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A INFLUÊNCIA DO INFILTRADO DE GORDURA MUSCULAR E DA COMPOSIÇÃO CORPORAL NO CONTROLE POSTURAL EM PACIENTES COM OSTEOARTRITE DE JOELHO

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Se te contentas com os frutos ainda verdes,
toma-os, leva-os, quantos quiseres.
Se o que desejas, no entanto, são os mais saborosos,
maduros, bonitos e suculentos
deverás ter paciência.
Senta-te sem ansiedades.
Acalma-te, ama, perdoa, renuncia,
medita e guarda silêncio.
Aguarda.
Os frutos vão amadurecer

- José Hermógenes de Andrade Filho –

RESUMO

Objetivos: O objetivo desta tese foi investigar a quantidade de infiltrado de gordura na coxa e no tronco e sua associação com controle postural e capacidade funcional em pessoas com osteoartrite (OA) de joelho. Assim, foram realizados três estudos: Estudo I: Infiltrado de gordura nos músculos da coxa na OA de joelho: uma revisão sistemática e meta-análise; Estudo II: Infiltração de tecido adiposo na coxa de pacientes com OA de joelho influencia mudanças no controle postural; Estudo III: Relação entre composição do tronco e capacidade funcional em indivíduos não obesos com OA de joelho. **Métodos:** No estudo I, a revisão sistemática foi realizada por buscas em bases de dado científica. A qualidade metodológica dos artigos selecionados foi realizada por meio do *checklist* de Downs e Black e a meta-analise pelo software RevMan. Nos estudos II e III, foram avaliados 27 indivíduos com OA de joelho, entre 40 a 65 anos de idade, pareados por idade e índice de massa corporal com 22 indivíduos sem OA de joelho. A composição da coxa e do tronco foi avaliada por tomografia computadorizada segmentadas em: gordura subcutânea, intermuscular, músculo e infiltrado de gordura muscular. No estudo II, o controle postural foi avaliado por plataforma de força, onde os indivíduos permaneceram em postura ortostática em superfície firme e macia com olhos abertos e fechados. As diferenças entre os grupos para as variáveis do controle postural foram testadas por meio de teste T e Man-Whitney. A composição da coxa foi avaliada por meio de MANCOVA. A correlação de Spearman foi utilizada para avaliar a correlação entre a composição da coxa e os parâmetros do controle postural. A influência do infiltrado de gordura da coxa no controle postural foi avaliada por meio de análise de regressão linear múltipla. No estudo III, a média da atenuação muscular foi utilizada como medida de infiltrado de gordura muscular. A capacidade funcional foi avaliada por meio de testes funcionais de sentar e levantar da cadeira, caminhada de 40 metros e subida e descida de escada. As diferenças entre os grupos para a composição do tronco foram avaliadas por meio do teste de MANCOVA, e teste T para desempenho físico. O teste de correlação de Pearson foi usado para avaliar a correlação entre a composição do tronco e o desempenho físico. **Resultados:** No estudo I 7 foram selecionados para revisão sistemática e 6 incluídos na meta-análise. A variável em comum entre os estudos foi a gordura intermuscular. Os estudos foram de boa qualidade e a meta-analise mostrou que pessoas com OA de joelho possuem maior quantidade de gordura intermuscular do que indivíduos saudáveis, mostrado por uma diferença padronizada das médias de 0,39 (IC 95% de 0,25 a 0,53). No estudo II indivíduos com OA de joelho apresentaram maior quantidade de infiltrado de gordura muscular e essa gordura foi capaz de explicar 52% da variabilidade do controle postural de pessoas com OA de joelho. No Estudo III encontramos que indivíduos com OA de joelho apresentam maior área de gordura subcutânea e intermuscular, menor área muscular e maior infiltrado de gordura muscular no tronco. O infiltrado de gordura muscular apresentou correlação com o desempenho físico. **Conclusão:** Os resultados apontam que indivíduos com OA de joelho possuem maior infiltrado de gordura na musculatura da coxa e do tronco. O acúmulo de infiltrado e de gordura na coxa pode explicar parte da redução do controle postural apresentado pelos indivíduos com OA de joelho, enquanto que o acúmulo de gordura no tronco é associado com a diminuição da capacidade funcional dessa população.

Palavras-chave: Artrite. Composição corporal. Equilíbrio. Capacidade Funcional. Tecido Adiposo

ABSTRACT

Objectives: The aim of this thesis was to investigate the amount of fat infiltrate in the thigh and trunk and its association with postural control and functional capacity in people with knee osteoarthritis (OA). Thus, three studies were performed: Study I: Fatty infiltration in thigh muscles in knee osteoarthritis: a systematic review and meta-analysis; Study II: Infiltration of adipose tissue in the thigh of patients with knee osteoarthritis influences changes in postural control; Study III: Relationship between trunk composition and physical function in non-obese individuals with knee osteoarthritis. **Methods**: In the first study, the systematic review was performed by searching in scientific databases The methodological quality of the articles selected was assessed by Downs and Black checklists and the meta-analysis was performed through RevMan software. For study I and II, twenty-seven non-obese subjects with knee OA, aged 40-65 years were matched by age and BMI with twenty-two individuals without knee OA. The thigh and trunk composition was evaluated by computed tomography, segmented into: subcutaneous fat, intermuscular fat and muscle. Muscle attenuation was used to evaluate the muscular fatty infiltration. In study II; the postural control was evaluated through a force platform, where the subjects remained in orthostatic in a firm surface with open and closed eyes and in a soft surface with open and closed eyes. The differences between groups for the postural control variables were tested by Student's test and Man-Whitney. The thigh composition was evaluated by MANCOVA. Spearman's correlation was used to evaluate the correlation between thigh composition and postural control parameters. The influence of thigh fat infiltrate on postural control was assessed by multiple linear regression analysis. In study III, the muscle attenuation mean was used to measure the muscular fatty infiltration; the physical function was assessed through the sit-to-stand, 40 m walk, and stair climbing tests. The differences between the groups for the trunk composition variables were evaluated using the MANCOVA test, while the physical performance was evaluated by Student's test. A Pearson correlation test was performed to evaluate the correlation between trunk composition and physical performance. **Results:** In study I, 7 studies were selected for systematic review and 6 were included in the meta-analysis. The common variable of all studies was intermuscular fat. The studies were of good quality, and the meta-analysis showed that people with knee OA have greater amounts of intermuscular fat than healthy individuals, as shown by a standardized difference of averages of 0.39 (95% CI 0.25 to 0.53). In study II we found that individuals with knee OA had a greater amount of muscle fat infiltration. The muscle fatty infiltration was able to explain up to 52% of the variability of the postural control of people with knee OA. In Study III we found that individuals with knee OA have a greater cross-sectional area of subcutaneous fat, intermuscular, muscle fat infiltration and smaller muscle area in the trunk. Among the components of the trunk composition, the muscular fatty infiltration showed a greater correlation with the performance in the physical function tests. **Conclusion**: The results indicate that individuals with knee OA have greater fat infiltration in the musculature of the thigh and trunk. The accumulation of fat infiltration in the thigh may explain part of the decrease in postural control presented by individuals with knee OA, whereas the accumulation of fat in the trunk is associated with the deficit of the physical function of this population

Keyword: Arthritis. Body composition. Balance. Physical function. Adipose tissue

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CONTEXTUALIZAÇÃO

Essa tese foi desenvolvida com o intuito de revisar e avaliar os achados científicos na temática de infiltrado de gordura na musculatura da coxa e osteoartrite de joelho, investigar sua associação com o controle postural e avaliar também a associação entre o infiltrado de gordura muscular no tronco e a capacidade funcional em pacientes com osteoartrite de joelho. Uma vez que a osteoartrite é uma das doenças crônicas musculoesqueléticas que mais cresce no mundo, levando ao declínio da função física, consideramos que o melhor entendimento da doença e consequências é uma temática relevante no âmbito da saúde pública.

A dor, rigidez articular e o processo inflamatório crônico encontrados em pacientes com osteoartrite de joelho levam a alterações dos tecidos articulares, como cartilagem, tecido ósseo e capsula articular, assim como altera os tecidos periarticulares como ligamentos e músculos. Todas essas alterações levam ao prejuízo da função física do paciente e consequente piora da qualidade de vida. Dificuldade em realizar atividades físicas do dia a dia como caminhar, sentar-se e subir e descer escadas são frequentemente relatadas pelos pacientes e, com a piora dos sintomas e progressão da doença, podem levar a perda da dependência física. Além dessas alterações, alguns estudos apontam para a diminuição do controle postural em pessoas com osteoartrite de joelho. O controle postural é a integração dos sistemas nervoso, sensorial e motor que trabalham em sincronia para manutenção da postura adotada, sendo essencial para a manutenção do equilíbrio corporal estático e dinâmico. Alterações no controle postural podem levar a um maior risco de queda desses indivíduos. A literatura aponta como possíveis causas das alterações do controle postural em indivíduos com osteoartrite de joelho: a diminuição da propriocepção da articulação do joelho e tecidos peri-articulates e a fraqueza da musculatura do quadríceps.

Nessa temática, pesquisas recentes mostram que o acúmulo de gordura no tecido muscular pode exercer papel importante na diminuição da força muscular. Maiores quantidades de gordura infiltrada na musculatura da coxa parecem estar associadas a pior desempenho físico e força muscular em pacientes com OA de joelho. Sugere-se que esse tecido gorduroso possa estar associado a ampliação do processo inflamatório local e sistêmico, alterações no metabolismo e nas fibras musculares. Por fim, o infiltrado de gordura na musculatura do tronco tem sido associado a diminuição do desempenho físico e aumento do risco de quedas em idosos, porém ainda não foi explorado na população com OA de joelho.

Dessa forma, esta tese reuni três estudos que visam avaliar o infiltrado de gordura muscular em pacientes com OA de joelho e seu impacto no controle postural e capacidade funcional. O primeiro estudo reuni evidências da literatura por meio de uma revisão sistemática e meta-análise sobre o infiltrado de gordura muscular na coxa dessa população. O segundo estudo reuni dados sobre influência do infiltrado de gordura da musculatura da coxa no controle postural em pacientes com OA de joelho. Por fim o terceiro estudo reuni evidências sobre a associação entre o infiltrado de gordura na musculatura do tronco e a capacidade funcional em pacientes com OA de joelho.

Assim, os resultados desta tese fornecem um maior entendimento sobre a influência do infiltrado de gordura muscular nas disfunções físicas de pacientes com OA de joelho, podendo contribuir para ampliar os horizontes da prática clínica.

2 REVISÃO DA LITERATURA

A osteoartrite (OA) é a forma mais comum de doença articular, com um grande impacto na qualidade de vida dos pacientes e altos custos na assistência médica (JOHNSON; HUNTER, 2014; MCALINDON et al., 2014). Estima-se que 20 a 30% da população mundial acima de 60 anos até 2030 apresentará OA (CROFT, 2005). Caracteriza-se pela degeneração articular progressiva, formação de osteófitos marginais e esclerose do osso subcondral (FELSON et al., 2000). O diagnóstico de OA tem sido realizado com base nos critérios clínicos recomendados pelo *American College of Rheumatology* (2000) e nos achados radiológicos descritos por Kellgren and Lawrence, os quais avaliam a severidade da doença (KELLGREN; LAWRENCE, 1957; FELSON; CHAISSON, 1997). Os principais sintomas são dor e rigidez articular que interferem nas atividades de vida diária dos pacientes, diminuindo sua independência de forma progressiva (LIIKAVAINIO et al., 2008). A OA é uma doença multifatorial e, dentre os fatores de risco associados à OA de joelho, a obesidade se destaca como um dos mais importantes devido sua contribuição mecânica, por meio da sobrecarga articular, e metabólica por meio da produção e liberação de fatores inflamatórios e adipocinas (POTTIE et al., 2006).

O tecido adiposo produz e libera adipocinas que levam ao catabolismo de condrócitos podendo ser a principal ligação entre obesidade e OA (FRANCISCO et al., 2017). Dentre as adipocinas, a leptina e a adiponectina são as mais exploradas dentro da OA de joelho (WANG et al., 2015; TANG et al., 2018; YAN et al., 2018). A leptina sérica é positivamente correlacionada com índice de massa corporal (IMC), massa de gordura e peso corporal (VUOLTEENAHO et al., 2014). Na OA, a leptina aumenta a expressão de interleucina-1beta, interleucina-6 e fator de necrose tumoral-alfa, considerados citocinas pró-inflamatórias centrais na OA envolvidos no catabolismo da cartilagem articular contribuindo para o risco de desenvolvimento e progressão da OA de joelho (TU et al., 2019(KARVONEN-GUTIERREZ et al., 2016).

Já a adiponectina é a adipocina encontrada em maiores níveis circulantes, sendo que indivíduos com OA possuem maiores níveis séricos comparados com indivíduos saudáveis, se correlacionando positivamente com severidade radiográfica da OA (CUZDAN COSKUN et al., 2017), dor, desconforto e incapacidade física (FIORAVANTI et al., 2011). Os níveis de adiponectina encontrados na articulação e séricos foram positivamente correlacionados com biomarcadores de degradação de cartilagem, além de estimularem a liberação de fatores pró-inflamatórios envolvidos na degradação da matriz cartilaginosa da articulação com OA (TU et al., 2019).

Alterações físicas e funcionais como diminuição de força muscular, propriocepção e controle postural, são algumas consequência da OA de joelho (O’REILLY et al., 1998; HORTOBÁGYI et al., 2004). Capacidade funcional é resultado da relação entre saúde física, mental e independência, estando relacionada à habilidade de se movimentar e de realizar atividades diárias (FIEDLER; PERES, 2008). Sua análise é complexa e abrange, dentre outras analises, o desemprenho funcional em de atividades físicas diárias (BARBOSA et al., 2014). A dor na OA de joelho ocorre principalmente durante o movimento articular e durante atividades físicas diárias levando a incapacidades físicas desses pacientes (DAVISON et al., 2014). A avaliação da função física pode feita por meio de testes funcionais tais quais recomendados pela *Osteoarthritis Research Society International* (OARSI). Dentre os testes de caminhada, o teste de caminhada rápida de 40 metros é o mais indicado para avaliação na OA de joelho (DOBSON et al., 2013). Para realização da caminhada rápida é necessária a integração de várias estruturas e funções corporais, força de membros inferiores, capacidade aeróbica e equilíbrio (MIDDLETON et al., 2015). A atividade de sentar e levantar da cadeira é uma das demandas mais frequentes dentre as atividade de vida diária (SCHENKMAN et al., 1990), exigindo grande atividade muscular do quadríceps, mas também é dependente de velocidade e equilíbrio (LORD et al., 2002). Por fim, a atividade de subir e descer escadas é uma das mais desafiadoras no dia a dia dos indivíduos com OA de joelho, pois exige grandes momentos da articulação do joelho (ASAY et al., 2009), além de grande demanda de força, potência e amplitude de movimento (REID et al., 2007). Os testes de capacidade funcional são ótimas ferramentas clínicas e cientificas para avaliação da função física por serem de fácil aplicação e terem boa reprodutibilidade.

A manutenção do controle postural é essencial para realização das atividades da vida diária e as alterações estruturais e sistêmicas provocadas pela OA podem levar ao prejuízo dessa função, aumentado assim o risco de quedas (LYYTINEN et al., 2010). Na postura ortostática, o controle postural depende de informações dos sistemas sensorial (visual, somatossensorial e vestibular) e motor integrados pelo sistema nervoso central e periférico (FITZPATRICK; MCCLOSKEY, 1994; HORAK, 2006; HUE et al., 2007). O sistema sensorial é responsável por informações relacionadas ao posicionamento dos segmentos corporais em relação ao ambiente e aos outros segmentos, enquanto que o sistema motor é responsável pela ativação muscular necessária para realização do movimento adequado (DUARTE; FREITAS, 2010). A propriocepção periférica envolve vários receptores sensoriais, inclusive os mecanorreceptores da articulação sinovial, que são importantes nos movimentos extremos da articulação, por detectar o alongamento de ligamentos e tecidos profundos da articulação (HASSAN et al., 2001). A alteração de um ou mais sistemas involvidos no controle postural pode levar a alterações na postura e consequente prejuizos nas capacides funcionais. Alguns estudos reportam que sujeitos com OA de joelho possuem alteração da propriocepção do joelho e diminuição da força do músculo quadríceps (HURLEY, 1997; HASSAN et al., 2001) quando comparados com sujeitos sem OA da mesma idade. Essas alterações dos componentes sesorio motores podem levar a alterações no controle postural dos sujeitos com OA de joelho (MASUI et al., 2006; HIRATA et al., 2013).

O controle postural pode ser avaliado em exame de posturografia, por meio de uma plataforma de força, que analisa a oscilação postural qualitativamente e quantitativamente, baseada no padrão de oscilação e mudanças no centro de gravidade dentro da base de suporte (DUARTE; FREITAS, 2010). A plataforma de força registra forças de reação do solo projetadas pelo corpo durante a oscilação postural (PALMIERI et al., 2002). As forças de reação do solo são registradas nos eixo anteroposterior, mediolateral e vertical e então o centro de pressão é calculado (DUARTE; FREITAS, 2010). O comportamento do centro de pressão pode ser avaliado por diversas variáveis, como a amplitude de deslocamento a velocidade de deslocamento anteroposterior e mediolateral ou mesmo a área de deslocamento (DUARTE; FREITAS, 2010). A avaliação do controle postural pode ser realizada em posturas dinâmicas, enquanto realiza-se um movimento, ou estáticas onde se avalia a habilidade de manter o equilíbrio em várias situações em que os diferentes sistemas (sensorial, motor ou nervoso) são manipulados (PALMIERI et al., 2002; TAKACS et al., 2013). .

Alterações neuromusculares e diminuição da capacidade funcional em diversas populações, como idosos, portadores de diabetes tipo 2, obesos e artrite reumatoide, tem sido associadas também à presença de infiltrado de gordura no músculo esquelético (ADDISON et al., 2014; KHOJA et al., 2018). Esse infiltrado de gordura pode ser observado tanto dentro das fibras e células musculares (gordura intramuscular) quanto ao redor da fáscia muscular, acumulando-se entre os grupos musculares (gordura intermuscular) (ADDISON et al., 2014). A avaliação do infiltrado de gordura tem sido realizado em diversas musculaturas, como musculatura da coxa, panturrilha e tronco (DANNHAUER et al., 2015; DAVISON; MALY; ADACHI; et al., 2017; HICKS et al., 2018).

Em indivíduos com OA de joelho, musculatura da coxa, principalmente os músculos extensores do joelho, é a mais explorada pois acredita-se que o infiltrado de gordura nessa localidade está relacionado a alterações neuromusculares, como fraqueza do músculo quadríceps, frequentemente observados nessa população (MALY et al., 2013; KUMAR et al., 2014). Maly et al. (2013), mostraram que mulheres com OA de joelho possuem maior quantidade de gordura intermuscular na coxa quando comparadas com mulheres sem OA, e observou uma correlação negativa desse infiltrado de gordura com o desempenho físico e força muscular dos extensores de joelho (MALY et al., 2013; KUMAR et al., 2014). Do mesmo modo, Kumar et al. (2014) encontraram que a fração de gordura intramuscular da coxa foi negativamente associada a função física auto relatada e mensurada, além de associação negativa com o grau de severidade. Porém, DAVISON et al. (2017) não encontraram correlação entre infiltrado de gordura na região da coxa (gordura intramuscular) com capacidade funcional, força ou potência muscular na população com OA de joelho.

A musculatura do tronco tem recebido atenção crescente como parte importante do tratamento de lesões de membros inferiores (ZAZULAK et al., 2007; MYER et al., 2008). Em mulheres com síndrome femoropatelar, a inclusão de exercícios que fortalecem a musculatura do tronco junto ao fortalecimento padrão de membros inferiores se mostrou eficiente na redução dos sintomas da doença, assim na melhora de parâmetros biomecânicos e força muscular (BALDON et al., 2014). Em pacientes com OA de joelho, a realização de exercícios de fortalecimento e recrutamento da região do tronco junto com fortalecimento de membros inferiores se mostrou eficiente na melhora dos sintomas e força muscular dos membros inferiores (SELISTRE et al., 2017)

O infiltrado de gordura na região do tronco tem sido associado com declínio da função física e aumento do risco de queda em idosos (HICKS et al., 2005; GRANACHER et al., 2013). Em um estudo que avaliou 1152 adultos, idade média de 66 anos, maior concentração de infiltrado de gordura no músculo paraespinhal foi associado com menor velocidade de marcha, indicando que o infiltrado de gordura está associado com diminuição da mobilidade (THERKELSEN et al., 2016). Postula-se que um menor controle neuromuscular da musculatura do tronco pode aumentar o momento adutor do joelho, aumentando assim a carga articular (HEWETT; MYER, 2011).

Existem alguns possíveis mecanismos que podem explicar a associação entre o aumento de infiltrado de gordura muscular e as alterações musculares e funcionais. O deposito de gordura intramuscular na coxa pode levar à alteração do ângulo de penação sem aumento do número de fibras contráteis, diminuindo assim a capacidade de geração de força pela musculatura (MEYER et al., 2004). O depósito de gordura intramiocelular também compromete o metabolismo muscular, levando à resistência à insulina e formação de produtos associados à produção de oxido nítrico, culminando em um processo de lipotoxicidade (COEN; GOODPASTER, 2012).

Tendo em vista a influência negativa que o infiltrado de gordura muscular apresenta na atividade motora musculoesquelética e suas consequências no declínio da função física, a proposta desse estudo foi avaliar a influência da composição corpora e do infiltrado de gordura da coxa no controle postural de pessoas com OA de joelho. Considerando o processo inflamatório presente na OA assim como na presença de gordura localizada e sistêmica de tecido adiposo e a possível liberação de citocinas inflamatórias pela IMAT, sugerimos que a soma desses processos inflamatórios poderia agir nos receptores articulares e musculares, inibindo a ação do neurônio motor e, afetando assim a musculatura periarticular do joelho levando a alterações neuromusculares e alteração do controle postural. Além disso, sugeriu-se que esses processos inflamatórios estariam associados ao o metabolismo da cartilagem articular, acentuando o processo degenerativo deste tecido.

A necessidade de formular condutas de tratamento para indivíduos com OA de joelho, com embasamento nas alterações metabólicas, composição corporal e funções físicas, torna essa proposta de estudo justificada. Por esta razão, torna-se importante a realização de mais estudos envolvendo a quantificação e analise dos tecidos adiposo e muscular e suas consequências no tecido articular e nas funções físicas como o controle postural. A prevenção de agravos consequentes à OA também é de suma importância para a qualidade de vida dos indivíduos com OA de joelho. Assim, a análise do controle postural e suas possíveis alterações, ajudam a formular propostas de intervenções a fim de minimizar os riscos de queda por essa população.

3. OBJETIVOS DA TESE

Por meio de três estudos, os objetivos desta tese foram:

- Avaliar, por meio de uma revisão sistemática e meta-analise, se indivíduos com osteoartrite de joelho apresentam maior quantidade de infiltrado de gordura na musculatura da coxa quando comparado com indivíduos saudáveis e quais as evidencias científicas sobre essa diferença.
- Investigar se existe correlação entre o infiltrado de gordura da coxa e o controle postural em indivíduos com osteoartrite de joelho.
- Avaliar o infiltrado de gordura na musculatura do tronco em indivíduos com osteoartrite de joelho e sujeitos saudáveis.
- Avaliar se existe correlação entre os músculos do tronco e o infiltrado de gordura nesses músculos com a capacidade funcional de indivíduos com osteoartrite de joelho.

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5. Manuscrito I

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

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ABSTRACT

Background: 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 dysfunction.

Objective. To systematically review the literature comparing the amount of fatty infiltration between people with knee osteoarthritis and healthy controls.

Methods. 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 (6 studies).

Results. 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. **Conclusion**. People with knee osteoarthritis have more fatty infiltration around the tight 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.

Keywords: arthritis; adipose tissue; fat distribution; body composition; muscle fat;

1. INTRODUCTION

Osteoarthritis (OA) is a chronic degenerative joint disease that affects the cartilage and surrounding tissues leading to impairments 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 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 intraMAT, between healthy people and people with knee OA.

2. 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-review journals and excluded conferences 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 (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 of 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

(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 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 (**Table1)**.

2.1 Synthesis and data analysis

Demographic and anthropometric data including Body Mass Index (BMI), age, gender, and OA grade were collected from all studies. Data related to inter and intraMAT 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 interMAT concentration. For that, data from at least one OA group and one control group for each included study was 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 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).

3. RESULTS

Study Selection

Database search identified 1035 studies, which 66 were duplicated. After screening of abstracts and titles, 18 studies were assessed for full text eligibility which lead 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 seven included papers were also screened for potential inclusion, however none was included in the final selection.

Table 1. Methodological quality assessment for included studies

Study	1.	2.	3.	4.	5.	6.	7.
Ikeda et al, 2005	√	√	√	√	√	√	*x*
Beattie et al, 2012	√	√	√	√	√	√	√
Conroy et al, 2012	*x*	√	√	√	*x*	*x*	√
Maly et al, 2013	√	√	√	√	√	*x*	√
Kumar et al, 2014	√	√	√	√	√	*x*	√
Ruhdorfer et al, 2015	√	√	√	√	√	*x*	*x*
Dannhauer et al, 2015	√	√	*x*	√	√	√	*x*

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; *x* = no;

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 was collected also varied among the studies. In 4 studies, data was collected from a point 10 cm proximal to the epiphyseal line of the femur [26,31–33]. For one study, data was collected from a point 14 cm proximal to the superior pole of the patella [20], and for another study the selected area was a point 20 cm proximal to the tibial tuberosity [34]. One of the studies did not report the point from where data was collected [29]. Four studies used data from the same multicenter study, the Osteoarthritis Initiative (OAI) [26,31–33].

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 non-pain; non-ROA with pain; ROA non-pain; ROA with pain	Discordant pain; Discordant osteophyte; Discordant JSN, Structural progressor vs nonprogressor	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

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 was collected also varied among the studies. In 4 studies, data was collected from a point 10 cm proximal to the epiphyseal line of the femur [26,31–33]. For one study, data was collected from a point 14 cm proximal to the superior pole of the patella [20], and for another study the selected area was a point 20 cm proximal to the tibial tuberosity [34]. One of the studies did not report the point from where data was collected [29]. Four studies used data from the same multicenter study, the Osteoarthritis Initiative (OAI) [26,31–33].

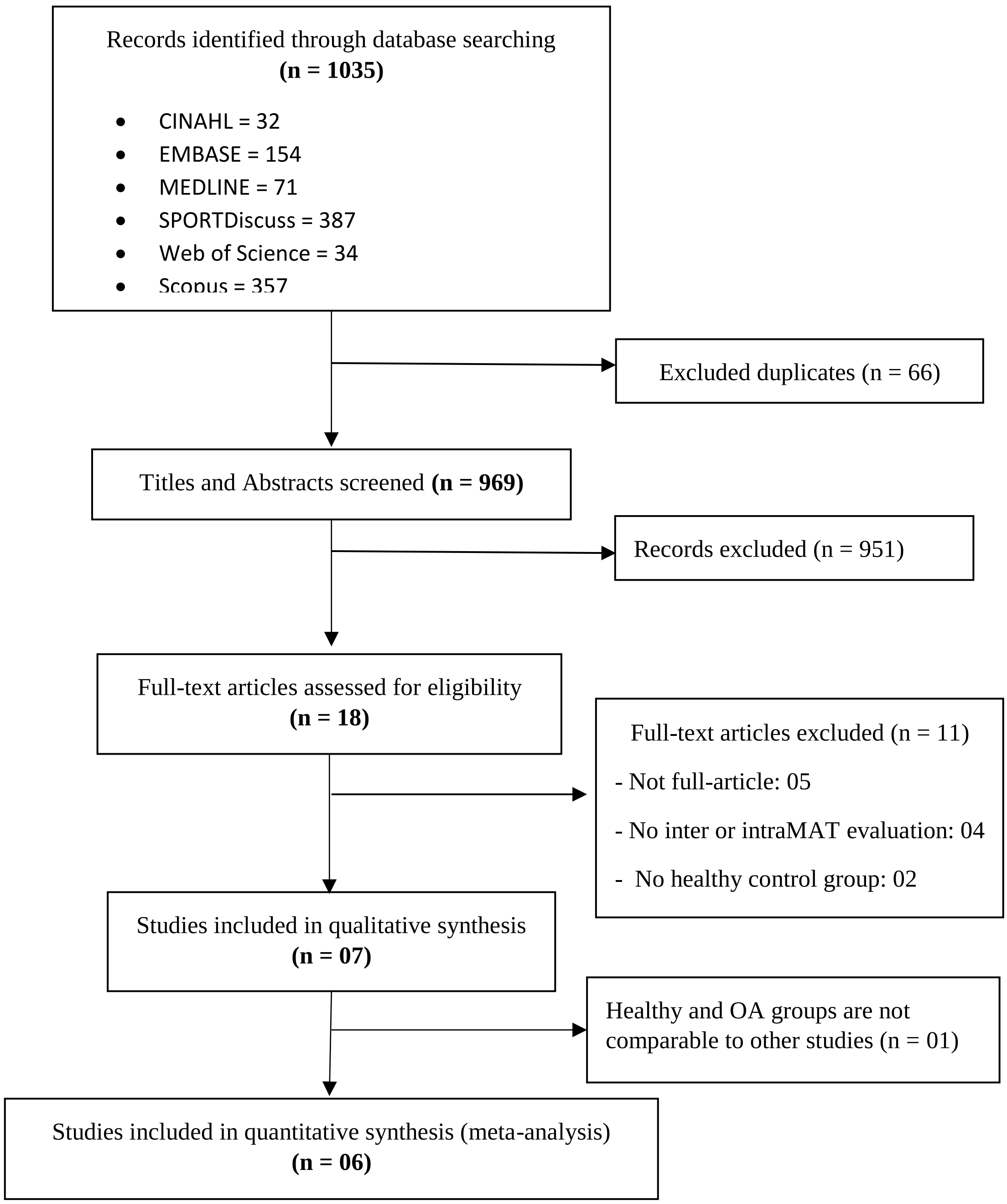

Figure 1 Flow diagram for search and selection of studies.

Quality of Studies

Overall, the included studies presented good methodological quality, ranging from 4 to 7 points **(Table 1)**. All studies included had 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 six 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 significant 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, for a group of subject 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 to 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 to 0.61), still showing a significant different [29,31,33].

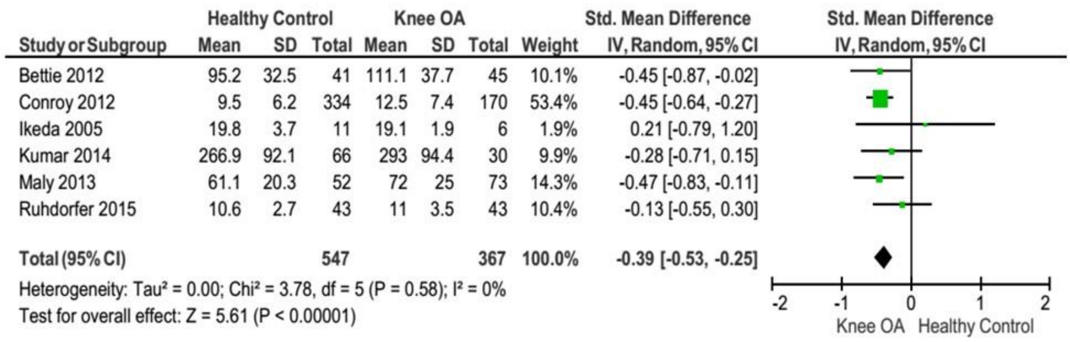

Figure 2. *Meta-analysis for intermuscular adipose tissue between knee OA subjects and healthy controls*

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 ± 87.7 cm^3, Control = 218.8 ± 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].

4. 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 to muscle function and muscle strength.

Despite the small amount of eligible studies, the included papers were generally of good quality. The results from the 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 world widely 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 significant correlation between interMAT and BMI, weight, waist circumference, fat mass and percentage of fat mass [21]. In contrast, Sowers & Karvonen-Gutierrez (2010) reported that in women with knee OA the prevalence and the increase in knee OA severity had 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 are significant [39]. Therefore, the difference seem 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, showing that 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 minute 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 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' τ

= 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 have 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 an aging are stronger predictors than fatty infiltration alone [31,46]. Thus, 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 impairments 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 muscles impairments, with reductions 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.

5. 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 to muscle quality, strength and physical function.

COMPLIANCE WITH ETHICAL STANDARDS

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ETHICAL APPROVAL

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

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6. Manuscrito II

Infiltration of adipose tissue in the thigh of patients with osteoarthritis influences changes in postural control.

Artigo submetido ao periódico Clinical Biomechanics

ABSTACT

Background**:** The deposit of adipose tissue around and within skeletal muscle has been associated with a decrease in muscle strength and in physical function in knee osteoarthritis populations. Impairments in postural control are related to risk of fall in knee OA population. The aim of this study was to evaluate the influence of fat infiltration in thigh muscles on the postural control of people with knee osteoarthritis.

Methods**:** A total of twenty-seven non-obese knee osteoarthritis patients and twenty-two non-obese healthy controls were evaluated. The % body fat was assessed by dual-energy X-ray absorptiometry scan. Thigh composition (muscle, subcutaneous fat, intermuscular fat and low-attenuation muscle was assessed through computed tomography scans. All subjects underwent a balance test on a force plate in four conditions: standing in firm and soft surfaces with eyes open and closed. The center of pressure area sway, *root mean square* and velocity for anteroposterior and mediolateral displacement were calculated.

Findings**:** The knee osteoarthritis group had more low-attenuated muscle than the control group ($p = 0.011$) and greater COP sway area in all conditions ($p < 0.05$). There was a moderate correlation between low-attenuated muscle and postural control variables in the knee osteoarthritis group. A multiple regression showed that low-attenuated muscle explained about 50% of the area sway in absence of vision, while % body fat was not statistically significant as predictor.

Interpretation**:** Greater fat infiltration within muscles from the thigh, rather than whole body fat, is associated to poor postural control in people with knee osteoarthritis.

Keywords: balance; fatty infiltration; arthritis, body composition; skeletal muscle;

1. INTRODUCTION

The increase in adipose tissue and decrease in skeletal muscle tissue is related to aging and chronic diseases (GOODPASTER et al., 2006; DELMONICO et al., 2009) and it is associated with poor muscle strength, physical function, and decrease in functional independence (STEFANO et al., 2015). The presence of infiltrated fat in skeletal muscles has been associated with local and systemic inflammation in overweight and obese elderly (ZOICO et al., 2010). Knee osteoarthritis (OA) is a degenerative joint disease that has obesity and aging as strong risk factors for disease incidence and progression (ANDRIACCHI et al., 2015). In addition, it is well known that the inflammation has an important role in disease pathogenesis process (ATTUR et al., 2015).

The adipose tissue has a key role in OA cartilage damage, as it is an important source of proinflammatory factors, such as adipokines and cytokines, which act in chondrocyte metabolism (AZAMAR-LLAMAS et al., 2017). Adipokines, specially leptin, are associated with the decrease in chondrogenesis and with an increase in osteogenesis in cartilage progenitor cells (URBAN; LITTLE, 2018). Therefore, high levels of fat infiltration, and not only total body fat, might be an important link between knee OA, inflammation and muscle impairments.

Through image acquisition equipment, such as computed tomography (CT), it is possible to identify and quantify different tissues according to their density (GOODPASTER, BRET H et al., 2000). The acquired images allow the quantitation of the fat infiltration in skeletal muscle by two major depots: the fat tissue found between the muscle known as intermuscular adipose tissue (interMAT); and fat tissue within the muscle, classified as intramuscular adipose tissue or low attenuation muscle (LAM) (GOODPASTER, B H et al., 2000; ADDISON et al., 2014).

The accumulation of fat infiltration in skeletal muscle tissue has been explored as an important influencing factor of muscle weakness and impairments in physical performance in healthy elderly and knee OA population (MARCUS et al., 2010; SCHAAP et al., 2013; MALY et al., 2013; KUMAR et al., 2014). Previous studies with knee OA population, found that quadriceps muscle volume was unrelated with knee extensor strength, OA symptoms and severity, while interMAT was negatively correlated with strength and physical performance (MALY et al., 2013; KUMAR et al., 2014). In older adults, the fat infiltration was inversely related to central activation resulting in low muscle force (YOSHIDA et al., 2012) and reduced gains in muscle quality after resistance training (MARCUS et al., 2013). Although it is unknown exactly how the fat infiltration acts on the skeletal muscle system, it is suggested that there is an interaction with muscle fibers leading to muscle dysfunction and insulin resistance (MANINI et al., 2007; BEASLEY et al., 2009). Some authors suggest that the high inflammatory levels associated with muscle fat infiltrates may lead to degradation of contractile units resulting in muscle dysfunction (MANINI et al., 2007).

Postural control is the ability to maintain balance during quiet standing that requires the combination of information from different physiological systems (KU et al., 2012). Postural instability leads to increased risk of fall and dependence (MOCHIZUKI et al., 2006; LIHAVAINEN et al., 2010). In knee OA population, the lack of postural control has been associated with biomechanics factors, articular injury, and neuromuscular impairments (TAKACS et al., 2013; DUFFELL et al., 2014). In reaction to joint damage and the presence of inflammation, the abnormal afferent information reduces quadriceps activation, while also decreasing the proprioceptive acuity by reducing the γ-motoneurone excitability (HURLEY, 1997).

The global burden of obesity is a public health concern and is a well-known risk factor for OA, acting in incidence, progression and disability (TEICHTAHL et al., 2008). Much of the previous researches has focused on OA associations with fat in populations with high fat indexes. Nevertheless, the potential interactions between knee OA and fat depots in non-obese population is yet under explored. Knowing the negative influence of fat infiltration on skeletal muscle activity and the importance of the neuromuscular changes in the postural control of people with knee OA, our proposition was to evaluate the influence of fat infiltration from thigh muscles and total body fat in postural control in people with knee OA. We hypothesized that non-obese people with knee OA will have greater fat infiltration in thigh, less muscle area, and poor postural stability. In addition, we hypothesized that fat infiltration in thigh muscles will be correlated with postural control and it will explain a large proportion of the variance in postural control in people with knee OA.

2. METHODS

2.1 Sample

Participants aged between 45 and 65 years old with and without knee pain were recruited using local media (newspaper, magazines, and social media). An *a priori* power analysis was performed to determine the sample size (G*Power v 20.0). It was considerate two sample and the difference between them, with a power = 0.08 and α=0.05 for an effect size = 0.8, resulting in a minimum of twenty-one participants per group. A total of forty-eight individuals participated in this study. Participants were divided into two groups: the non-OA control group (CG) with no knee pain and OA radiographic (n = 22), and the knee OA group (OAG) (n = 27) with symptoms and radiograph diagnoses of knee OA. OA participants were included if they fulfilled the American College of Rheumatology criteria (ALTMAN et al., 1986) and Kellgren and Lawrence (KL) grade 2 or 3 on weight-bearing X-ray. Participants were included in the CG if they had KL grade 0 and no knee pain or knee injury in the past 5 years. Exclusion criteria for both groups included: body mass index (BMI) > 30 kg/m^2; previous knee, hip or ankle surgery; current or past (within 3 months) oral or intra-articular corticosteroid use; rheumatoid arthritis or other arthritic condition; inability to walk unaided; history of muscle-skeletal or neurological disorder. The Human Ethics in Research Committee of the University of São Carlos approved this study. All participants signed the informed consent form.

2.2 Procedures

2.2.1 Questionnaires

Knee pain, joint stiffness and physical function were assessed by the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index (BELLAMY et al., 1988). WOMAC is a self-reported questionnaire with 24 items about symptoms divided in pain, stiffness, and physical function subscales. The total score ranges from 0 to 96, with higher scores indicating worse symptoms. Habitual physical activity level was measured by the Baecke questionnaire. It consists of 16 items related to physical activities performed at work, sports, and leisure time (BAECKE et al., 1982; GARCIA et al., 2013). The total score ranges from 3 to 15, with higher scores indicating higher physical activity level.

2.2.2 Adipokines assay

Blood samples were collected in a specialized laboratory after 12h overnight fasting. All blood samples were centrifuged and plasma samples were stored at -80°C until analysis. After all samples were collected, plasma adiponectin and leptin was measured in duplicate by enzyme-linked immunosorbent assay (ELISA) kits from R&D Systems (Minneapolis, MN) and assayed in the same run. The detectable limit was 0.246 ng/mL for adiponectin (by DRP300 Quantikine Kit) and 7.8 ng/mL for leptin (by DY389, DuoSet Kit). ELISA analyses were performed according to the manufacturer's instructions. Leptin was diluted in a 1:100 proportion, while adiponectin was diluted in a 1:4 proportion.

2.2.3 Body and thigh composition

The total body fat percentage was assessed by Dual-energy X-ray Absorptiometry (DXA, Hologic Discovery A, Bendford, MA) exam. All participants underwent a total body DXA scan. The cross-sectional CT scan of the thigh was performed by a specialized radiologist using a Multi-slice Computed Tomography (Brilliance CO 16-slice, Phillips). The protocol of image acquisition and processing was described by Almeida et al. (2018). Briefly, participants were placed supine with their legs held in a neutral position and a frontal scout image was obtained to identify the region of interest. A region was set at the middle point between the femoral greater trochanter and the femoral lateral. Scan parameters were standardized: helical mode, 120 kV, 150 mAs, scan time 2.95 s, and 50 cm display field of view (DFOV) and 5 mm slice thickness. The analysis of the slice referring to mid-thigh CT images was performed through the ITK-SNAP software version 3.6 (YUSHKEVICH et al., 2006). For that, two trained researchers manually drew contours in the slice image to delineate the deep fascia that surrounds the thigh tissue muscles and the bone marrow region. We used the bone contour to exclude this tissue from the fat-tissue calculations. By using the 2D manual-annotated slice images, a computer software (FELINTO et al., 2018), applying a set of a fixed tissue-attenuation thresholds (Hounsfield - HU values), computed the areas of the fat tissue (-190 ≤ HU≤ -30), the low-attenuation muscle tissue (0≤ HU≤ 29) and the normal-attenuation muscle tissue (30≤ HU≤ 100) (GOODPASTER, B H et al., 2000; LANG et al., 2010; MURPHY et al., 2014). The LAM is considered a good representation for intramuscular fat (RYAN; HARDUARSINGH-PERMAUL, 2014; MALTAIS et al., 2018).Test-retest reliability on thigh scans was analyzed in 20 random images by interclass correlation coefficient (ICC), where two experts and trained researchers made the analysis from the same images in two different days 1 week apart. The reliability between days was ICC = 0.973 and between evaluators was ICC = 0.986.

2.2.4 Postural Control

The center of pressure (COP) data was measured using a force platform (Bertec, Columbus, OH, USA), with a fixed sample rate of 1000 Hz. Each participant was tested in a standing position under four conditions: (1) Firm surface with open eyes; (2) Firm surface with closed eyes; (3) Soft surface with open eyes; (4) Soft surface with closed eyes. For all postures, participants stood barefoot on the force plate, with arms hanging at the side, looking forward, and standing still but relaxed during the trials (HINMAN et al., 2002; SHANAHAN et al., 2014). During open-eyed conditions, the subjects had to look at a target fixed at eye level 3 meters ahead. In the conditions without vision, the subjects were asked to keep their eyes closed. Due the risk of an unexpected loss of balance, a blindfold was not advised, as there was only one researcher present during the tests (RASOULI et al., 2018). At bipodal stance, subjects were asked to place their feet at hip width. A balance pad (Airex, AG, Switzerland), with 50 cm length x 41 cm width x 6 cm height, was placed on the top of the platform as a soft surface. The trial was started once the subject was positioned on top of the platform and feeling stable in the posture. Each trial was recorded for 30 seconds, repeated for three times, with at least one-minute rest between each trial. If the subject lost his balance, produced excessive movements with the arms or trunk, or if they reported pain, the trial was ended and repeated, not exceeding a maximum of five trials. The sequence of postures was randomized among the subjects.

For postural sway analysis, the following COP parameters were calculated: sway area (mm^2), by 95% confidence ellipse area, velocity (mm/s) and Root Mean Square (RMS) from displacement in the anteroposterior (AP) and mediolateral (ML) axes. The mean of three trials was computed. All data were analized in Matlab (The Mathworks, Inc., Nattick, MA). After spectral analysis, the signals were preprocessed with 5 Hz low-pass second-order Butterworth filter. It was considered that higher values denoted worse postural control.

2.3 Data Analysis

Statistical analyses were conducted with SPSS Software (v. 21, IBM Corporation, USA). For all analyses, the level of statistical significance was set at $p < 0.05$. The normality of distribution and homogeneity of variance were performed by Shapiro-Wilk test and Levene’s test, respectively. Student’s t-test was used to compare leptin, adiponectin, and normal data from postural control. Mann-Whitney test was used to access difference between group for nonparametric data (Hodges-Lehmann for MD and 95% CI). A multivariate analysis of covariance (MANCOVA) was performed to access group differences for thigh composition adjusted for age, sex, and BMI. The correlation among thigh composition and postural control variables was performed by Spearman's correlation and it was classified in weak when $r < 0.50$, moderated when $0.50 < r < 0.70$, and strong when $r > 0.70$ (COHEN, 1988). It was performed a backward multiple regression from knee OA group with a single model including body fat percentage and LAM as predictor for COP area sway.

3. RESULTS

Table 1 shows the anthropometric data and questionnaire scores. The knee OA group had twenty-two individuals with KL grade 2 and five with grade 3. Individuals with knee OA had higher levels of leptin [CG = 33.20 (13.66) ng/ml; OAG: 54.75(16.23) ng/ml; p < 0.001] and adiponectin [CG = 6.41 (2.84) µg/ml; OAG = 9.99 (5.10) µg/ml; p = 0,004].

Table 3. Mean (standard deviation) for age, anthropometric data, physical activity, women proportion and WOMAC score

	CG	**OAG**
Age (years)	52.59 (6.59)	54.33 (6.92)
Height (m)	1.60 (0.50)	1.65 (0.78)
Weight (kg)	64.05 (8.68)	71.37 (10.15)
BMI (kg/m^2)	24.86 (5.50)	26.10 (3.04)
% Body Fat	36.58 (4.61)	38.96 (6.61)
Gender % Women	86.4	85.2
BAECKE	7.16(1.84)	7.63(2.42)
WOMAC Pain	0.29(0.56)	8.11(3.71)
WOMAC Stiffness	0.00 (0.00)	2.78(2.04)
WOMAC Physical Function	0.29(0.64)	22.96(13.39)
WOMAC Total	0.57(1.02)	33.85(17.50)

The difference between OAG and CG from thigh composition is showed in **Table 2**. There was no difference between groups for total fat, subcutaneous adipose tissue, interMAT and muscle area. Therefore, OAG showed greater area of low-muscle attenuation area compared with control group. After adjusted for age, sex, and BMI, OAG showed poor postural control (greater values) for the majority of variables in all conditions, except for ML velocity

ML in firm surface and eyes open, AP velocity in soft surface with eyes closed ($p > 0.05$). All values for postural control are presented in **Table 3**.

Table 4. Cross-sectional area of thigh composition in mean (95% confidence interval) adjusted for age, sex, and BMI, mean difference (95% confidence interval from difference)

	CG (n=22)	OAG (n=27)	Mean Diference (95%CI)	p value
Total Fat (cm^2)	90.38 (80.29-100.47)	98.21 (89.13-107.30)	7.84 (-5.91, 21.59)	0.257
Subcutaneous adipose tissue (cm^2)	80.00 (69.97-90.03)	86.97 (16.36-20.87)	6.97 (-6.71, 20.64)	0.310
InterMAT (cm^2)	16.08 (13.58-18.59)	18.62 (16.36-20.87)	2.54 (-0.88, 5.95)	0.142
Muscle (cm^2)	86.41 (81.42-91.41)	80.18 (75.68-84.68)	-6.23 (-13.04, 0.58)	0.072
LAM (cm^2)	12.36 (10.48-14.25)	15.77 (14.07-17.46)	3.41 (0.84, 5.97)	**0.011**

Bold = *Statistical significance; InterMAT= Intermuscular adipose tissue; LAM= Low-Attenuation muscle*

Table 5. Difference between groups for postural control parameters in four conditions. Mean (SD) for each variable, mean difference (95% confidence interval) for difference

	CG	OAG	Mean Difference (CI)	p value
Firm Surface EO				
Area COP (mm^2)	75.05 (37.25)	133.15 (82.35)	-42.73 (-80.39, -11.34)	**0.004** †
Vel AP (mm/s)	4.06 (1.34)	5.24 (1.58)	-1.08 (-2.07, -0.31)	**0.007** †
RMS AP	3.33 (0.82)	3.98 (1.21)	-0.48 (-1.07, 0.06)	0.073 †
Vel ML(mm/s)	6.39 (1.52)	6.64 (1.25)	-0.28 (-1.15, 0.69)	0.669 †
RMS ML	2.04 (1.08)	2.72 (0.98)	-0.75 (-1.19, -0,26)	**0.004** †
Firm Surface EC				
Area COP (mm^2)	97.57 (72.45)	159.69 (95.09)	-50.53 (-90.10, -19.19)	**0.005** †
Vel AP (mm/s)	5.20 (2.18)	6.36 (1.91)	-1.15 (-2.35, 0.05)	0.060
RMS AP	3.59 (0.94)	4.62 (1.23)	-1.03 (-1.69, -0.37)	**0.003**
Vel ML (mm/s)	7.74 (2.17)	9.40 (2.42)	-159 (-2.99, -0.30)	**0.022** †
RMS ML	2.19 (1.15)	2.73 (0.98)	-0.55 (-1.10, -0.10)	**0.020** †
Soft Surface EO				
Area COP (mm^2)	442.40 (185.33)	667.56 (336.69)	-162.8(-333.6, -36.57)	**0.018** †
Vel AP (mm/s)	12.52 (3.81)	14.60 (3.75)	-2.08 (-4.31,0.16)	0.068
RMS AP	6.45 (1.33)	7.93 (2.28)	-1.25 (-2.18, -0.24)	**0.017** †
Vel ML (mm/s)	14.41 (4.59)	15.93 (3.98)	-1.79 (-3.45, 0.05)	0.060 †
RMS ML	5.58 (1.38)	6.82 (1.77)	-1.24 (-2.19, -0.29)	**0.012**
Soft Surface EC				
Area COP (mm^2)	1128.67 (453.68)	1682.18 (893.09)	-378.7 (-676.0, -34.65)	**0.029** †
Vel AP (mm/s)	22.87 (6.81)	24.75 (5.06)	-1.88 (-5.42, 1.65)	0.289
RMS AP	10.72 (1.84)	13.12 (3.11)	-1.83 (-3.13, -0.57)	**0.007** †
Vel ML (mm/s)	30.11 (8.94)	36.09 (11.81)	-4.91 (-10.02, -0.30)	**0.040** †
RMS ML	8.47 (2.30)	10.08 (2.53)	-1.19 (-2.63, 0.17)	0.091 †

Bold = *Statistical significance; † Values from Mann-Whitney test; EO= eyes open; EC= eyes closed; Vel= velocity; AP= anteroposterior; ML= mediolateral;*

Table 4 shows the relationship between tissue area and postural control variables in different postures. The low-muscle attenuation showed positive correlation with area, AP velocity and ML velocity, and RMS ML in the firm surface with eyes open. In a firm surface with eyes closed, the low-muscle attenuation showed positive correlation with area, velocity ML, and both RMS AP and ML. When subjects were in the soft surface with eyes closed, the low muscle attenuation showed positive correlation with area, RMS AP, and velocity ML. There was no relationship between thigh content and postural control variables when subjects were in the soft surface with eyes open.

Table 6. Correlation between thigh composition and postural control presented with correlation coefficient r (p-value)

	Area COP	Vel AP	RMS AP	Vel ML	RMS ML
			Firm Surface EO		
InterMAT	-.003(0.982)	-.059(0.699)	-.063(0.678)	-.013(0.931)	.116(0.438)
LAM	**.457(0.001)****	**.470(0.001)****	**.339(0.021)***	**.312(0.033)***	.499(0.000)
Muscle	.173(0.246)	.156(0.300)	.240(0.109)	.236(0.111)	.083(0.580)
			Firm Surface EC		
InterMAT	.065(0.659)	.029(0.847)	.103(0.490)	-.021(0.887)	.046(0.757)
LAM	**.493(0.000)****	**.435(0.002)****	**.466(0.001)****	**.434(0.002)****	**.424(0.003)****
Muscle	.175(0.234)	.185(0.213)	.238(0.107)	.318(0.030)*	.122(0.413)
			Soft Surface EO		
InterMAT	-.086(0.560)	-.060(0.687)	-.089(0.553)	-.123(0.409)	-.074(0.620)
LAM	.263(0.71)	.196(0.187)	.265(0.072)	.094(0.531)	.253(0.086)
Muscle	-.023(0.875)	.002(0.992)	-.013(0.931)	.023(0.876)	-.030(0.840)
			Soft Surface EC		
InterMAT	.057(0.705)	-.037(0.806)	.054(0.718)	.037(0.807)	.045(0.765)
LAM	**.349(0.016)***	.172(0.254)	**.379(0.009)****	**.331(0.023)***	.270(0.066)
Muscle	.009(0.952)	.205(0.171)	.073(0.628)	.209(0.159)	-.072(0.631)

Bold *= significant correlation; **significant correlation at 0.01 level; *significant correlation at 0.05 level; InterMAT = intermuscular adipose tissue; LAM= Low-Attenuation Muscle; EO= eyes open; EC= eyes closed; Vel= velocity; AP= anteroposterior; ML= mediolateral;*

Table 5 presents the multiple regression analysis for area COP as dependent variable and LAM and % body fat as predictor. When standing with eyes open, the LAM was able to predict 42% of COP variation in firm surface, while in soft surface it was not significant. With eyes closed, LAM was able to explain 52% of COP area variance in firm surface and 48.7% of

COP area variance when standing in a soft surface. The % body fat had no significant interaction in the with COP area sway in any tested condition (p > 0.05).

Table 7. Multiple linear regression results

			COP Area- Firm Surface EO				
	B	**SE B**	**β**	**p**	**R2**	**R2 adjusted**	**p**
Model 1					0.180	0.109	0.102
Constant	10.82	104.86		0.919			
LAM	7.04	3.13	0.424	**0.035**			
%Body Fat	0.23	2.31	0.019	0.921			
Model 2					0.180	0.146	0.921
Constant	19.82	51.57		0.703			
LAM	7.04	3.07	0.424	**0.031**			
			Firm Surface EC				
Model 1					0.275	0.212	**0.025**
Constant	34.09	113.89		0.238			
LAM	9.95	3.40	0.519	**0.006**			
%Body Fat	-0.889	2.51	-0.063	0.705			
Model 2					0.271	0.240	0.727
Constant	-0.732	56.14		0.087			
LAM	9.97	3.34	0.520	**0.005**			
			Soft Surface EO				
Model 1					0.156	0.082	0.143
Constant	-184.04	435.09		0.676			
LAM	19.23	13.00	0.284	0.152			
%Body Fat	13.95	9.60	0.278	0.160			
Model 2					0.078	0.040	0.160
Constant	362.42	223.51		0.118			
LAM	18.96	13.29	0.280	0.167			0.167
Model 3					0.000	0.000	
Constant	667.56	66.03		<0.001			
			Soft Surface EC				
Model 1					0.346	0.289	**0.008**
Constant	-1467.99		0.162				
LAM	87.69	0.487	**0.008**				
%Body Fat	44.75	0.337	0.058				

Bold *= Statistical significance; EO= Eyes Open; EC= Eyes Closed; OA= osteoarthritis; LAM= Low-Attenuation Muscle*

4. DISCUSSION

The major finding of this study was that high levels of muscle fatty infiltration in thigh was correlated with poor postural control in knee OA people, being able to explain about 50% of the COP sway area variability in a situation without vision. We found that non-obese people with knee OA have more fatty infiltration in thigh muscle, no difference in muscle quantity, higher levels of adiponectin and leptin compared with individuals without knee OA matched by age and BMI.

The amount of fatty infiltration, specifically the fat located within the thigh muscles, was able to explain between 48 to 52% the variability in COP area when standing in a firm and soft surface without vision, and 42% in a firm surface with vision, while percentage of body fat was not a significant predictor. It is known that postural control depends on integration from sensory systems (somatosensory, vestibular and visual) and motor system (FITZPATRICK; MCCLOSKEY, 1994), but in knee OA people, neuromuscular impairments seem to play an important role in the deficit of postural control (HURLEY et al., 1997; HASSAN et al., 2001). Moreover, it is known that muscle fatty infiltration can negatively affect muscle function, so we suggest that this fat can also affect postural control. In elderly, high levels of InterMAT have negative relationship with quadriceps muscle activation (YOSHIDA et al., 2012). The presence of fat within skeletal muscle tissue can also increase the pennation angle without increasing the amount of contractile fibers, leading to a decrease in the capacity to produce force (MEYER et al., 2004). The fat depot also works as an endocrine organ, being able produce and release proinflammatory factors such as cytokines and adipokines resulting in local inflammation inside the muscle, creating a detrimental environment for neuromuscular function (BEASLEY et al., 2009; KALINKOVICH; LIVSHITS, 2017). In the absence of visual information, other systems responsible for postural control are overloaded, requiring greater performance. Therefore, if there is any neuromuscular impairment that limits a proper neuromuscular performance, the ability to restore postural balance will be affected. The exact pathway through which fatty infiltration influences muscle function is still unknown. However, all the possibilities explained above contribute to muscle function deficit, which may lead to impairment in postural control, especially in people with knee OA.

Some authors suggest that in people with knee OA, the alterations in the musculoskeletal system can be explained by arthrogenic muscle inhibition (RICE; MCNAIR, 2010), being associated with inflammation, pain, joint laxity, and structural damage. The knee OA joint damage associated with inflammation, pain, swelling, and joint can alter the excitability of α-motoneurones leading to decreased quadriceps activation, but also can reduce γ-motoneurones excitability decreasing proprioceptive acuity (HURLEY; NEWHAM, 1993; RICE; MCNAIR, 2010). With increased fatty infiltration in thigh muscles presented in knee OA people, the local inflammation that may be produced by this fat tissue could enhance the effects of arthrogenic muscle inhibition.

As expected, we found higher leptin and adiponectin levels in knee OA group compared with control group. Leptin has been considered the major link between OA and obesity since leptin may enhance proinflammatory factors production and others destructive mediators in OA cartilage (VUOLTEENAHO et al., 2014; URBAN; LITTLE, 2018). In our study, the leptin and adiponectin levels were used as a marker for presence of inflammation.

A significant moderate association was found between muscle fatty infiltration and postural control in all postural conditions, excepted for soft surface with eyes open. However, the amount of muscle was associated to postural control only in one condition. Therefore, it seems that muscle fat has more influence in postural control than the amount of muscle in the thigh. These results agree with other studies that show the association between muscle fat and physical function and thigh muscle strength, while there was no relationship with muscle (MALY et al., 2013). According to Goodpaster et al. (2006), the same proportion of lean mass decline did not follow the loss of muscle strength found in 1800 healthy older adults in a 3-year longitudinal study. The average loss of lean mass was 1% per year, while the muscle strength declined about 4%, showing that other factors besides muscle mass are responsible for muscle weakness. In women with knee OA, Maly et al. (2013), found that lower quadriceps muscle strength was associated with higher amount of interMAT, whereas there was no association with muscle volume. Khoja et al., (2018) has shown that fatty infiltration in thigh muscles independently explains the variability in physical function, independently of muscle strength in patients with rheumatoid arthritis. Therefore, it seems that fatty infiltration in muscles, particularly in the thigh, play an important role in muscle strength and physical function, revealing an important target for studies and treatments aiming improving muscle function.

We found that people with knee OA presented higher COP sway area in all conditions compared with the people without knee OA. Our results are in agreement with those reported in other studies that found greater postural sway in people with knee OA compared to control subjects (MASUI et al., 2006; HSIEH et al., 2013; VAHTRIK et al., 2014; KHALAJ et al., 2014). Furthermore, in line with other studies (HASSAN et al., 2001; HIRATA et al., 2013; PIRAYEH et al., 2018), the knee OA group presented greater postural sway in the ML direction, measured by RMS of displacement, in all conditions, excepted for soft surface with eyes open.

In elderly, greater postural sway in the ML direction was identified as good predictor of fall (PIIRTOLA; ERA, 2006). In knee OA population, Pirayeh et al. (2018), suggested that the weakness of hip abductor muscles, found with severe OA grades, may be responsible for greater ML postural sway (PIRAYEH et al., 2018).

Obesity is a risk factor for knee OA and aggravates the pathology due to joint overload (MESSIER et al., 2005), kinematics alterations during daily activities (PAMUKOFF et al., 2016), and inflammatory factors (URBAN; LITTLE, 2018). However, there is a lack of evidence about the influence of fat tissue in non-obese individuals. We found that in an eutrophic and over-weight population, people with knee OA have more fat infiltration in muscle and higher serum levels of adiponectin and leptin when compared to healthy control people with similar BMI. This suggest that increased fat infiltration in muscle does not depend on obesity and it may contribute to increase the levels of inflammation in people with knee OA.

The knee OA management focuses on physical activity and exercise therapy as the main non-pharmacological treatment to reduce pain, increase lower limb strength, and increase physical function (PATTERSON, 2018). Knowing the negative influence of fatty infiltration in muscle function and postural control, future researches should be done in order to develop exercise programs capable of reducing fat infiltration aiming at improving muscular activation, postural control, and physical function.

Our study has some limitations. The absence of a gold-standard variable from postural control analysis made us choose the COP sway area as a representative of postural control in the regression analyses. There is no standardization of COP data analysis with no indication of which variable would better represent alterations in postural control (LAWSON et al., 2015).

5. CONCLUSION

In conclusion, our study shows that non-obese people with knee OA have increased fat infiltration in thigh muscles and that it has significant influence in the variability of postural control. The amount of fat infiltration in thigh muscles has a moderate association with postural control in people with knee OA. Further work is required to investigate the association between muscle fat infiltration and muscle activation during balance tests to improve our understanding of the consequences of muscle fat in postural control.

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7. Manuscrito III

Relationship between trunk composition and physical function in non-obese individuals with knee osteoarthritis

ABSTRACT

***Introduction**:* Knee osteoarthritis leads to decreased physical function, leading to physical dependence and decreased quality of life. Fat infiltration in the trunk muscles is associated with decreased functional capacity and increased risk of falls in the elderly. Thus, the purpose of this study was to compare the composition of the trunk in individuals with knee osteoarthritis compared with control subjects and to evaluate the association between the amount of muscle and fat of this region with the physical function.

***Methods*:** Twenty-seven individuals with diagnosis of knee osteoarthritis grade 2 and 3 and 22 individuals without knee osteoarthritis were evaluated. The area of the trunk muscles, subcutaneous fat and intermuscular fat, as well as the mean of muscle attenuation (related to intramuscular fat), were evaluated by computed tomography of the trunk in the L4-L5 region. Physical function was assessed by 30s chair stand, 40m fast-paced walk and stair climb tests.

Results: Individuals with knee osteoarthritis presented greater subcutaneous fat, intermuscular and muscle fat infiltration and smaller muscle area when compared with control subjects ($p < 0.05$). The physical function performance of the osteoarthritis group in all the tests showed a correlation with muscle fat infiltration (chair stand $r = 0.55$, walk $r = -0.50$, stair climb $r = -0.46$). Both subcutaneous fat and muscle area has correlation with walking test ($r = 0.50$ and $r = -0.49$) and stair climb ($r = 0.42$ and $r = 0.40$) tests.

***Conclusion*:** Individuals with knee osteoarthritis present lower muscle area and more fat infiltration in the trunk muscles compared to control subjects. The accumulation of fat infiltration in the trunk musculature is associated with poor physical functional capacity in individuals with knee osteoarthritis

Keywords: arthritis; body composition; adipose tissue; sarcopenia; intramuscular fat

1. INTRODUCTION

The weakness of trunk muscles has been associated with knee injures such as patellofemoral pain syndrome and anterior cruciate ligament rupture. (LEETUN et al., 2004; HEWETT; MYER, 2011; BALDON et al., 2014). In knee osteoarthritis (OA), exercises that aim to improve trunk muscle has been incorporated to the strengthening of lower limbs and shown efficient in improving pain and physical function in this population (ROOS; ARDEN, 2016; SELISTRE et al., 2017). Functionally, the trunk region, known as core, is the kinematic link that facilitates the torque transference and angular moment between upper and inferior body during the movement execution (BEHM et al., 2010). Thus, structural and muscular alterations in this region can compromise the movement effectiveness from lower limbs, including during daily physical activities (HICKS et al., 2005a; MYER et al., 2008).

Patients with knee OA has pain and difficult during daily physical activities such as walking, climbing stairs, squat, sit and stand up from the chair, leading to greater physical inactivity, thus decreasing the functional capacity and mobility (FELSON et al., 2000; FUKUTANI et al., 2016). The OA have multiple risk factors that compromises the functionality, among them obesity is one of the most important and modifiable, being able to promote disability and physical inactivity in this population (FELSON et al., 2000; CHUN et al., 2013). In addiction to overloading on joints that support body weight, the increase of fat tissue is related to OA by metabolic pathway due to pro-inflammatory cytokines (POTTIE et al., 2006). The fat tissue distribution along the body has been studied have different responses and consequences depending on its location (ADDISON et al., 2014).

The fat infiltration in musculoskeletal tissue has been associated with muscle weakness and decrease in physical function among different populations (ADDISON et al., 2014; STEFANO et al., 2015; KHOJA et al., 2018). In knee OA individuals, the fat infiltration in thigh muscles was associated with decrease in knee extensors muscles strength and worse physical function in sit to stand task and walking (MALY et al., 2013; KUMAR et al., 2014). In elderly, according to Hicks et al. (2005), the fat infiltration in trunk muscles was able to explain around 13% of the decrease in physical function (sit to stand and walking), mainly balance, while the fat infiltration in the thigh could explain 6% (HICKS et al., 2005a).

Since greater amount of fat infiltration in trunk muscles can be associated with muscle weakness in this region leading to functional impairments in daily activities and, consequentially, decrease in physical capacity in individuals with knee OA, the aim of this study was: 1) compare the trunk composition between individuals with knee OA and non-OA control individuals; 2) investigate the relationship between the fat infiltration in trunk muscles and physical function in knee OA population. Our hypothesis is that individuals with knee OA had more fat infiltration in muscle trunk them individuals without knee OA and that fat infiltration in the trunk muscles would present a negative correlation with physical capacity in the knee OA population.

2. METHODS

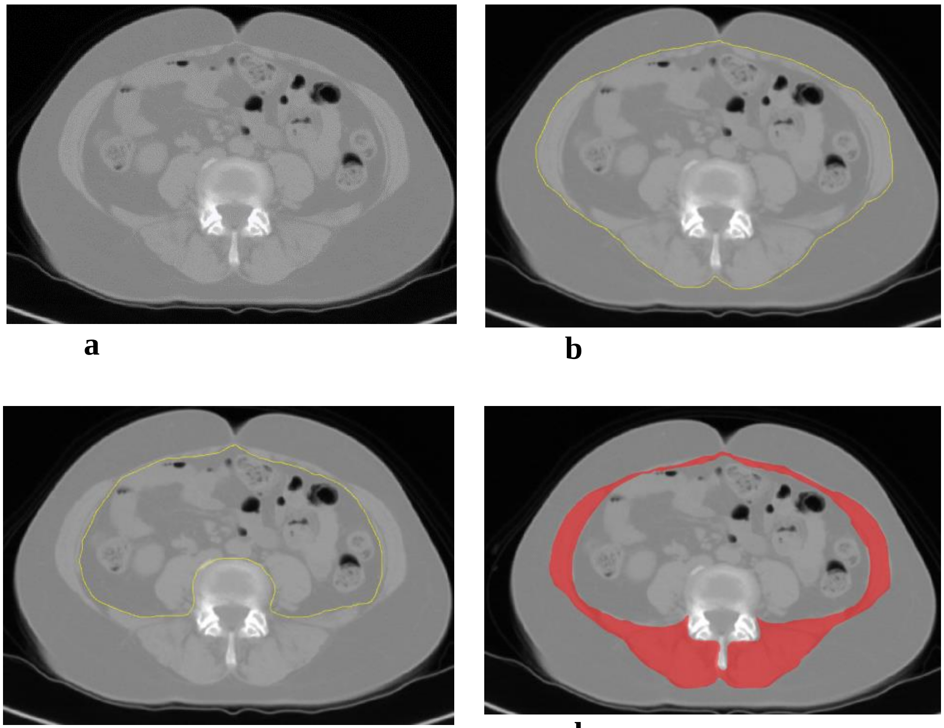
2.1 Sample

This research Project was widely disseminated in the city of São Carlos and region through digital and printed media. In the OA group (OAG) it was included individuals aged between 40 and 65 years old, body mass index (BMI) < 30 kg/m^{2,} sedentary, with knee OA radiographic grade 2 and 3 from Kellgren and Lawrance (KL), and OA clinical signals according to American College of Rheumatology (ALTMAN et al., 1991). The exclusion criteria were: previous hip and/or lower limbs surgery, neurological diseases, history of meniscus and/or knee ligaments injuries, presence of OA or rheumatic arthritis in other joints, corticosteroid application in knee joint in the last six months. Individuals without knee pain, without knee OA radiographic signs, who did not presented any of the exclusion criteria were inserted in control group (CG), matched by age, sex and BMI with knee OA group. The radiographic exam for OA diagnosis and classification were performed at the *Hospital Universitario de São Carlos* by a radiology technician. The x-ray was acquired in the anteroposterior view with the knees flexed at 45 degrees weight-bearing in order to identify tibiofemoral OA, while the skyline view was performed in order to identify patellofemoral OA (ALTMAN et al., 1987; BHATTACHARYA et al., 2007). The study was approved by the Federal University of São Carlos Research Ethics Committee (000696/2015) and all participants read and provided the informed consent.

2.2 Computed Tomography and image assessment

The assessment of trunk muscles was performed by Computed Tomography (Brilliance CT 16-slice,Phillips) at the *Hospital Universitario de São Carlos* by a single trained radiology technician specialist. It was performed a scout from trunk region to locate the lumbar vertebra L4-L5 and then 10 slices with 5mm thickness was acquired from the selected region. The image acquisition parameters was standardized at 120kV scout, 200 mA, and acquisition time of 2.5s.

It was used a slice referring to the midpoint between L4-L5 in order to evaluate the trunk tissues. The ITK-SNAP software was used to perform the images segmentation drawing a line at the abdomen external wall, internal wall, and vertebrae (**figure 1**). From this segmentation, it was possible to assess the area from subcutaneous fat (between skin and abdomen external wall), muscle (between abdomen external and internal wall), visceral fat (inside abdominal internal wall). The vertebrae bone area was deducted from muscle area due to the presence of fat tissue in spinal canal. After the area segmentation, the tissues density were assessed by Hounsfield Unit (HU), in order to distinguish fat and muscle tissue. A range from -190 to -30 HU was used to identify fat tissue and from 0 to 100 HU to identify muscle tissue (FELINTO et al., 2018). The muscle mean attenuation was used to evaluated the fat infiltration within the muscles, since a low attenuation muscle mean is highly related with intramuscular fat tissue assessed by biopsy (GOODPASTER et al., 2000).



a b c d

Figure 1. Trunk composition assessment:. a) Original image; b) external abdominal wall; c) Internal abdominal wall; d) Trunk muscles area

2.3 Physical function

The physical function was assessed through the following tests: 30-s chair-stand, 40m fast-paced walk and stair-climb. All the test was performed according to the *Osteoarthritis Research Society International* – OARSI orientations (DOBSON et al., 2013) in random order. Before each test and at the end of it, all participants report the knee pain through a visual analogic scale with range from 0 to 10, were 10 was considered maximum pain. All tests were performed in the same places, with the same instruments (same chair and stair) with standardized instructions for all participants.

For the 30 s chair stand test, the participants were instructed to start the test in the sited position, arm crossed at the chest, stand completely up and then sit completely as fast as possible during the period of 30s. It was counted the total number of completely chair stand. Higher number of repetitions was considered greater physical performance.

The 40 m fast-paced walk test was performed in a corridor with 10-meter markers, with a cone at the ends, where the participant was instructed to walk as quickly but in a safe manner and without running. They had to walk along the 10 m, turn around the cone, return to the first cone and then repeat again for the total of 40 m distance. The acceleration and deceleration times were discounted from total time. It was considered that shorter time to perform the walk, greater is the physical performance in the activity.

The stair-climb test was performed in one flight of stair with 11-steps, with each step measuring16 cm height and 30 cm deep. The participants was asked to ascend and descend the flight of stair as quickly as possible in a safer manner. The handrail was allowed if the participant felt safer. The time to complete the test was recorded, starting with the command voice to begin the activity and finishing when the participant placed both feet at the initial point. The total time to complete the task was used for analysis. The shorter time to perform the task the better the physical perform. It was allowed to use a regular walking aid to perform the stair-climb test and 40m fast-paced walk test, and it was recorded by the tester.

2.4 Data analysis

All the statistic analysis were performed in IBM SPSS (version 21, IBM Corporation, Chicago, EUA). First, it was ran an exploratory analysis in order to obtain the mean and standard deviation from all variables. The data normality and homogeneity were checked using Shapiro-Wilk and Levene's tests, respectively. The difference between groups for the physical performance was made using Student's t test. It was calculated the effect size by Cohen index (d) and it was characterized as weak, moderate and strong effects when is $d = 0.2$, $d = 0.5$ and $d= 0.8$, respectively. The difference between groups for trunk fat and muscle areas was assessed using a multiple analysis of covariance (MANCOVA), using age, sex, and BMI as covariables. The effect size from MANCOVA analysis were reported using partial eta-square (partial η^2) were 0.01 is considered low, 0.06 moderate and 0.14 high effect (COHEN, 1988). The relationship of trunk muscle, mean muscle attenuation an fat tissues with 30-s chair stand test, walking and stair climb tests were investigated using Pearson's correlation. The statistical significance was set at $P < 0.05$.

3. RESULTS

The OAG was composed by twenty seven participants with clinical and radiographic knee OA (n = 22 KL 2; n = 5 KL 3), while CG was composed by twenty tree individuals with no knee pain or OA. The participant's characteristics are shown in **table 1**.

Table 8. Mean ± standard deviation from subject's characteristics

	CG	OAG
Age (years)	52.59±6.59	54.33±6.92
Height (m)	1.60±0.50	1.65±0.78
Weight (Kg)	64.05±8.68	71.37±10.15
BMI (kg/m^2)	24.86±5.50	26.10±3.04
Gender % Women	86.4	85.2

The results from trunk muscle and fat are presented in **table 2**. After adjust by age, sex, and BMI, the OAG shown higher subcutaneous fat and intermuscular fat, while lower muscle area and lower muscle attenuation, with high ES (more than 0.14). There was no difference between groups for visceral fat (p > 0.05).

Table 9. Trunk muscle and fat areas, muscle attenuation and difference between groups

	CG		OAG			
	Mean	**IC 95%**	**Mean**	**IC 95%**	**p value**	**ES**
Subcutaneous fat (cm^2)	259.15	235.29 - 283.01	321.68	300.20 - 343.16	< 0.001*	0.254
Intermuscular fat (cm^2)	28.09	24.59 - 31.59	33.33	30.18 - 36.48	0.032*	0.100
Visceral fat (cm^2)	147.28	129.49 - 165.08	132,00	115.98 - 148.02	0.211	0.035
Muscle (cm^2)	109.52	103.04 - 115.99	98.24	92.41 - 104.07	0.013*	0.131
Mean attenuation muscle (HU)	51.19	48.23 - 54.16	42.07	39.40 - 44.74	< 0.001*	0.320

*Mean values adjusted by age, sex, and BMI. * Statistical significance; ES= partial eta-square; HU = Hounsfield Unit*

The OAG shown worst physical performance (longer time to complete the task) in the walking and stair climb tests, but there was no difference between groups in the sit-to-stand task (*p* > 0.05) presented in **table 3**. Even if it was allowed the use of walking aid, no one needed to use any assistance device during the tests.

Table 10. Performance in the physical function tests (mean ± standard deviation) and the difference between groups

	CG	OAG	p value	ES
30 s chair stand (repetition)	13.68±2.48	12.04±3.90	0.092	0.503
40 m fast-paced walk (s)	21.71±2.64	25.16±4.17	0.002*	0.987
Stair climb (s)	9.93±2.13	13.61±4.02	<0.001*	0.971

**Statistical significance; ES= Effect Size*

The **table 4** shows the correlation between trunk muscle and fat with physical performance for OAG. There was a moderate positive correlation between subcutaneous fat and walking test (r = 0.49) and stair climb test (r = 0.42). There was no correlation between visceral fat and any functional test. The trunk muscles had a moderate negative correlation with walking test (r = -0.47) and stair climb test (r = -0.40). The muscle attenuation had a moderate positive correlation with walking test (r= -0.50) and with stair climb test (r = -0.46).

Table 11. Correlation between physical function and trunk composition presented in r (p value)

	30 s chair stand	40 m walk	Stair climb
Subcutaneous fat	-0.342 (0.081)	0.498 (0.008)*	0.415 (0.031)*
Visceral fat	-0.056 (0.781)	0.052 (0.798)	0.144 (0.475)
Muscle	0.343 (0.080)	-0.468 (0.014)*	-0.395 (0.041)*
Intermuscular fat	-0.176 (0.379)	0.145 (0.470)	-0.048 (0.812)
Mean attenuation muscle	-0.554 (0.003)*	-0.504 (0.007)*	-0.462 (0.015)*

* Statistical significance

4. DISCUSSION

We found that individuals non-obese with knee OA have more muscle fat infiltration in trunk muscles when compared with age-matched individuals non-obese without knee OA. The fat infiltration was greater both between the muscles (intermuscular fat) and within muscles (intramuscular fat). In addition, individuals with knee OA had smaller are of trunk muscles when compared with individuals without knee OA. We also evaluated the relationship between trunk muscles, subcutaneous fat, muscle fat infiltration and physical function in people with knee OA. It was found that fat infiltration in trunk muscles is associated with worst physical performance in sit to stand from a chair, walking and stair climb tests. The subcutaneous fat and muscles from trunk also had association with physical function tests, but only with walking and stair climbing tests, showing that greater amount of subcutaneous fat is negatively associated with physical performance while muscle area has a positive correlation.

Compared with people without knee OA and adjusting the body composition by age, sex and BMI, people with knee OA presented greater of subcutaneous fat, intermuscular fat, intramuscular fat (assessed by low mean muscle attenuation), and lower muscle area in the trunk. Although there are several previous studies that evaluated the muscles from trunk in diverse population, few studies had a control group in order to compare the results (HICKS et al., 2005b; ANDERSON et al., 2013; FORTIN; MACEDO, 2013). Studies with low back pain, reported that people with low back pain have smaller muscle area and greater fat infiltration in trunk muscles when compared with age matched people without back pain (HICKS et al., 2005b; FORTIN; MACEDO, 2013). Healthy elderly individuals aged 75-87 years old also presented less muscle and greater fat infiltration in the trunk muscles when compared with healthy young people aged 35-50 years (ANDERSON et al., 2013). In knee OA population, greater fat infiltration was found in the thigh muscles in some studies (BEATTIE et al., 2012; MALY et al., 2013; DANNHAUER. et al., 2014; KUMAR et al., 2014). It is possible that the knee OA process, such as pain, decreased physical activities and presence of inflammation process, lead to a more favorable condition to the fat infiltration in the skeletal muscle tissue, besides the subcutaneous fat accumulation.

As expected, our results showed that people with knee OA presented poor physical function during walking and stair climb tasks. However, no difference was found for the sit-to-stand task between people with knee OA and without knee OA. The effect size assessment shows that, among the physical function tests applied, only the 30-s chair-stand test presented low effect, suggesting that the sample size might not have been enough to show the difference between groups.

In the knee OA individuals, the physical function presented a moderate relationship with the trunk muscles and with the fat infiltration, indicating that the fat infiltration may negatively affect the physical performance as much as skeletal muscle tissue. Hicks et al. (2005) evaluated healthy elderly (739 men and 788 women) between 70 and 79 years, and found that the increase in fat infiltration in the trunk musculature, in addition to being associated with the presence of low back pain, was considered a better predictor of physical capacity and risk when compared to muscle area. In another study, Therkelsen et al. (2016) evaluated the volume of visceral fat, subcutaneous fat of the trunk and fat infiltration in the paravertebral muscles and its association with grip strength and walking speed of 1152 men and women with a mean age of 66 years. The decrease in muscle attenuation (greater fat infiltration) was associated with lower walking speed, regardless of sex, BMI and visceral fat, besides being associated with lower grip strength in men (THERKELSEN et al., 2016). In this way, fat infiltration in the trunk muscles seems to interfere negatively in the performance of daily physical activities, which would help to explain the correlations found in the present study.

The mechanisms by which the accumulation of fatty tissue in muscle tissue can affect muscle function are still unclear. It is known that the accumulation of intramyocellular fat changes the metabolism of the muscle cell leading to the production of metabolites that impair muscle contraction (lipotoxicity) (COEN; GOODPASTER, 2012). The fatty tissue also can of release proinflammatory factors, such as cytokines and adipokines, which may impair the mechanism of muscle contraction, as well as impair the muscle repair process (BEASLEY et al., 2009; KALINKOVICH; LIVSHITS, 2016). In addition, increased fat in muscle tissue is associated with the mechanism of insulin resistance in the musculature, impairing muscle metabolism (PAN et al., 1995; COEN; GOODPASTER, 2012).

According to Granacher et al. (2013), the increased strength of the trunk muscles can lead to more effective movements of the lower limbs (GRANACHER et al., 2013). Studies that aimed to improve the trunk stabilization through exercises focused on the coordination and activation of the abdominal and lumbar muscles during static and dynamic activities, suggesting that a greater stabilization of this region of the trunk is due to the improvement of the activation of these muscles (MYER et al., 2008; BALDON et al., 2014). Hogges and Richardson (1997) recorded the activity of the abdominal muscles with hip movements and found that the deep abdomen muscles (transverse and oblique) are activated in anticipation of movements preparing the trunk for movement disorders (HODGES; RICHARDSON, 1997). In patients with patellofemoral pain syndrome, it was found that delayed activation of the transverse abdominals and oblique muscles relative to the gluteus medius during the plantar flexion task in closed kinetic chain, whereas in healthy subjects the activation of these muscles occurred simultaneously (BIABANIMOGHADAM et al., 2016). Those data suggest that people with knee pain have different muscle activation in the abdominal area compared with people without pain. In the thigh muscle, Yoshida et al. (2012) found an association between increased fat infiltration and decreased muscle activation rate suggesting that fat infiltration in muscle tissue may interfere with its activation (YOSHIDA et al., 2012). Therefore, we suggest that the increase of fat infiltration in the trunk muscles may contribute to lower muscle strength and activation, impairing the correct movement of the lower limbs.

Clinically, our results suggest that patients with knee OA may benefit from therapies that decrease the amount of muscle fat infiltrate in the trunk, increase the muscle mass or prevent the imbalance between those tissues, thereby improving functional physical performance focusing on their physical independence.

This study has some limitations. We did not performed analysis of muscle strength or muscle activation (by electromyography) in the trunk muscles to assess muscle function in this region. The evaluation of muscular strength or muscle activation directly from this region would help us to better understand if there is a muscular dysfunction in the region of the trunk evaluated and if the decrease of muscle mass and increase of the fat infiltrate would be related to muscular function. A kinematic analysis also could clarify the influence of the trunk and the lower limbs in the physical functional tests. Some studies have shown the negative influence of fat infiltration in the thigh muscles on the functional performance of patients with knee OA. Further studies are needed to assess whether fat infiltration in the trunk musculature and thigh musculature occur concomitantly and whether one of them has a greater influence on the daily physical activities of the patients.

5. CONCLUSION

In conclusion, individuals with knee OA have a lower muscle area in the trunk and greater amounts of subcutaneous, intermuscular and infiltrated fat in the trunk muscles compared to individuals without knee OA. This study shows that the fat infiltration in the trunk muscles has a moderate correlation with functional capacity in subjects with knee OA, evaluated by walking test, sit to stand and stair climb tests. The trunk muscles and the subcutaneous fat were correlated with the physical capacity, but only in the walking and stair climb tests.

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8. CONSIDERAÇÕES FINAIS

Os estudos apresentados nesta tese mostram:

- Indivíduos com osteoartrite de joelho possuem maior quantidade de infiltrado de gordura na musculatura da coxa e do tronco quando comparados a indivíduos saudáveis.
- O acúmulo de gordura de gordura na musculatura da coxa é associado com pior controle postural, influenciando negativamente o equilíbrio postural.
- O infiltrado de gordura na musculatura do tronco, assim como menor área muscular dessa região é associado a menor capacidade funcional.

Dessa forma, podemos concluir que o infiltrado de gordura muscular prejudica as funções físicas e habilidade de manter o equilíbrio em pessoas com osteoartrite de joelho. Assim, a diminuição da gordura infiltrada na musculatura tanto da coxa quanto do tronco ou a prevenção de seu acúmulo deve ser incluída no tratamento de pacientes com osteoartrite de joelho visando a melhora da capacidade funcional e do controle postural, afim de preservar a independência física e qualidade de vida dessa população.

9. ATIVIDADES RELACIONADAS À TESE

Durante o desenvolvimento dos estudos da presente tese, outras atividades foram desenvolvidas paralelamente que visaram contribuir para aperfeiçoamento do trabalho final.

Bolsa Estágio de Pesquisa no Exterior (BEPE)

Realização de estágio em pesquisa na *East Carolina University* (ECU), Greenville (North Carolina), Estados Unidos, sob a supervisão do Prof. Dr. Paul DeVita com financiamento da Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP; Processo: 2016/24802-7), no período de março a agosto de 2017. Nesse período foi realizado o estudo intitulado "*Quadriceps strength training and knee joint motion training in knee osteoarthritis*".

Durante esse período, a aluna participou do recrutamento de voluntários, avaliações, intervenções e reavaliações. Os dados coletados geraram um manuscrito intitulado "*Motion Training improves pain and disabilities in people with knee osteoarthritis*", o qual encontra-se em processo de submissão.

Participação em projetos do Laboratório de Análise da Função Articular (LAFAr) – Dfisio

Almeida, A.C

1) Influência de um protocolo de treinamento em circuito na gordura intermuscular da coxa, composição corporal, parâmetros clínicos, funcionais e metabólicos de pacientes com osteoartrite de joelho. Doutorado

Aily, J.B

1) Avaliação da arquitetura muscular e aspectos biopsicossociais em indivíduos com osteoartrite de joelho em diferentes faixas etárias - Mestrado
2) Avaliação da concentração de tecido adiposo muscular em pacientes com osteoartrite de joelho - Doutorado
3) Efeitos da telerreabilitação no tecido adiposo intermuscular de pacientes com osteoartrite de joelho - Doutorado

Projeto Temático FAPESP (Processo 2013/00798-2)

A matriz extracelular no envelhecimento, no exercício e no microambiente tumoral

Projetos de extensão

1) Atendimento Fisioterapêutico e Pilates para pessoas com dor no joelho
2) Análises Bioquímicas, Celulares e de Imagens Biológicas

PRODUÇÃO CIENTÍFICA

Artigos Publicados

Almeida, A. C.; **Pedroso, M. G**.; Aily, J. B.; Goncalves, G. H.; Pastre, C.M.; Mattiello, S. M. Influence of a periodized circuit training protocol on intermuscular adipose tissue of patients with knee osteoarthritis: protocol for a randomized controlled trial. *BMC Musculoskelet Disord*. 2018 Nov 30;19(1):421.

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Aily JB; Carvalho GF; Almeida AC; **Pedroso MG**; Mattiello-Sverzut AC; Mattiello SM. Biopsychosocial aspects of patients with knee osteoarthritis according to age and gender groups: a cross-sectional study. Submetido no periódico *International Journal of Rheumatic Diseases.* 2018.

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Almeida, A.C.; Aily, J.B.; **Pedroso, M.G**.; Gonçalves, G.H.; Pastre, C.M.; Mattiello, S.M. Influences of a periodized circuit training protocol on body composition of older adults with knee osteoarthritis: results from a randomized controlled trial. Submetido em 13 de novembro de 2018 no periódico *Journal of Physiotherapy.*

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Almeida, A. C.; **Pedroso, M**. G.; Aily, J. B.; Goncalves, G. H.; Mattiello, S. M. Relationship between parameters of metabolic syndrome and pain, stiffness and physical function by WOMAC questionnaire and pain catastrophizing scale in patients with knee osteoarthritis. **XXXV Brazilian Congress of Rheumatology (SBR 2018)**, 2018, Rio de Janeiro (RJ). Advances in Rheumatology, 2018. v. 58. p. 89-90.

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Aily, J. B.; Almeida, A. C.; **Pedroso, M. G**.; Goncalves, G. H.; Mattiello, S. M. Can fat mass, and lean mass indexes be better predictors of body composition than BMI between sexes in patients with knee osteoarthritis? **2017 OARSI World Congress on Osteoarthritis**

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Pedroso, M. G.; Goncalves, G. H.; **Almeida, A. C.**; Petrella, M.; Selistre, L. F. A.; **Mattiello, S. M**. Obesity and presence of patellofemoral osteoarthritis influence the stair climbing ability of individuals with tibiofemoral osteoarthritis in early degrees - a pilot study. In: **OARSI 2016 World Congress, 2016, Amsterdam. Osteoarthritis and Cartilage, 2016.** Amsterdam, The Netherlands. Osteoarthritis and Cartilage (April 2016, Vol. 24, Supl. 1, Page S451).

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Pedroso, M.G. - "Alterações na Funcionalidade em Doenças Articulares Crônicas: Osteoartrite", palestra ministrada no I Ciclo de Palestras em Dor Crônica (Processo Pro-Ex UFSCar: 23112.003911/2016-01) oferecido pela Universidade Federal de São Carlos, Departamento de Fisioterapia em novembro de 2016.

Pedroso, M.G. - **"**Exercício físico na dor do joelho", palestra ministrada no Projeto de extensão "Educação ao paciente com osteoartrite de joelho".

Coorientações

Coorientação do Trabalho de conclusão de curso de graduação em Fisioterapia do aluno Rodrigo Simão Gibertoni, intitulado " Associação entre o nível de atividade física e o desempenho funcional em sujeitos com osteoartrite de joelho" pela Universidade Federal de São Carlos.

Banca Avaliadora de Trabalho de Conclusão de Curso e Trabalhos De Graduação

Adriana Francisca Vieira- Trabalho de conclusão de curso de curso de graduação em Fisioterapia da UFSCar 2018. Título do trabalho: Análise comparativa da composição corporal entre atletas de diferentes esportes e indivíduos não atletas.

Lillian Yukimi Watanabe- Trabalho de conclusão de curso de curso de graduação em Fisioterapia da UFSCar 2018. Título do trabalho: relação entre questionários de auto relato e testes baseados no desempenho em indivíduos com osteoartrite de quadril e em indivíduos com dores inespecíficas no quadril.

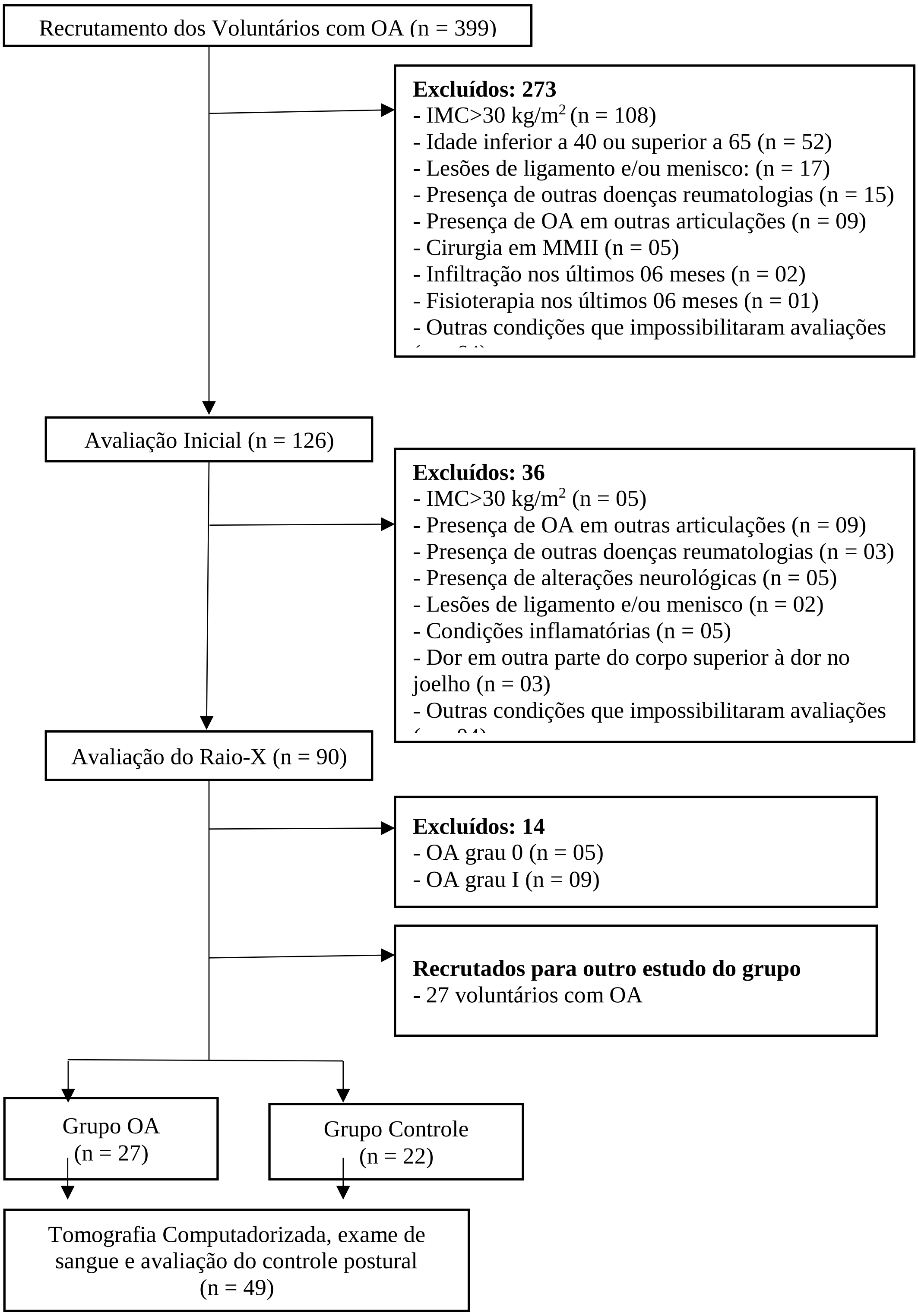
Amanda Iglesias– Trabalho de Graduação 1 (2018). Título do projeto: Influência de um protocolo de tratamento com o método pilates na dor, composição corporal, função física e qualidade de vida em pacientes com osteoartrite de joelho.

Adriana Francisca Vieira- Trabalho de Graduação 1 (2017). Título do projeto: Análise comparativa da composição corporal entre atletas de diferentes esportes e indivíduos não atletas.

Julia Rissi Bergamaschi– Trabalho de Graduação 1 (2016). Projeto: Avaliação da sarcopenia em pacientes com osteoartrite de joelho e sua relação com o teste de sentar e levantar da cadeira.

Gabriel de Carvalho Silva– Trabalho de Graduação 1 (2016). Projeto: Avaliação da sarcopenia em pacientes com osteoartrite de joelho e sua relação com o teste de subir e descer escadas.

APÊNDICE A – Fluxograma de recrutamento dos voluntários



APÊNDICE B – Termo de consentimento livre e esclarecido

UNIVERDIDADE FEDERAL DE SÃO CARLOS
DEPARTAMENTO DE FISIOTERAPIA
Laboratório de Análise da Função Articular
Profª Drª Stela Márcia Mattiello
Via Washington Luiz, Km 235 – C.P 676 – 13565-905
São Carlos/SP- Brasil
TEL: (16) 3351 8031/ (16) 3351 9579

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO
(Resolução 466/2012 do CNS)

Grupo Controle

Nome:____ Registro nº: __________
Data de Nascimento: ____/___/____ RG:______________________
Endereço:____
Cidade: ____________________________________ Estado: ____________________

Sr (a) está sendo convidado para participar da pesquisa "***A influência da gordura intermuscular no equilíbrio postural em pacientes com osteoartrite de joelho***". Você foi selecionado (a) por estar cadastrado na lista de projetos do Laboratório da Função Articular (LAFAr) do Departamento de Fisioterapia da Universidade Federal de São Carlos (UFSCar) ou por ter entrado em contato conosco pelo telefone, e sua participação não é obrigatória. Esta pesquisa tem como objetivo avaliar a quantidade de gordura na musculatura da coxa e do abdômen, a quantidade de conteúdo inflamatório na circulação sanguínea e sua possível relação o equilíbrio postural e com a dor, rigidez e função física em sujeitos com e sem osteoartrite (OA) de joelho.

Sua participação envolverá algumas avaliações que acontecerão em etapas. Primeiramente será realizada avaliação inicial com dados de peso, altura e histórico de dor na articulação do joelho com duração total de 30 minutos (Local: Departamento de Fisioterapia da UFSCar). Em seguida, o (a) senhor (a) responderá um questionário sobre a dor e a função de seus joelhos, mesmo que não sinta dor. Na primeira visita, o (a) sr(a) será encaminhado (a) para realizar os exames que será a segunda etapa:

a) Hemograma: queremos saber se os níveis de colesterol e glicemia podem influenciar ou não na OA de joelho. Esse exame será feito em um laboratório conveniado com o nosso grupo de pesquisa, em ambiente confortável e privativo por profissional habilitado. Uma amostra de sangue será retirada de uma veia do braço usando luvas, máscara, agulha e seringa descartáveis, após serem tomados todos os cuidados de anti-sepsia preconizados para este tipo de procedimento. A coleta, normalmente, não acarreta maiores riscos para a saúde do paciente. Entretanto, em alguns casos poderá surgir nas primeiras horas, no local da punção, um hematoma ou pequeno desconforto que deverá desaparecer em no máximo 3 a 4 dias. Algumas pessoas poderão sentir tonteira durante ou após o procedimento. Para minimizar esse acontecimento, você será orientado a permanecer sentado durante alguns minutos até que se sinta confortável para levantar. Será colhida uma amostra de 4ml de sangue para análise do colesterol, triglicérides e glicemia. Uma pequena amostra de sangue será congelada em nosso laboratório para analisarmos possíveis marcadores inflamatórios que podem estar associados à OA de joelho. Tempo de duração de 15 minutos. Local: Laboratório Maricondi, rua Major José Inácio, 2392, centro;

b) Raio-x dos joelhos: pela imagem radiográfica conseguimos analisar alguns desgastes na articulação. Por essa analise conseguimos saber qual o grau da lesão de seus joelhos de 0 (sem lesão) à 4 (lesão grave). Esse exame será realizado em uma clínica especializada e conveniada com nossa pesquisa. Ressaltamos a importância da realização desse exame nos voluntários que não possuem dor no joelho, pois não há como garantir que indivíduos sem dor no joelho não possuem desgaste ou outros sinais radiográficos da OA. Tempo de duração do exame: 20 minutos. Local de realização: Centro Integrado de Diagnóstico por Imagem (CIDI), Rua Paulino Botelho de Abreu Sampaio, 573, Vila Pureza;

c) Tomografia computadorizada do abdômen e das coxas: O exame de tomografia computadorizada será realizado por um radiologista capacitado, e serão captadas imagens das coxas (direita e esquerda) e do abdômen. Com essas imagens nós iremos analisar a quantidade de músculo e gordura presente nesses segmentos. O exame consiste em permanecer deitado (a) de barriga para cima por, aproximadamente 3 min, na maca pertencente ao aparelho de tomografia computadorizada. Tempo de duração do exame: 10minutos. Local de realização: Hospital Escola de São Carlos;

O exame de raio-x do joelho expõe ao paciente uma dose de radiação aproximada de 0,005 mSv(mili Sievert), enquanto que o exame de tomografia computadorizada que iremos realizar expõe uma dose aproximada de 2,75 mSv para a imagem do abdômen, e 2,81 mSv para a imagem da coxa. Essas doses de radiação estão da dose de radiação permitida na população.

A terceira etapa da sua participação será sua segunda visita ao Departamento de Fisioterapia da UFSCar, onde será revelado o resultado do raio-x e do hemograma (glicemia e colesterol) e será realizada a avaliação do equilíbrio postural. Essa avaliação ocorre em uma sala que possui uma plataforma de força, aparelho que capta os dados de quanto o indivíduo oscilou em uma determinada postura. Esse teste será realizado por meio de testes em quatro posturas:

a) dois pés apoiados no chão com olhos abertos;
b) dois pés apoiados no chão com olhos fechados;
c) um pé apoiado no chão com olhos abertos;
d) um pé na frente do outro com olhos abertos;
e) um pé na frente do outro com olhos fechados.

O (a) senhor (a) permanecerá 30segundos em cada postura e o tempo total da avaliação é de aproximadamente 1hora. Esse teste pode levar a perda de equilíbrio, para evitar qualquer tipo de queda haverá sempre um fisioterapeuta ao seu lado a fim de prezar pela sua segurança durante a realização dos testes. Possivelmente, o (a) Sr (a) poderá se sentir cansado (a) por permanecer alguns minutos em pé ou pela repetição de alguns movimento, e assim sendo o (a) senhor (a) poderá descansar quando quiser.

Os riscos envolvidos neste estudo são mínimos e caso se perceba qualquer risco ou dano a sua saúde, não previstos neste termo, as atividades desta pesquisa serão imediatamente suspensas. Caso seja identificado qualquer problema de saúde, o (a) senhor (a) será encaminhado (a) para o serviço de saúde do município. Caso haja algum desconforto durante a aplicação dos instrumentos ou na coleta de sangue, pedimos que nos informe para que possamos corrigi-lo. Antes e durante a sua participação em nosso estudo, estamos à disposição para esclarecer qualquer tipo de dúvida que o (a) senhor (a) tiver a respeito da pesquisa, dos exames ou dos testes a serem realizados.

Ao final do estudo, o (a) senhor (a) será informado sobre a saúde do seu joelho, os resultados do exame de sangue, os resultados dos testes de equilíbrio e será orientado às melhores condutas para cada caso. Forneceremos também uma cartilha com exercícios de fortalecimento e de equilíbrio para serem realizados em casa, ou com a ajuda de um profissional capacitado, a fim de tentar atenuar a progressão do desgaste do joelho e prevenir contra quedas. Além da cartilha, o nosso grupo de pesquisa fornecerá tratamento supervisionado para fortalecimento das pernas e do tronco com o propósito de atenuar o desgaste no joelho, melhorar a condição muscular a ser trabalhada e diminuir os possíveis processos inflamatórios decorrentes da osteoartrite. Esse tratamento será realizado no Departamento de Fisioterapia da UFSCar por fisioterapeutas que compõem a equipe do projeto de osteoartrite de joelho.

Sua participação é voluntária, isto é, a qualquer momento você pode recusar-se a responder qualquer pergunta ou desistir de participar e retirar seu consentimento. Sua recusa não trará nenhum prejuízo em sua relação com o pesquisador ou com a instituição que forneceu os seus dados. É importante que informe a equipe sobre todo e qualquer tipo de procedimento (e/ou tratamento) externo que está sendo ou será realizado no futuro, para não comprometer os dados coletados durante a pesquisa.

Você não receberá nenhuma remuneração por sua participação nesta pesquisa, entretanto todas as despesas com o transporte e a alimentação decorrentes da sua participação na pesquisa, ou da sua ausência, quando for o caso, serão ressarcidas em dinheiro no dia da coleta. Os resultados obtidos a partir desta pesquisa serão de propriedade exclusiva dos pesquisadores e poderão ser divulgados a critério dos mesmos, entretanto sua identidade estará sempre preservada e não será revelada em momento algum.

É importante que informe a equipe sobre todo e qualquer tipo de procedimento (e/ou tratamento) externo que está sendo ou será realizado no futuro, para não comprometer os dados coletados durante a pesquisa. O (a) Sr (a) não terá nenhum custo ou quaisquer compensações financeiras.

Suas respostas serão tratadas de forma anônima e confidencial, isto é, em nenhum momento será divulgado o seu nome em qualquer fase do estudo. Quando for necessário exemplificar determinada situação, sua privacidade será assegurada uma vez que seu nome será substituído de forma aleatória. As informações obtidas nesta pesquisa não serão, de maneira alguma, associadas à sua identidade e não poderão ser consultadas por pessoas leigas sem sua autorização oficial. Estas informações poderão ser utilizadas para fins estatísticos ou científicos, ficando resguardados a sua total privacidade e anonimato. Os responsáveis pelo estudo explicaram ao senhor (a) todos os riscos envolvidos, a necessidade da pesquisa e se prontificam a responder todas as questões sobre o experimento.

O (a) senhor (a) receberá uma cópia deste termo, no qual consta o telefone e o endereço da pesquisadora responsável, podendo tirar suas dúvidas sobre sua participação, agora ou a qualquer momento. Desde já agradecemos!

____
Maria Gabriela Pedroso
Pesquisadora
Contato: (14)98169 1407

____
Prof. Dra. Stela Márcia Mattiello
Orientadora

Departamento de Fisioterapia da Universidade Federal de São Carlos (UFSCar), Rod. Washington Luiz, 235 – CEP: 13565-905- São Carlos – SP. Telefone: (16) 3351 8031

Declaro que entendi os objetivos, riscos e benefícios de minha participação na pesquisa e concordo em participar. Declaro também que concordo com a coleta, o depósito, o armazenamento e a utilização do material biológico humano (sangue) para investigações futuras.

O pesquisador me informou que o projeto foi aprovado pelo Comitê de Ética em Pesquisa em Seres Humanos da UFSCar na Pró-Reitoria de Pós-Graduação e Pesquisa da UFSCar, localizada na Rodovia Washington Luiz, Km. 235 - Caixa Postal 676 - CEP 13.565-905 - São Carlos - SP. Fone (16) 3351-8110. Endereço eletrônico: cephumanos@power.ufscar.br.

São Carlos, ____ de ____________ de _____.

____
Assinatura do participante

ANEXO A – Aprovação do Comitê em Ética e Pesquisa de Seres Humanos

UNIVERSIDADE FEDERAL DE SÃO CARLOS/UFSCAR

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: A influência da gordura intermuscular no equilíbrio postural em pacientes com osteoartrite de joelho

Pesquisador: Maria Gabriela Pedroso

Área Temática:

Versão: 4

CAAE: 40396614.4.0000.5504

Instituição Proponente: Centro de Ciências Biológicas e da Saúde

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.109.849

Data da Relatoria: 09/06/2015

Apresentação do Projeto:

Trata-se de estudo prospectivo, caso-controle. Voluntários entre 40 e 70 anos, divididos em dois grupos: controle e portadores de osteoartrite (OA) do joelho, serão submetidos a entrevistas, exames radiológicos (Raios-X simples joelho – controle e Tomografia Computadorizada coxa – portadores OA) e exames sanguíneos, posteriormente serão submetidos à avaliação do equilíbrio postural por uma plataforma de força e eletromiografia dos músculos da coxa.

Objetivo da Pesquisa:

Primariamente, pretende quantificar a gordura intermuscular do músculo quadríceps e citocinas inflamatórias e relacioná-las com o controle postural, além da função física, dor e rigidez autorrelatadas em pacientes com OA de joelho. Como objetivos secundários, a pesquisadora informa que também pretende quantificar a gordura intermuscular do quadríceps em indivíduos com OA de joelho e sem OA de joelho; quantificar as citocinas pró-inflamatórias e relacioná-las com a quantidade de gordura intermuscular em indivíduos com e sem OA de joelho; avaliar o controle postural em indivíduos com e sem OA de joelho; relacionar o controle postural com os achados de gordura intermuscular e citocinas e identificar se há relação entre quantidade de tecido adiposo intermuscular, citocinas e controle postural com a dor, rigidez e funções físicas autorrelatadas.

Avaliação dos Riscos e Benefícios:

A pesquisadora aponta como riscos o cansaço e a perda de equilíbrio, hematoma na coleta de sangue, além de serem submetidos a radiação devido aos exames radiológicos.

Como benefícios, assinala que os indivíduos que participarem do estudo terão o diagnóstico da osteoartrite de joelho realizado pela radiografia, avaliação do controle postural e avaliação dos níveis sistêmicos de fatores inflamatórios circulantes no organismo. Ao final o participante será informado sobre a saúde do seu joelho, os resultados do exame de sangue, os resultados dos testes de equilíbrio e será orientado às melhores condutas para cada caso. No caso de presença inicial de desgaste de joelho, o participante irá ser informado sobre as melhores condutas para evitar ou atenuar a progressão do desgaste. O resultado do exame de equilíbrio é comparativo com os outros voluntários. Caso seja constatado um desempenho abaixo da média, o participante será auxiliado a melhorar o equilíbrio através de orientações e cartilha com exercícios de fortalecimento e equilíbrio.

Comentários e Considerações sobre a Pesquisa:

O projeto de pesquisa possui relevância à área em questão.

Considerações sobre os Termos de apresentação obrigatória:

O pesquisador apresentou todos os documentos obrigatórios.

Recomendações:

Sem novas recomendações.

Conclusões ou Pendências e Lista de Inadequações:

Pendências anteriores resolvidas a contento.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

UNIVERSIDADE FEDERAL DE
SÃO CARLOS/UFSCAR

Plataforma Brasil

Continuação do Parecer: 1.109.849

SAO CARLOS, 16 de Junho de 2015

Assinado por:
Ricardo Carneiro Borra
(Coordenador)

Endereço: WASHINGTON LUIZ KM 235
Bairro: JARDIM GUANABARA **CEP:** 13.565-905
UF: SP **Município:** SAO CARLOS
Telefone: (16)3351-9683 **E-mail:** cephumanos@ufscar.br