from at least one OA group and one control group for each included study were extracted. For longitudinal studies, the baseline data were used for analysis. One of the selected studies [29] had four different groups of which only two were chosen for meta-analysis: painless non-ROA (subjects with no radiographic osteoarthritis) was used as the control group, and ROA with pain (with radiographic osteoarthritis) was used as the OA Group. The study by Ruhdorfer et al. [33] presented the anthropometric data from OA and control group divided by sex, therefore the data from men and women were combined [30].

Due to the expected variability among included studies, the meta-analysis was run with a random effects model and statistical heterogeneity was analyzed considering the I^2 generated by the RevMan software (Review Manager 5.3, The Nordic Cochrane Centre: Copenhagen, The Cochrane Collaboration, 2014). Due to the different methods used to calculate interMAT concentration (volume and area), means and standard deviations (SD) were transformed into standardized mean differences (SMD).

Results

Study selection

Database search identified 1035 studies, among which 66 were duplicated. After screening of abstracts and titles, 18 studies were assessed for full text eligibility which led to 7 studies being included in qualitative syntheses, and 6 in the meta-analysis Fig. 1. Using the tool "cited by" at Google Scholar, 343 titles that cited the 7 included papers were also screened for potential inclusion, however none was included in the final selection.

Study characteristics

The selected studies were published between 2005 and 2015, and comprised a total of 914 participants, 367 people with knee OA and 547 people without knee OA (Table 2). The assessment of interMAT varied among studies regarding the evaluation method used (CT and MRI) and units of measure (volume and area). The region of the thigh from where data were collected also varied among the studies. In four studies, data was collected from a point 10 cm proximal to the epiphyseal line of the femur [26, 31–33]. For one study, data were collected from a point 14 cm proximal to the superior pole of the patella [20], and for another study the selected

Table 2 Study design, characteristic for included studies, instrument used for image acquisition, and unit used to measure the interMAT content

Author/year	Beattie et al. 2012	Conroy et al. 2012	Dannhauer et al. 2015	Ikeda et al. 2005	Kumar et al. 2014	Maly et al. 2013	Ruhdorfer et al. 2015
Study design	Longitudinal cohort	Longitudinal cohort	Cross-sectional and longitudinal cohort	Cross-sectional	Cross-sectional	Cross-sectional	Longitudinal cohort
Groups	Non-ROA; ROA	Non-ROA with no pain; non-ROA with pain; ROA with no pain; ROA with pain	Discordant pain; discordant osteophyte; discordant JSN, structural progressor vs. non-progressor	Non-ROA; ROA; thirties; sixties	Control; ROA	Non-ROA; ROA	Control; case (OA)
OA K&L grade	0–1; 2–3	≥ 2	2	≥ 2	0–1; > 1	0–1; 2–3	0–1; 2–3
Sample size	41; 45	334; 263; 91; 170	48; 55; 44; 23	11; 6; 21; 17	66; 30	52; 73	43; 43
% Women	100	58; 58; 58; 59	64; 52; 70; 69.5	100	57; 50	100	53.5
Age mean	61; 64	73; 73; 74; 74	63; 61; 64; 63	64; 65; 34; 64	51; 58	61; 65	61; 61
BMI mean	25.6; 29	26; 27; 30; 30	30; 28; 31; 30	21; 20; 21; 21	24; 27	26; 29	28; 28
Image acquisition	MRI	CT	MRI	CT	MRI	MRI	MRI
Unit	cm^3	cm^2	cm^2	cm^2	cm^3	cm^3	cm^2
Quality score	7/7	4/7	5/7	6/7	6/7	6/7	5/7

ROA radiographic osteoarthritis, *non-ROA* non-radiographic osteoarthritis, *OA K&L grade* knee OA grade according to Kellgren and Lawrence criteria (1, 2, 3, or 4), *BMI* bone mass index, *MRI* magnetic resonance image, *CT* computed tomography

area was a point 20 cm proximal to the tibial tuberosity [34]. One of the studies did not report the point from where data were collected [29]. Four studies used data from the same multicenter study, the Osteoarthritis Initiative (OAI) [26, 31–33].

Quality of studies

Overall, the included studies presented good methodological quality, ranging from 4 to 7 points (Table 1). All studies included had a clear description of the main outcome, except for one [29]. Three studies reported that a blinded assessor extracted data on adipose tissue (Table 1). To evaluate the characteristics of participants, the minimum requirement was the description of age, number of participants, type of OA and side(s) affected by OA.

Fatty infiltration

As studies analyzing the difference in interMAT between people with knee OA and healthy controls were similar, it was possible to perform a meta-analysis to compare interMAT concentration for that population. The meta-analysis included 6 studies, 367 people with knee OA and 547 healthy people (Fig. 2). One study was not included in the meta-analysis because the criteria used to define the OA group and the control group were not comparable to the criteria used in the remaining studies [32]. The meta-analysis shows a significantly higher amount of interMAT for the OA group when compared to the control group (SMD 0.39, 95% CI from 0.25 to 0.53). There was no statistical heterogeneity among the studies in the meta-analysis ($I^2 = 0$, Fig. 2). The only study on interMAT not included in the meta-analysis showed that, in a group of subjects that had frequent pain in one knee and no pain in the contralateral knee with similar radiographic results in both knees, only the women with frequently unilateral painful knees had greater interMAT areas ($p = 0.05$) than the contralateral pain free knees [32].

After considering the included studies in the meta-analysis, two sensitivity analyses were performed. For the first sensitivity analysis, we removed one study from the meta-analysis due to the difference in mean BMI between the knee OA group and the control group [29]. For the second sensitivity analysis, we removed three of the four studies which recruited participants from the same source, the OAI, as there was the possibility of an overlap in participants between these studies. When removing only the study by Conroy et al. (2012), the meta-analysis showed an SMD between groups of 0.32 (0.12–0.55), similar to the original meta-analysis [29]. When the study by Conroy et al. (2012) was removed along with the studies by Beattie et al. (2012) and Ruhdorfer et al. (2015), keeping only the largest study that recruited participants from the OAI, the SMD between groups was 0.35 (0.08–0.61), still showing a significant difference [29, 31, 33].

Only one study was found that met our inclusion criteria on the analysis of intraMAT [20]. After adjusting for age, gender, and BMI, there were no difference for intraMAT in thigh (OA $= 258.2 \pm 87.7$ cm^3, Control $= 218.8 \pm 72.0$). Kumar et al., also analyzed the IntraMAT fraction, a techniques for chemical shift-based water/fat separation method, for the thigh muscles reporting larger intraMAT fraction for the knee OA group only for the quadriceps muscle [20, 35].

Discussion

This is the first systematic review and meta-analysis focusing on the analysis of fatty infiltration in thigh muscles in people with knee OA. This study found that people with knee OA have more fatty infiltration, seen by inter- and intraMAT, in thigh muscles than people without knee OA. These findings could have implications for muscle function and muscle strength.

Despite the small amount of eligible studies, the included papers were generally of good quality. The results from the
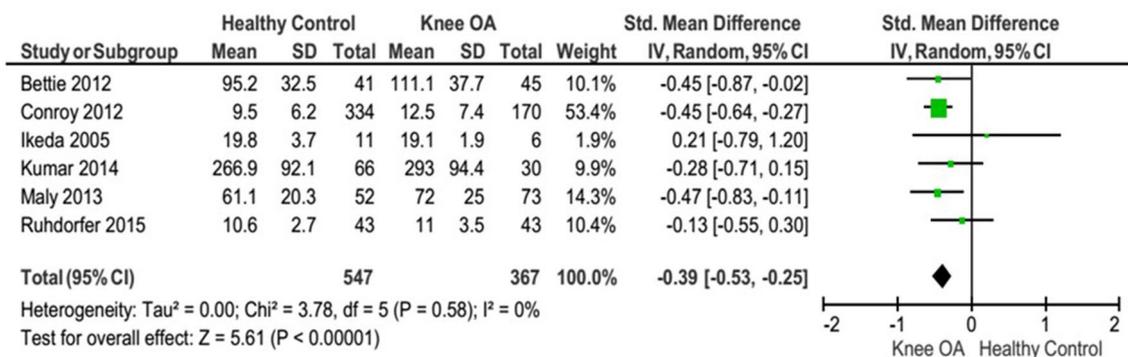

Study or Subgroup	Healthy Control Mean	SD	Total	Knee OA Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bettie 2012	95.2	32.5	41	111.1	37.7	45	10.1%	-0.45 [-0.87, -0.02]
Conroy 2012	9.5	6.2	334	12.5	7.4	170	53.4%	-0.45 [-0.64, -0.27]
Ikeda 2005	19.8	3.7	11	19.1	1.9	6	1.9%	0.21 [-0.79, 1.20]
Kumar 2014	266.9	92.1	66	293	94.4	30	9.9%	-0.28 [-0.71, 0.15]
Maly 2013	61.1	20.3	52	72	25	73	14.3%	-0.47 [-0.83, -0.11]
Ruhdorfer 2015	10.6	2.7	43	11	3.5	43	10.4%	-0.13 [-0.55, 0.30]
Total (95% CI)			547			367	100.0%	-0.39 [-0.53, -0.25]

Heterogeneity: Tau² = 0.00; Chi² = 3.78, df = 5 (P = 0.58); I² = 0%
Test for overall effect: Z = 5.61 (P < 0.00001)

Fig. 2 Comparison of Intermuscular adipose tissue in the thigh between people with knee osteoarthritis (OA) and healthy controls

meta-analysis showed high statistical homogeneity among studies, increasing the confidence in the results. Our analysis is that risk of bias is unlikely to have had any major impact in the overall results of this systematic review, but it should be noted that some studies did not attempt to blind the examiners for the morphometric evaluation of fatty infiltration on thigh muscles.

The meta-analysis showed that people with knee OA had more interMAT content than people without knee OA regardless of BMI. Even when we analyzed only the studies with similar BMI between groups, the difference found between groups was similar to that before the sensitivity analysis. BMI is worldwidely used to measure and quantify obesity, and is considered a risk factor for knee OA [36, 37]. However, the positive relationship between BMI and interMAT is not a consensus among researchers. In overweight and obese elderly men, Zoico et al. (2010) found a significant correlation between interMAT and BMI, weight, waist circumference, fat mass and percentage of fat mass [21]. In contrast, Sowers and Karvonen-Gutierrez (2010) reported that in women with knee OA, the prevalence and the increase in knee OA severity had a stronger association with body composition (the amount of fat mass and muscle mass) than BMI alone [38]. Furthermore, Maly et al. (2013) found a moderate relationship ($r^2 = 0.52$) between BMI and interMAT [26]. Perhaps, future research should consider a more consistent analysis of interMAT, and not only of BMI, as these factors seem to reveal different aspects of the disease.

The meta-analysis also showed minimal change in results when the sample size was decreased due to the exclusion of three studies in the second sensitivity analysis. Even after removing 676 participants from the analysis (74%), the pooled result still showed a larger amount of interMAT in the group with knee OA, reinforcing the original findings that there is in fact a difference between these groups. Another point worth noting is that the age between the groups compared in the meta-analysis was very similar (Table 1), with the majority of subjects around sixties, when the process of changes in skeletal muscles due to aging already is significant [39]. Therefore, the difference seen in interMAT cannot be attributed to aging.

Among all studies included in this review, only one reported intraMAT content in the thigh of people with knee OA showed that the intraMAT fraction was negatively associated with a self-reported functional assessment (Knee Injury and Osteoarthritis Outcome Score—KOOS) and performance-based tests (stair climbing test and the 6 min walk test) [20]. IntraMAT was also positively associated to the severity of knee OA and aging. For a population of older adults, the intraMAT amount was associated with impairment in neuromuscular activation and decreased quadriceps and hamstring strength [40, 41]. Furthermore, Marcus et al.

(2013) found that older people with high and medium intraMAT levels around the thigh had no change in muscle quality (muscle strength relative to unit of muscle mass) after exercise when compared to a similar group in age with low intraMAT levels [42]. Marcus et al. (2013) considered the intraMAT as one possible reason why some older adults do not respond well to strength training [44]. Moreover, future research should consider further evaluating the intraMAT content and its influence in muscle function in people with knee OA.

Among all studies included in the systematic review, only one reported the radiographic severity of participants and investigated the correlation between OA severity and the amount of intraMAT. From the 30 participants in the knee OA group, 20 had a KL score of 2, 16 a KL score of 3, and 4 a KL score of 4. There was a positive, however small, correlation (Kendall' $\tau = 0.25$; $p = 0.001$) between intraMAT fraction and severity [20]. Moreover, Dannhauer et al. (2015) shows an interMAT increase, as well as radiographic OA progression, in women with knee OA after a 2 year follow-up [32]. That result raises the possibility that there could be an increase in fatty infiltration with the increase in knee OA severity, however, a correlation index was not calculated by authors. Therefore, due to lack of data and weak evidence, we cannot conclude that there is a relationship between increase in fatty infiltration and radiographic or symptomatic knee OA severity. Future studies comparing different radiographic and symptomatic severity levels of OA and potential changes in thigh composition could be helpful in understanding whether knee OA severity is affected by fatty infiltration.

The exact pathway that fatty infiltration acts in the skeletal muscle has not been totally clarified. Some authors suggest that the accumulation of lipid in muscle tissue leads to a change in the metabolism due to production of ceramide and consequently synthesis of nitric oxide synthase, creating a toxic environment for muscle contraction [43]. As an endocrine organ, the adipose tissue produces and releases cytokines and adipokines that can stimulate muscle catabolism [44]. In addition, the depot of fat within skeletal muscle fibers can change the fibers orientation, with increase in pennation angle, affecting muscle function [45]. All these physiological changes in the skeletal muscle may negatively influence muscle strength and physical function.

Few studies have evaluated the association between muscle fatty infiltration and changes in muscular and physical function in people with knee OA. Maly et al. (2013) found that high levels of interMAT had a moderate correlation with poor physical function and weakness of quadriceps. However, the IMAT was able to explain only a small part of the variance in physical performance and muscle strength [26]. Kumar et al. (2014) also found a negative correlation between intraMAT fraction and physical performance

during walking in people with knee OA [20]. Furthermore, recently Davison et al. (2017) found no correlation between intraMAT and knee extensor and flexor strength in women with knee OA [25]. Given the lack of studies that aimed to explore the possible influences of fatty infiltration in muscle strength and physical function, and the current controversial results, further studies are necessary to clarify that relationship.

Another aspect that has been somewhat presented in the literature is whether the presence of fatty infiltration is a risk factor for knee OA. Some studies have in fact shown that fatty infiltration is a result of obesity and aging process, which are risk factors for knee OA [14, 21]. However, when BMI, aging and fatty infiltration are evaluated separately, as a predictor for knee OA incidence, BMI and aging are stronger predictors than fatty infiltration alone [31, 46]. Thus, a greater amount of fatty infiltration found in people with knee OA might be a consequence of muscle impairments and systemic inflammation seen in this population. It is known that quadriceps weakness and atrophy found in patients with knee OA are likely the consequence of disuse secondary to joint pain [47]. It is suggested that the quadriceps-specific muscle atrophy is followed by increase in fatty infiltration in the quadriceps muscles [48]. Also, it has been suggested that the systemic inflammation seen in this population is associated with impairment in fatty acid oxidation, which leads to an ectopic fat accumulation in the body, including skeletal muscles [21].

Considering the findings from the current systematic review, people with knee OA have more fatty infiltration and it can lead to muscle impairment, with reduction in muscle strength, muscle quality and muscle activation [20, 26, 29, 31]. The Osteoarthritis Research Society International recommends exercise therapy for management of knee OA, and muscle strengthening must be included [49]. To date, there is no study assessing the effects of exercise on muscle fatty infiltration in people with knee OA. There is evidence that exercise can decrease the fatty infiltration from the thigh muscles in obese and overweight adults, however, these effects from exercise do not seem to have the same effect in the elderly [50, 51] Further studies should be made to understand the effects of exercise in fatty infiltration in knee OA population.

Limitations of the current systematic review are the small number of included studies, perhaps due to the high costs associated with MRI imaging assessment and the radiation exposure in CT scans. Unfortunately, some studies that assessed people with knee OA via MRI and CT scans were excluded due to the lack of a control group, which was essential to answer the question of our review. We were also unable to identify whether thigh fat is a risk factor or a consequence of knee OA, as the studies investigated were not set to answer that question. Furthermore, the lack of details

regarding OA severity prevented a better understanding on whether different knee OA levels are likely to present different levels of inter and intramuscular fat infiltration. Lastly, no studies paired participants from both groups according to BMI and we wonder how it could influence the results of individual studies in a meta-analysis.

Conclusion

Despite the small number of studies found in this systematic review, the evidence shows that people with knee OA have more fatty infiltration in the thigh muscles when compared to healthy people, particularly for interMAT, as intraMAT was only analyzed by one study [20]. Further investigation on fatty infiltration in people with knee OA is important, as it may have implications for muscle quality, strength and physical function.

Compliance with ethical standards

Conflict of interest Maria G. Pedroso declares that she has no conflict of interest. Aline C. de Almeida declares that she has no conflict of interest. Jéssica B. Aily declares that she has no conflict of interest. Marcos de Noronha declares that he has no conflict of interest. Stela M. Mattiello declares that she has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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