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Momento Adutor do joelho durante a marcha, torque abdutor do quadril e biomarcadores: estudo na progressão da Osteoartrite de Joelho.

Tese de Doutorado apresentada ao Programa de Pós-graduação em Fisioterapia da Universidade Federal de São Carlos, como parte dos requisitos para a obtenção do título de Doutor em Fisioterapia, área de concentração: Processos de Avaliação e Intervenção em Fisioterapia

DISCENTE
Luiz Fernando Approbato Selistre

ORIENTADOR
Profa. Dra. Stela Márcia Mattiello
Departamento de Fisioterapia da Universidade Federal de São Carlos

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Folha de Aprovação

Assinaturas dos membros da comissão examinadora que avaliou e aprovou a Defesa de Tese de Doutorado do candidato Luiz Fernando Approbato Selistre, realizada em 30/03/2017:

Profa. Dra. Stela Marcia Mattiello
UFSCar

Profa. Dra. Tania de Fatima Salvini
UFSCar

Prof. Dr. Renan Alves Resende
UFMG

Prof. Dr. Renato de Moraes
USP

Profa. Dra. Paula Regina Mendes da Silva Serrão
UFSCar

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RESUMO DA TESE

Introdução: A osteoartrite do joelho (OAJ) tem como principais fatores etiológicos as alterações metabólicas e carga mecânica. Para avaliação das alterações metabólicas, os biomarcadores são importantes ferramentas capazes de identificar desequilíbrios metabólicos dos condrócitos. Por outro lado, o momento adutor, impulso do momento adutor e momento flexor do joelho têm sido utilizados para avaliação da carga imposta no joelho. Embora essas variáveis sejam adequadas para avaliação da carga no joelho, outros fatores como a força dos abdutores do quadril, além de variáveis como o momento adutor do quadril e a cinemática no plano frontal do tronco, pelve e quadril durante a marcha. Considerando que os fatores biológicos e mecânicos têm relação direta com o onset e progressão da doença, a investigação da relação destes fatores com medidas clínicas como dor e função física poderia auxiliar o entendimento do papel destes fatores na condição clínica dessa população. Dessa forma, o objetivo desta tese foi de investigar a relação de fatores biológicos e mecânicos com a dor e função física de pacientes com osteoartrite do compartimento medial do joelho. **Método:** Foram avaliados sujeitos de ambos os sexos, com diagnóstico de osteoartrite medial do joelho e estes foram classificados quanto ao grau de severidade (Kellgren e Lawrence, 1957). Os participantes responderam ao questionário WOMAC (dor, rigidez e função física), foram submetidos à avaliação tridimensional da marcha realizada por meio do sistema Qualisys Motion Capture (Qualisys Medical AB, Suécia) sincronizado a duas plataformas de força (Bertec, OH, USA). A avaliação da força muscular de abdutores do quadril foi realizada por meio do dinamômetro isocinético (Biodex Medical System, NY, USA) e por fim, a concentração de uCTX-II (urinary C-Teleopeptide of type II collagen) foi analisada a partir de amostras de urina pelo método ELISA (*Enzyme-Linked Imunnosorbent Assay*) e normalizado pela creatinina total na urina (mmoles/L). **Resultados:** Os abdutores do quadril explicaram 17% da queda da pelve contralateral, 21% do ângulo de adução do quadril e de 1 a 4% da função física em indivíduos com osteoartrite de joelho. A concentração do biomarcador uCTX-II explicou 9% da dor e 7 a 27% da função física em indivíduos com osteoartrite de joelho. **Conclusão:** Exercícios para abdutores do quadril devem enfatizar sua função estabilizadora da pelve, objetivando melhorar a função física dessa população. Além disso, considerando que as medidas mecânicas do joelho não apresentam nenhuma associação com o

desequilíbrio metabólico dos condrócitos, o mecanismo de ação destas variáveis parece ser diferente um do outro em pacientes com osteoartrite do joelho. Por fim, uma vez que o uCTX-II demonstra associação com medidas clínicas (dor e função física), este biomarcador pode ser usado para melhor entender os efeitos de uma intervenção sobre a saúde da cartilagem.

Palavras-chaves: osteoartrite de joelho, momento adutor do joelho, biomarcadores, abdutores do quadril, marcha.

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Sumário

CONTEXTUALIZAÇÃO

A osteoartrite do joelho (OAJ) tem como principal característica a degeneração da cartilagem articular (Umlauf et al. 2010) e como consequência os pacientes com OAJ apresentam dor e déficit funcional (Brooks 2002). Por ser uma doença crônico-degenerativa e evolutiva, muitas pesquisas têm buscado a identificação de fatores relacionados ao seu início e progressão. Considerando a importância em integrar os componentes biológicos, mecânicos e estruturais envolvidos na osteoartrite, como proposto por Andriacchi et al. (2004), a presente tese teve como objetivo abordar os parte dos aspectos mecânicos e biológicos da doença.

Os aspectos mecânicos abordados nos estudos realizados nesta tese foram feitos a partir dos momentos articulares do joelho, considerando as variáveis relacionadas ao compartimento medial do joelho, sendo elas: o momento adutor, impulso do momento adutor e momento flexor do joelho (Baliunas et al. 2002; Bennell et al. 2011; Chang et al. 2015; Chehab et al. 2014). Para uma adequada abordagem destes momentos foram consideradas variáveis, que possivelmente poderiam influenciar o comportamento das mesmas, como o momento adutor do quadril, a força dos abdutores do quadril e a cinemática no plano frontal do tronco, pelve e quadril durante a marcha (Powers 2010; Hunt et al. 2008; Hunt et al. 2010).

Os aspectos biológicos abordados nesta tese foram estudados a partir da análise da concentração do biomarcador uCTX-II (*urinary C-Telopeptide of type II collagen*), considerado ser este um dos biomarcadores mais confiáveis e utilizados para identificação de alterações no metabolismo da cartilagem articular (Wang et al. 2014; Tanishi et al. 2009a; Saberi Hosnijeh et al. 2015). Por fim, o questionário WOMAC (*Western Ontario and McMaster Universities Osteoarthritis Index*) e o teste de

caminhada de 40 metros foram utilizados como medidas clínicas, a fim de analisar o papel destas variáveis mecânicas e biológicas na condição clínica, dos pacientes com OAJ. Dessa forma, o objetivo desta tese foi de investigar a relação de fatores biológicos e mecânicos com a dor e função física de pacientes com osteoartrite do compartimento medial do joelho.

REVISÃO DA LITERATURA

A osteoartrite do joelho (OAJ) é uma das doenças mais prevalentes em todo o mundo e apresenta um crescimento exponencial principalmente após os 55 anos (Losina et al. 2013; Felson and Zhang 1998), resultando em consequências sociais e econômicas negativas (Reyes et al. 2015; Cross et al. 2014). Apresenta como principal característica a degeneração da cartilagem articular (Umlauf et al. 2010), além do comprometimento dos tecidos articulares adjacentes (Roos et al. 2011). Como consequência, pacientes com OAJ apresentam dor e déficit funcional, resultando em uma redução de sua qualidade de vida (Brooks 2002).

Considerando que a OAJ é uma doença crônica degenerativa, a identificação de fatores relacionados ao início, bem como a progressão da doença se tornam importantes, visto que a maioria das propostas de reabilitação encontrados na literatura, focam os sintomas e déficits funcionais (Andriacchi et al. 2015). Por esta razão, Andriacchi et al, (2004) propôs um modelo de abordagem para a OA integrando os componentes biológicos, mecânicos e estruturais. Os componentes biológicos incluem fatores que influenciam o metabolismo celular, os níveis de inflamação sistêmica e as etiologias genéticas. Os componentes mecânicos incluem qualquer tipo de estímulo mecânico, como exemplo, a marcha, subida e descida de degraus, entre outros. Por fim, os componentes estruturais incluem o alinhamento mecânico, espessura da cartilagem e propriedade dos ligamentos, como exemplo. Dessa forma, a interação equilibrada entre esses componentes, representa uma homeostasia saudável para a articulação do joelho. Assim, quando um destes componentes se mover para fora dos limites fisiológicos, os demais componentes irão reagir, a fim de compensar essa alteração. Caso essa compensação não seja suficiente, a homeostase saudável de funcionamento será perdida

e a saúde da articulação estará comprometida (Andriacchi et al. 2015; Andriacchi et al. 2004).

A OAJ tem caráter multifatorial, porém a literatura aponta os fatores mecânicos como um dos responsáveis principais pelo surgimento e progressão da doença (Varady and Grodzinsky 2016; Felson 2013). A cartilagem articular do compartimento medial do joelho é dez vezes mais acometida que a do compartimento lateral (Bartel 1992; Dearborn, Eakin, and Skinner 1996) Considerando esta diferença de sofrimento entre os compartimentos do joelho, diversos estudos têm investigado a carga imposta no compartimento medial (Baliunas et al. 2002; Bennell et al. 2011; Chang et al. 2015; Chehab et al. 2014), assim como, possíveis mecanismos para reduzi-la (Favre et al. 2016; Hunt et al. 2008; Simic et al. 2011; Simic et al. 2012; Sled et al. 2010).

O momento adutor do joelho (MAJ) tem sido utilizado como preditor indireto da carga imposta no compartimento medial do joelho, durante a marcha (Baliunas et al. 2002; Bennell et al. 2011; Chang et al. 2015; Chehab et al. 2014). O MAJ é descrito como o produto dos componentes: força de reação do solo (FRS) e braço de alavanca no plano frontal. A magnitude do braço de alavanca é representada pela distância entre o centro de rotação da articulação do joelho e o vetor da linha de ação da FRS, determinada a partir do centro de pressão do pé em direção ao centro da massa corporal (Hunt et al. 2008). Essa variável apresenta dois picos de força durante a marcha, o primeiro refere-se à resposta a carga após o toque inicial do calcanhar no solo, estando aumentado em indivíduos com OA do joelho, enquanto o segundo pico refere-se a fase de impulsão da marcha (Roos et al. 2011; Simic et al. 2011; Simic et al. 2012). Em paciente com OAJ, o MAJ apresenta-se aumentado (Baliunas et al. 2002; Hurwitz et al. 2000; Sharma et al. 1998), além de estar associado com a presença e intensidade de dor (Thorp et al. 2007; Hurwitz et al. 2000), grau de acometimento da doença (severidade)

(Thorp et al. 2006; Sharma et al. 1998) e também progressão da doença (Chang et al. 2015; Miyazaki et al. 2002).

Embora o MAJ seja uma medida confiável e amplamente utilizada para mensuração da carga medial do joelho, outra medida muito utilizada é o impulso do momento adutor (*knee adduction angular impulse* - KAAI), que representa o tempo integral do MAJ durante a fase de apoio da marcha (Thorp et al. 2006). Assim, como o MAJ, o KAAI está associado a presença, severidade, dor e incapacidade funcional em pacientes com OAJ (Maly et al. 2015; Kean et al. 2012; Thorp et al. 2006; Kito et al. 2010). Mais recentemente, foi proposta a utilização do momento flexor do joelho de forma associada ao MAJ, o que resultaria em uma melhor mensuração da carga no compartimento medial, visto que o momento flexor do joelho também contribui na distribuição da carga, entre os compartimentos do joelho (Manal et al. 2015).

A análise da carga no compartimento medial do joelho deve levar em consideração, outras variáveis que influenciam diretamente no seu comportamento. Como exemplo, a contração dos músculos abdutores do quadril desempenha um importante papel no alinhamento dinâmico do membro inferior, durante a marcha, porém quando os abdutores estão fracos, a carga articular tende a aumentar no compartimento medial do joelho (Powers 2010; Thorp et al. 2010). A fraqueza dos abdutores do quadril foi inclusive apontada como um fator de risco para a progressão da doença, tendo em vista que quando presente, a fraqueza permite uma queda pélvica contralateral, deslocando o centro de massa em direção ao membro em apoio e desta forma, aumentando a carga no compartimento medial do joelho (Chang et al. 2005). Embora estudos recentes tenham apontado que a força dos abdutores do quadril não tem nenhuma relação com o MAJ e KAAI (Kean et al. 2015; Rutherford, Hubley-Kozey, and Stanish 2014), esses estudos não consideraram o comportamento cinemático de

outros segmentos do corpo, como o tronco, pelve e quadril no plano frontal. Estes segmentos corporais são considerados determinantes no comportamento do MAJ, no KAAI e também na exigência sobre os abdutores do quadril (Hunt et al. 2008; Hunt et al. 2010; Powers 2010). Dessa forma, um melhor entendimento da associação entre a força dos abdutores do quadril com o MAJ, KAAI, cinemática do tronco, pelve e quadril no plano frontal, contribuiria em um melhor entendimento do papel destes fatores durante a marcha em pacientes com osteoartrite do joelho.

Para uma melhor abordagem do paciente com OAJ é importante levar em consideração o fator biológico, que também é apontado como um dos principais responsáveis pelo aparecimento e progressão da doença (Bay-Jensen et al. 2016; Erhart-Hledik et al. 2012; Henrotin et al. 2007; Røtterud et al. 2014). O fator biológico é caracterizado pelo desequilíbrio entre as atividades de síntese e degradação dos condrócitos. Para avaliação dessa condição, os biomarcadores têm excelente capacidade de apontar essa relação (anabolismo/catabolismo) e também informar a condição de saúde da cartilagem (Henrotin et al. 2007). Atualmente, diversos biomarcadores têm sido utilizados para essa medida, a partir de fluídos biológicos como a urina, sangue e líquido sinovial (Rousseau and Delmas 2007; Petersson et al. 1997; Kraus 2011; Mobasheri et al. 2017). Estudos têm apontado o uCTX-II (*C-terminal telopeptide of collagen)* como os um dos mais sensíveis na detecção de alterações no metabolismo da cartilagem em pacientes com OAJ (Henrotin et al. 2007; Bauer et al. 2006; Rousseau and Delmas 2007), além de ser facilmente coletado por meio da urina do paciente. O uCTX-II é um biomarcador da quebra do colágeno II, principal colágeno da cartilagem articular, sendo encontrado em alta concentração em pacientes com OAJ. Além disso, de acordo com os critérios BIPED (*Burden of disease, Investigative, Prognostic, Efficacy of Intervention, and Diagnostic*), o uCTX-II tem capacidade para diagnóstico,

prognóstico, predição da progressão da doença e detecção da severidade da doença (Henrotin et al. 2007; Wang et al. 2014; Sowers et al. 2009; Tanishi et al. 2009a; Saberi Hosnijeh et al. 2015). Dessa forma, o uCTX-II é um biomarcador confiável para avaliação da condição metabólica da cartilagem e portanto, seu uso está fortemente recomendado para estudos em pacientes com OAJ.

Embora os fatores mecânicos e biológicos sejam apontados como os principais causadores da OAJ é importante considerar a relação destes fatores, com a dor e função física dos pacientes com OAJ, para melhor compreensão clinicamente destes fatores. As avaliações de dor e função física são comumente utilizadas para avaliar o resultado de propostas de tratamento e reabilitação, critério de prognóstico da doença e também para avaliar a condição clínica do paciente. Além disso, são recursos facilmente aplicados na prática clínica e podem ser quantificados por meio de testes e questionários. Para avaliação da função física, há uma recomendação do uso de testes baseado no desempenho físico e também questionários de avaliação funcional. Estudos prévios identificaram que há uma relação da carga no joelho, com os biomarcadores e também com a dor e função física (Garnero et al. 2001; Ishijima et al. 2011; O'Connell, Farrokhi, and Fitzgerald 2016). Entretanto, não existe uma associação conclusiva entre essas medidas. No estudo de Garnero et al (2001) não foi encontrada associação entre a concentração de uCTX-II, com a dor e função física, porém, em estudo mais recente, Ishijima et al (2011), observou uma associação entre a concentração do mesmo biomarcador, com dor em pacientes com OAJ.

Da mesma forma, a relação entre a carga no joelho e dor e função física é também incerta. Um estudo recente observou que a intensidade da dor tem relação direta com o momento flexor do joelho, mas não com o MAJ (O'Connell, Farrokhi, and

Fitzgerald 2016). De modo semelhante, outro estudo não encontrou nenhuma associação entre o MAJ e a dor e função física em pacientes com OAJ (Maly, Costigan, and Olney 2006a). Por outro lado, o impulso do MAJ parece estar associado a dor e função física (Kito et al. 2010). Dessa forma, a investigação dessas relações poderia auxiliar no entendimento da relação da carga no joelho e concentração de uCTX-II com a dor e função física.

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MANUSCRITO I

The role of hip abductors strength on the frontal plane of gait in subjects with medial knee osteoarthritis

Manuscrito submetido ao periódico *Clinical Biomechanics*.

Abstract

Introduction: Hip abductor strength has been targeted in rehabilitation programs for patients with knee osteoarthritis, however, as it explains only a small portion of medial knee load, the influence of trunk, pelvis, and hip kinematics in the frontal plane during gait in this population should be investigated. This study aimed to investigate the relationship of hip abductors strength with hip and knee adduction moments, pain and physical function, and trunk, pelvis, and hip kinematics during walking in the frontal plane in subjects with medial knee osteoarthritis. **Methods:** Twenty five subjects with medial knee osteoarthritis were included in the study. Participants were evaluated through an isokinetic strength test for hip abductors, three-dimensional gait analysis, the WOMAC pain and physical function scores, and walk test – 40m. First, the relationship of hip abductor strength with the other variables was investigated. Second, regression models were used to control the influence of other parameters such as pain, age, gender, severity, walking speed, mass and height. **Results:** Hip abductors strength explained 17% of contralateral pelvic drop and 21% of hip adduction angle. In addition, hip abductors strength explained 4% and 1% of the variance in the WOMAC physical function score and walk test (40m), respectively. **Conclusion:** Considering the relationship of hip abductors strength with contralateral pelvic drop and hip adduction angle, specific exercises should be used to improve physical function and the ability of hip abductors to stabilize the pelvis and the hip adduction angle during walking.

Keywords: Knee osteoarthritis; Hip abductors strength; Trunk lean; Pelvic drop; Gait; Knee adduction moment.

Introduction

Hip abductor strength has been found to be weak in subjects with knee osteoarthritis (KOA) compared to a healthy control group (Costa et al. 2010; Hinman et al. 2010; Sled et al. 2010). Weakness of hip abductors has been linked to an increased risk of disease progression (Chang et al. 2005), as it allows greater contralateral pelvic drop, shifting the centre of mass away from the stance limb, and increasing the medial knee load (Chang et al. 2005; Pohl et al. 2015). The medial knee load has been measured through three-dimensional gait analysis using the knee adduction moment (KAM) and the knee adduction angular impulse (KAAI), which is normally increased in this population (Maly et al. 2015; Miyazaki et al. 2002; Sharma et al. 1998). Recent studies have shown that hip abductor strength has no relationship with hip and knee adduction moments (Kean et al. 2015; Rutherford, Hubley-Kozey, and Stanish 2014). In addition, despite studies have shown that hip abductor strengthening exercises reduce pain and improve physical function, no change on knee and hip adduction moments was observed in subjects with KOA (Bennell et al. 2010; Sled et al. 2010). It is important to highlight that hip abductors might be associated to the behaviour of other segments of the body, such as the trunk, hip, and pelvis (Hunt et al. 2008; Powers 2010). For instance, trunk lean toward the stance limb is considered a compensation to reduce the effort of hip abductors (Powers 2010). However, none of these previous studies have considered the role of these other segments. Investigating the association of hip abductors with these other segments would contribute to understand the influence of these segments (Hunt et al. 2008; Hunt et al. 2010)on hip abductors during walking and provide important information for the development of intervention strategies.

Previous studies have suggested that hip abductors are associated with kinematics of the hip and proximal and distal segments (Linley et al. 2010; Powers 2010). For instance, as hip abductors stabilize the pelvis and hip on the frontal plane, increased contralateral pelvic drop (Trendelenburg sign) and a higher hip adduction angle may represent hip abductor weakness (Powers 2010; Neumann 2010). Which theoretically means that the higher is the strength of hip abductors, the less contralateral pelvic drop, hip adduction angle, and trunk lean toward to the stance limb.

Although this relationship seems to be present, to our knowledge, there is no study to support this association in subjects with medial KOA. Finally, investigating the relationship of hip abductors with hip and knee moments, pain and physical function, and other segments (trunk, hip, and pelvis) on the frontal plane would clarify the role of hip abductors and guide the development of specific exercises to improve its function. This study aimed to investigate the relationship of hip abductors with hip and knee adduction moments, pain and physical function, and trunk, hip, and pelvis kinematics during walking in the frontal plane in subjects with medial KOA. We hypothesized that hip abductors would have no relationship with hip and knee adduction moments, however, would be negatively correlated with ipsilateral trunk lean, contralateral pelvic drop, and hip adduction angle. We also hypothesised that hip abductors would be associated with pain and physical function in subjects with medial KOA.

Methods

Subjects

The sample size was calculated as the number of subjects necessary to reach a statistical significance level of 0.05, power of 95% and a medium effect size (d=0.5). Twenty five subjects were included in the study (Table 1). All participants underwent anteroposterior

semiflexed weight-bearing, lateral view, and skyline view radiographs. These were classified according to the Kellgren and Lawrence (KL) criteria (Kellgren and Lawrence 1957) and diagnosed as KOA if they met the American College of Rheumatology (clinical, radiographic, and history) criteria (Altman et al. 1986). In addition, only subjects with predominantly medial KOA were included, therefore subjects were excluded if they presented KL grades in the lateral or patellofemoral compartment greater than the medial compartment (Zeni, Rudolph, and Higginson 2010). Volunteers were excluded for any of the following criteria: body mass index greater than 35kg/m^2, unable to walk without any aid, history of hip or knee arthroplasty or osteotomy, had undergone knee surgery or other nonpharmacological treatment in the 6 months prior to the study (Kean et al. 2015). For bilateral knee OA volunteers the most symptomatic knee was evaluated. All participants provided written informed consent and the present study was approved by the Ethics committee for Human Investigations at the Federal University of São Carlos.

Pain and physical function evaluation

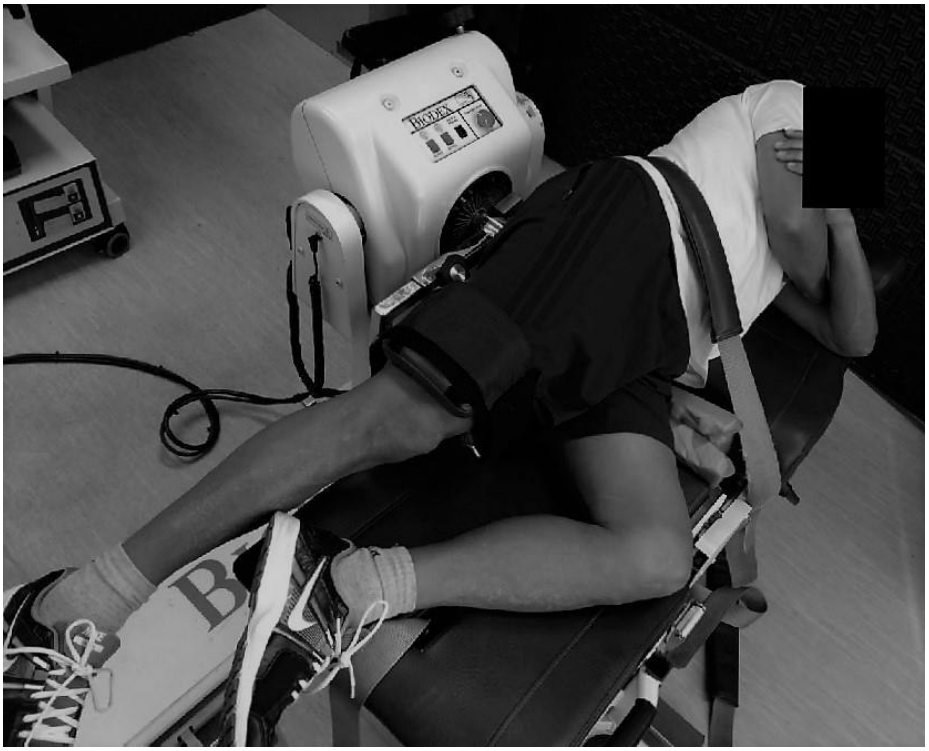
To evaluate pain and physical function we used the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire, Portuguese version (Serrao et al. 2012; Serrao et al. 2015). This is a self-administered questionnaire, specifically designed for subjects with KOA. We considered all the 24 questions, scoring each one according to the Likert scale (none=0, slight=1, moderate=2, severe=3, extreme=4). The total score ranged from 0 to 96 points and the higher scores indicated worse pain, stiffness, and physical function (Bellamy et al. 1988). In addition, to complement the evaluation of physical function, specifically related to walking ability, participants performed the walk test – 40m, a specific test for subjects with KOA in which subjects

have to walk as fast as possible without running (Dobson et al. 2013; Wright et al. 2011). The speed (speed=distance/time) was used for analysis.

Hip abductor strength evaluation

An isokinetic dynamometer (Biodex Multi-Joint System 3, New York, USA) was used to evaluate hip abductor concentric peak torque. In order to avoid compensatory movements the examiner instructed the volunteer on how to perform the movement avoiding external rotation, knee flexion, pelvis movement, or any other movements not related to hip abduction. The assessment was not performed on the same day as gait evaluation. Participants were placed in the side-lying position with the non-tested hip and knee flexed (45° and 90°, respectively) and fixed with straps (Nakagawa et al. 2008; Baldon Rde et al. 2014). The axis of the dynamometer was aligned with the hip joint centre, and the resistance arm of the dynamometer was attached to the lateral aspect of the thigh being tested, 5 cm above the base of the patella. The range of motion was from 0 (neutral position) to 30 degrees of hip abduction and we used 30°/s as angular speed.

Figure 1. Setup used to measure the hip abductors strength.



Prior to the test, participants performed 3 submaximal and 2 maximal concentric contractions in order to familiarize with the movement and equipment, for the examiner to observe if any compensatory movements were used and evaluate if any pain was present. A one minute rest interval separated the familiarization and 5 maximal concentric contractions. The peak torque of each contraction was used to calculate a mean and then the mean of peak torque was normalized by body mass (Nm/kg). Participants received verbal encouragement during all trials but no visual feedback was given. The procedures described above presented excellent reliability, with an Intraclass Correlation Coefficient (Standard Error of Measurement) of 0.97 (0.07 Nm/kg)(Baldon Rde et al. 2009). To correct for the influence of gravity on the torque data, the limb was weighed prior to the test, according to the instruction manual for the dynamometer. A single examiner completed all HAS testing.

Gait evaluation

An eight-camera Qualisys Oqus 300 motion analysis system (Qualisys, Gothenburg, Sweden) and two force plates (Bertec Corporation, OH, USA) were used to record kinematic and kinetic data at sampling frequencies of 120 and 1200 Hz, respectively. Volunteers walked barefoot at a self-selected speed along an 8 m walkway. For each subject, a static calibration trial, followed by five successful trials were collected for kinetic and kinematic analysis. A trial was considered successful when the subject walked naturally, landing with the whole foot of the affected limb on the covered force plate (Chapman et al. 2015).

The following reflective markers were located on anatomical landmarks bilaterally: acromia, iliac crests, anterior and posterior superior iliac spines, greater trochanters of the femur, medial and lateral femoral epicondyles, medial and lateral malleoli, first, second and fifth metatarsal heads, base of the fifth metatarsal, and calcaneus. A single marker was placed on the sternal notch and spinous process at C7. Four clusters built with 4 noncollinear markers were placed over the lateral side of the right and left thigh and shank. Two additional clusters built with 3 noncollinear markers were positioned on the spinous process at T4 and T12. The medial and lateral malleoli, femoral epicondyles, seventh cervical vertebrae, greater trochanters, and acromia were removed after the static standing calibration trial was performed. These markers were used to construct the anatomical coordinate system for the trunk, pelvis, thigh, shank, and foot segments.

The ankle and knee joint centres were calculated as midpoints between the malleoli and femoral epicondyles, respectively (Chapman et al. 2015). The hip joint centre was measured using the regression model based on the anterior and posterior

superior iliac spine markers(Bell, Brand, and Pedersen 1989). The pelvis was built from markers on the anterior and posterior superior iliac spines and then ipsilateral and contralateral pelvic drop with respect to the laboratory were measured using an anterior-posterior axis. The trunk was built from markers on the acromia and iliac crest (bilaterally), and the ipsilateral and contralateral trunk lean with respect to the laboratory were measured using an anterior-posterior axis (Resende, Kirkwood, Deluzio, Hassan, et al. 2016; Resende, Kirkwood, Deluzio, Morton, et al. 2016). The angular motion of all assessed joints was defined using Cardan angles in accordance with the recommendations of the International Society of Biomechanics (Wu et al. 2002).

The kinetic and kinematic data were processed using Qualisys Track Manager (Qualisys AB) and Visual3D software (C-motion Inc., Rockville, MD, USA). The data were filtered using a fourth-order, zero-lag, low-pass Butterworth filter at cut-off frequencies of 6 and 25 Hz, respectively. Hip and knee adduction moments were calculated using three-dimensional inverse dynamics and normalized by the body mass and height (%Bw*Ht). KAAI (integral of the knee adduction moment with respect to time) was normalized by the body mass, height, and time (%Bw*Ht*s). The peak of each movement, and hip and knee adduction moment were analysed throughout the stance phase. The kinematics and knee moment data were normalized to 101 points throughout the stance phase (initial contact (IC) to toe-off), using the force plate to identify the stance phase, both were determined automatically in Visual 3D using the vertical GRF with a threshold of 20N.

Statistical Analyses

Statistical analyses were performed using SPSS software (Version 20, Chicago, USA). The normality of distribution of all variables (hip abductors strength, WOMAC pain score, WOMAC physical function score, walk test – 40m, hip adduction angle, ipsilateral trunk lean, and contralateral pelvic drop) was analysed using the Shapiro-Wilk test. The Pearson's correlation coefficient test was used to examine the relationship of hip abductors with the other measures (hip and knee adduction moments, WOMAC pain score, WOMAC physical function score, walk test – 40m, hip adduction angle, ipsilateral trunk lean, and contralateral pelvic drop). The variables significantly correlated to the hip abductors (WOMAC physical function score, walk test 40-m, hip adduction moment, hip adduction angle, and contralateral pelvic drop) were individually analysed in a regression analysis. First, as kinematic variables (contralateral pelvic drop and hip adduction angle) did not present any relationship with pain, age, gender, and knee OA severity, a stepwise linear regression was performed to measure the portion of variance could be predicted by hip abductors. Second, considering that hip adduction moment, WOMAC physical function score, and walk test – 40m could be influenced by pain, age, gender, and knee OA severity, a bivariate correlation test was performed to evaluate their relationship. Significant correlated parameters were entered in the first step of the regression model. In addition, height and mass were controlled in all physical function analyses (Jaric 2003), while walking speed was controlled for hip adduction moment analysis. Therefore, the hierarchical linear regression had two steps. In the first step the covariates were entered and in the second step hip abductors strength was entered. As body mass was used as the covariate for physical function analysis, the non-normalized hip abductors strength (Nm) data were entered in the regression model. Differently, it was used the normalized data of KAAI (Nm/Kg.s.Ht) were used, knee and hip adduction moments (Nm/Kg.Ht) for all analysis, and for this reason height and

mass were not used as a covariate. Finally, an alpha level of 0.05 was set for all statistical tests.

Results

Descriptive values for subject demographics, WOMAC pain, and physical function scores, walk test – 40m, KOA severity, and kinetics and kinematic variables are presented in table 1.

Table 1. Demographic and subject gait characteristics.

	Mean (SD)	
N	25	
Female (%)	48	
Age (years)	58.2 (4.7)	
Height (m)	1.67 (0.09)	
Mass (kg)	79.5 (13.6)	
BMI (kg/m^2)	28.4 (3.9)	
WOMAC Pain score	8.2 (3.8)	
WOMAC Physical Function score	24 (13.5)	
Walk test – 40m (m/s)	1.71 (0.28)	
Disease characteristics	Number of subjects (%)	
Grade 2 (KL)	15 (60)	
Grade 3 (KL)	10 (40)	
Unilateral KOA	6 (24)	
Bilateral KOA	19 (76)	
		%Stance phase Mean (SD)
Gait Speed (m/s)	1.18 (0.16)	
Hip Abductor Strength (Nm/kg)	97.6 (18.7)	
Peak KAM (Nm/kg.Ht)	3.02 (0.82)	25 (4.6)
KAAI (Nm/kg.s.Ht)	1.19 (0.46)	-
Peak HAM (Nm/Kg.Ht)	5.56 (1.01)	25.7 (3.4)
Peak Hip Adduction Angle (Degrees)	8.53 (5)	29.3 (8.4)
Contralateral Pelvic Drop (Degrees)	2.2 (2.4)	25.1 (5.0)
Ipsilateral Trunk Lean (Degrees)	3.3 (1.9)	24.8 (9.4)

SD: standard deviation, N: sample size, m: meters, kg: kilograms, m²: meters squared, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, s: seconds, KL: Kellgren and Lawrence scale, Nm: Newton meters, KAM: knee adduction moment, Ht: height, KAAI: knee adduction angular impulse, HAM: hip adduction moment.

A significant correlation of hip abductors strength was found with the WOMAC physical function score, walk test - 40 m, peak hip adduction moment, peak hip adduction angle, and contralateral pelvic drop (Table 2). No correlation was found between hip abductors and the other measures (Table 2).

Table 2. Pearson's correlation coefficient of hip abductor strength with pain, physical function, kinetic, and kinematic variables in subjects with medial knee osteoarthritis.

	Hip Abductors Strength (Nm/kg) r (P-value)
WOMAC Pain score	-0.27 (0.19)
WOMAC Physical Function score	-0.49 (0.01)*
Walk test – 40m (s)	-0.65 (0.00)*
Peak KAM (Nm/kg.Ht)	0.39 (0.06)
KAAI (Nm/kg.s.Ht)	-0.27 (0.20)
Peak HAM (Nm/Kg.Ht)	-0.42 (0.02)*
Peak Hip Adduction Angle (Degrees)	-0.46 (0.02)*
Contralateral Pelvic Drop (Degrees)	-0.51 (0.02)*
Ipsilateral Trunk Lean (Degrees)	0.08 (0.7)

R: value of correlation, m: meters, s: seconds, kg: kilograms, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, Nm: Newton meters, KAM: knee adduction moment, Ht: height, KAAI: knee adduction angular impulse, HAM: hip adduction moment.

The stepwise linear regression showed that hip abductor strength explained 17% of contralateral pelvic drop (B = -0.42 (95% CI: -0.10, -0.003), p = 0.03) and 21% of peak hip adduction angle (B = -0.46 (95% CI: -0.23, -0.21), p = 0.02) (Figure 1).

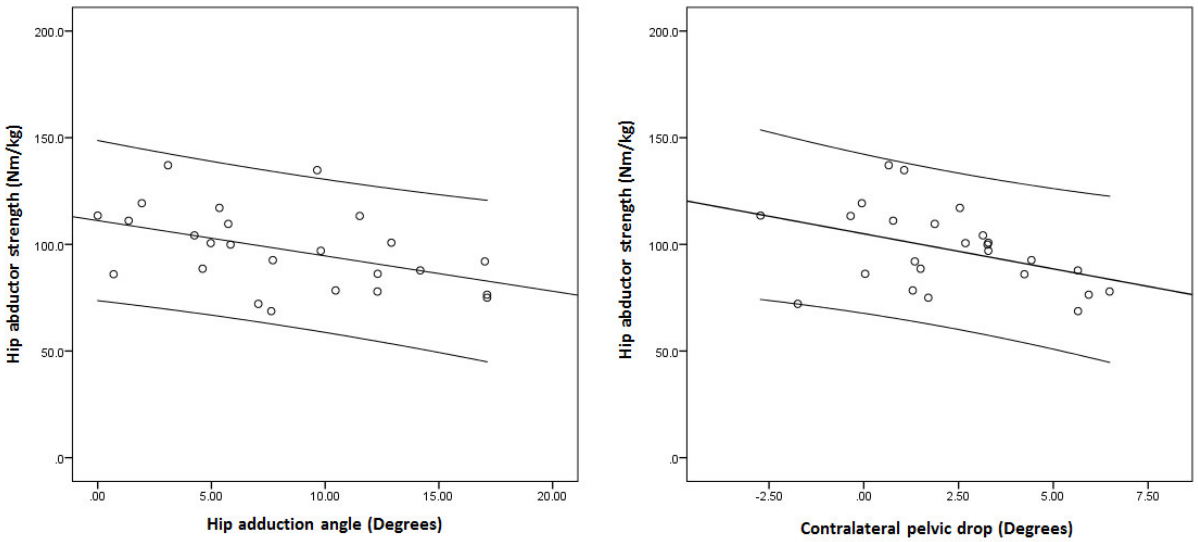


Figure 2. Scatterplots illustrating the relationship of hip abductor strength with hip adduction angle (left) and contralateral pelvic drop (right).

As we found a significant correlation between gender and peak hip adduction moment, gender, and walking speed were entered as covariates in a hierarchical linear regression. Gender and walking speed explained 53% of HAM variance, while hip abductors did not explain any additional variance.

In addition to height and mass, pain was controlled for the WOMAC physical function score regression model. Moreover, height, mass, pain, age, gender, and severity were controlled for the walk test (40m). Height, mass, and pain explained 64% of the variance in the WOMAC physical function score, while height, mass, pain, age, gender, and severity explained 75% of the variance in the walk test (40m). Hip abductors strength explained an additional 4% and 1% of the variance in the WOMAC physical function score and walk test (40m), respectively (Table 3).

Table 3. Hierarchical Linear Regression Predicting physical function

Dependent variable	Step	Independent variable	R	R^2	Adjusted R^2	ΔR^2	ΔF	p
WOMAC Physical Function Score	1	Height, mass, pain	0.80	0.64	0.59	0.64	12.7	<0.001
	2	Hip abductors strength	0.83	0.68	0.62	0.04	2.6	<0.001
Walk test - 40m	1	Height, mass, pain, age, gender, severity	0.86	0.75	0.68	0.75	11.3	<0.001
	2	Hip abductors strength	0.87	0.76	0.68	0.01	0.7	<0.001

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, m: meters.

Discussion

As hypothesized, hip abductors strength did not present a correlation with knee adduction moments and after controlling by walking speed, hip adduction moment presented the same result, showing that hip abductors do not explain any portion of knee or hip adduction moments variance. In addition, the results did not support the hypothesis that hip abductors have a relationship with trunk lean and pain. Finally, it was confirmed the hypothesis that hip abductors explain a portion of the variation of contralateral pelvic drop, hip adduction angle, and physical function (WOMAC physical function score and walk test-40m). The main contribution of this study was to confirm that hip abductors play a role in controlling contralateral pelvic drop and hip adduction angle, however, it has no relationship with hip and knee adduction moments. In addition, despite hip abductors strength seem to be a contributor for physical function, this result is clinically questionable given hip abductors explained only 4% and 1% of WOMAC physical function score and walk test (40m) respectively, in subjects with medial KOA.

The present findings demonstrated an inverse association (r= -0.46) between hip abductors and hip adduction angle during gait, confirming its role controlling hip adduction on the frontal plane. According to Neumann et al. (1988) (Neumann, Soderberg, and Cook 1988) 10 degrees of hip adduction is the position where hip abductors can generate the highest torque, which may support the fact that the peak of hip adduction angle happened at average 8.5 (±5) degrees. During the stance phase, single-limb support requires an important function of hip abductors in controlling the pelvis on the frontal plane. Therefore, hip abductor weakness would result in contralateral pelvic drop. Our results confirmed this hypothesis given hip abductors presented a negative correlation with contralateral pelvic drop (r= -0.51), which means the higher the strength of the hip abductor the less contralateral pelvic drop. These findings reinforce the importance of hip abductor strengthening in subjects with medial KOA and also, specific exercises targeting control of the hip adduction angle and pelvis during walking should be prescribed (Henriksen et al. 2014). Specific exercises for hip abductors are not only important to improve the quality of movement of pelvis and hip, but it may help to prevent injuries such as back pain, which is a common complaint in subjects with KOA (Wolfe et al. 1996).

Chang et al. (Chang et al. 2005) suggested that hip abductors protect against medial knee load by controlling the pelvis in the frontal plane and decreasing the knee adduction moment. However, this statement has been questioned given no difference in knee adduction moment was found after an intervention program targeting hip abductor strengthening (Bennell et al. 2010; Sled et al. 2010). In addition, Rutherford et al. (Rutherford, Hubley-Kozey, and Stanish 2014) found that hip abductors strength explained 9% of the variability in the peak of knee adduction moment in subjects with

KOA. Recently, Kean et al. (Kean et al. 2015) explored the relationship between hip abductors and hip and knee adduction moments in subjects with medial KOA and found that hip abductors have a positive relationship with KAAI (r=0.24), explaining 6% of its variance. Despite the present study finding a negative correlation between hip abductors and hip adduction moment (r= -0.42, p=0.02), after controlling by walking speed hip abductors did not predict any variance in hip adduction moment. Therefore, our findings advocate that hip abductors cannot predict hip and knee adduction moments. Additionally, these findings provide new information regarding the role of hip abductors in controlling the pelvis and hip in the frontal plane. As hip abductors explained only 17% of the small pelvic movement (average 2.2 (±2.4) degrees) on the frontal plane, it suggests that hip abductors strength have a very small influence on contralateral pelvic drop, which is likely not enough to affect the medial knee load. Our results complement the current literature supporting that although hip abductors have an influence on contralateral pelvic drop, no influence was found on hip and knee adduction moments. Therefore, hip abductor strengthening may be used for the rehabilitation of subjects with medial KOA aiming to reduce the hip adduction angle and improve pelvis control but not to reduce the medial knee load.

Despite trunk lean toward the stance limb having been indicated as a compensation when hip abductor weakness is present (Powers 2010), the present study did not find a correlation between hip abductors and trunk lean. This result may indicate that trunk lean over the stance limb is not a logical compensation of hip abductor weakness, but is likely to be more related to a strategy to decrease the KAM (Hunt et al. 2008; Favre et al. 2016; Hunt et al. 2010; Simic et al. 2012). Hunt et al. (2008) (Hunt et al. 2008) showed that trunk lean has a significant negative correlation with the first (r= -

0.39) and second (r= -0.33) peak KAM. A recent study (Simic et al. 2012) confirmed this relationship, demonstrating that trunk lean has a dose-response relationship with KAM. Moreover, our findings are in agreement with a recent study(Pohl et al. 2015) which experimentally reduced hip abductors strength through a nerve block intervention in healthy subjects. Authors did not find changes in hip and knee adduction moments or ipsilateral trunk lean, supporting our finding that trunk lean toward the stance limb may be not a compensation for hip abductor weakness.

The hypothesis that hip abductors are predictors of physical function is based on previous studies (Bennell et al. 2010; Sled et al. 2010) showing an improvement in physical function after an intervention targeting hip abductor strengthening in subjects with KOA. In addition, it is relevant to evaluate the objective (walk test – 40m) and subjective (WOMAC questionnaire) physical function given they complement each other (Dobson et al. 2013). Our findings showed that hip abductors predicted 4% and 1% of the variance in the WOMAC physical function score and walk test (40m) respectively. In contrast, Piva et al. (Piva et al. 2011b) found that hip abductors strength did not explain any additional variance in physical function measured by the WOMAC score and self-selected walking speed test in patients with total knee replacement (TKA). The role of hip abductors in predicting physical function performance might be related to the task, for instance hip abductors explained an additional 10% of the variance in the Stair Ascend/Descend test (Piva et al. 2011a). More recently, another study (Alnahdi, Zeni, and Snyder-Mackler 2014a) showed that hip abductors explained an additional 2.1% and 1.9% of TUG (Timed "Up & Go") and SCT (Stair Climbing Test), respectively, however, no additional contribution to explaining the 6MWT (6-minutes' walk test), KOS-ADLS (Knee Outcome Survey Activities of Daily Living

Scale), or GRS (Global Rating Scale). Moreover, both studies (Alnahdi, Zeni, and Snyder-Mackler 2014a; Piva et al. 2011b) showed that other measures such as age, pain, and gender influence physical function measures. In the same way, the present study showed that not only body size but also pain, age, gender, and KOA severity should be considered, given that these variables explained the greatest portion of the variance (64% and 75% of WOMAC physical function score and Walk test-40m, respectively) in physical function measures. Considering that hip abductors explained a very small portion of physical function, it should be carefully applied in the clinical practice. As physical function is influenced by many factors such as age, pain, gender, height, weight, and others (Alnahdi, Zeni, and Snyder-Mackler 2014a; Piva et al. 2011b; Iversen et al. 2016), it was expected that hip abductors strength would explain only a small portion of this variable. Although previous studies have shown positive results after an intervention of hip abductor strengthening exercises (Bennell et al. 2010; Sled et al. 2010), these positive results may be related to the increase of hip abductors strength and also to the effect of exercise (Tanaka et al. 2013). Finally, no correlation between hip abductors and the WOMAC pain score was found. As studies have shown a reduction in pain after an intervention with hip abductor strengthening exercises (Bennell et al. 2010; Sled et al. 2010), this reduction may be explained as an effect of exercise rather than an influence of hip abductors (Tanaka et al. 2013). This hypothesis is supported by a recent study (Henriksen et al. 2014) showing that exercise therapy decreases pain sensitivity in subjects with KOA.

The present study has some limitations. First, the cross-sectional design restricts a cause-and-effect relationship of hip abductors with physical function and pain. Longitudinal studies are needed to confirm these findings. Second, although we

controlled our association analyses of hip abductors and physical function by pain, we measured this variable on a different day to the functional test, which might have influenced our results. Future studies should measure pain during the functional test and use it as a covariate to better understand the effect of pain on performance-based physical function. Finally, as previous studies have shown the important role of quadriceps in physical function (Serrao et al. 2012; Serrao et al. 2015; Alnahdi, Zeni, and Snyder-Mackler 2014b), this might be considered for future analysis.

In conclusion, considering that hip abductors strength contributed to contralateral pelvic drop, hip adduction angle, and physical function, interventional studies should focus on the improvement of these movements prescribing specific exercises to improve physical function and the ability of hip abductors to stabilize the pelvis and hip adduction during walking.

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MANUSCRITO II

The relationship between urinary level of C-telopeptide fragments of type II collagen (uCTX-II), knee joint load, pain, and physical function in subjects with medial knee osteoarthritis

Manuscrito submetido ao *Journal of Orthopaedic Research*.

Abstract

Purpose: Considering the osteoarthritis system model that integrates the behavior of biological, mechanical, and structural components of the disease, the present study aimed to investigate the association between urinary C-Telopeptide fragments of type II collagen (uCTX-II), knee moments, pain, and physical function in subjects with medial knee osteoarthritis. **Methods:** Twenty-five subjects radiographically diagnosed with knee osteoarthritis were included in the study. Participants were evaluated through three-dimensional gait analysis, uCTX-II level, the WOMAC pain and physical function scores, and the walk test – 40m. The association between these variables was performed using Pearson´s product-moment correlation, followed by a hierarchical linear regression for significantly associated variables, controlled by severity and body mass index. **Results:** A significant correlation of uCTX-II level and pain, physical function, and the walk test (40m) was found. The hierarchical linear regression controlled for severity and BMI showed that uCTX-II level explained 9% of the WOMAC pain score, 27% of the WOMAC physical function score, and 7% of the walk test (40m). **Conclusions:** Apparently, the influence mechanisms of uCTX-II and knee moments for the onset and progression of the disease are different as no relationship was found between them. In addition, uCTX-II contributes to explaining a small portion of pain and physical function in subjects with medial KOA.

Keywords: mechanobiology, mechanics, osteoarthritis clinical.

Introduction

Knee osteoarthritis (KOA) is one of the most prevalent diseases in the world and considering the growing world population as well as life expectancy, there is a tendency for this prevalence to increase(Vos et al. 2012). As a consequence of KOA, patients frequently present pain, stiffness, and disability, impacting significantly on their quality of life and leading them to seek treatment(Brooks 2002). Considering no cure is available at the present time, it is important to identify factors related to the onset and progression of the disease(Chang et al. 2015; Erhart-Hledik et al. 2012; Maly et al. 2015; Hosnijeh et al. 2015). A better understanding of these factors would improve the development of treatments as well as strategies to decrease the progression of the disease. For this reason, Andriacchi et al.(Andriacchi et al. 2004) developed the osteoarthritis system model that integrates the behaviour of biological, mechanical, and structural components of the disease. These three components can be used as a surrogate to understand the onset, progression, and intervention responses of the disease, given that cartilage health (cartilage homeostasis) is determined by the balance between these components (Andriacchi et al. 2015; Andriacchi et al. 2004). In addition, considering the interaction between these components, when one or more of the components moves out of the normal range, the risk of developing KOA increases (Andriacchi et al. 2015). KOA is characterized by the degradation of articular cartilage, which means that the structural component has already moved out of the normal range. The degradation is considered to be a result of the behaviour of the biological and mechanical components (Erhart-Hledik et al. 2012; Chehab et al. 2014; Sharma et al. 1998). For this reason, studies have investigated which biological and mechanical factors are able to predict the

onset and progression of the disease (Houard, Goldring, and Berenbaum 2013; Maly et al. 2015; Miyazaki et al. 2002).

Regarding biological factors, biomarkers have been used in patients with KOA (Bay-Jensen et al. 2016; Erhart-Hledik et al. 2012; Røtterud et al. 2014). Considering that cartilage degradation is a consequence of the loss of the normal balance between the synthesis and degradation activity of the chondrocytes, biomarkers are able to measure this activity and thus, provide information on cartilage health (Henrotin et al. 2007). The present study focused on the behaviour of urinary C-telopeptide of type II collagen (uCTX-II), as it is specific for measuring type II collagen, the most abundant protein of the cartilage matrix (Christgau et al. 2001; Reijman et al. 2004). In addition, according to BIPED (Burden of disease, Investigative, Prognostic, Efficacy of Intervention and Diagnostic) criteria (Bauer et al. 2006), uCTX-II has the ability to diagnose, predict the progression, and identify the severity of the disease (Henrotin et al. 2007; Wang et al. 2014; Sowers et al. 2009; Tanishi et al. 2009a; Saberi Hosnijeh et al. 2015). Given these characteristics, uCTX-II can be used as a surrogate to investigate the behaviour of the biological component and thus, identify patients at high risk of developing KOA. For instance, a recent study (Saberi Hosnijeh et al. 2015) showed that high uCTX-II baseline levels predict the progression of KOA over 5 years of follow-up. Similarly, a positive correlation was found between the baseline levels of uCTX-II and radiographic progression of KOA (both patellofemoral and tibiofemoral) over 6 years of follow-up (Kumm et al. 2013). Despite uCTX-II being a well established biomarker to measure activity of the chondrocytes and provide information on cartilage health, some authors have advocated that the unbalanced activity of the chondrocytes is a result of

mechanical factors, attributing the abnormal loading as the main cause of unbalanced chondrocyte activity (Felson 2013; Varady and Grodzinsky 2016; Sharma et al. 1998).

Mechanical factors have been indicated as the main cause of KOA (Felson 2013; Varady and Grodzinsky 2016) and from these factors, knee adduction moment (KAM) has been used as a surrogate of knee joint load given it measures the distribution of load between medial and lateral compartments (Schipplein and Andriacchi 1991). In addition, increased KAM has been found in subjects with KOA (Baliunas et al. 2002; Hurwitz et al. 2000; Sharma et al. 1998) as well as being associated with pain (Thorp et al. 2007; Hurwitz et al. 2000), severity (Thorp et al. 2006; Sharma et al. 1998), and progression of the disease (Chang et al. 2015; Miyazaki et al. 2002). In the same way, knee adduction angular impulse (KAAI), which is the time integral of the KAM curve during stance, has also been used to measure knee load through a combination of the duration and amplitude of KAM (Thorp et al. 2006). KAAI is also associated with the presence (Maly et al. 2015), severity (Thorp et al. 2006), pain, and disability (Kito et al. 2010) of KOA. More recently, the use of the knee flexion moment (KFM) associated with KAM was proposed to improve the measurement of knee load (Manal et al. 2015). In agreement, a recent study (Erhart-Hledik, Favre, and Andriacchi 2015) showed an association between KFM and specific region cartilage thickness in early stages of the disease. Moreover, another recent study (Chehab et al. 2014) showed that KAM and KFM can predict cartilage changes over 5 years of follow-up in patients with KOA. Hence, it is clear that knee load has an important influence on cartilage degradation and KAM, KAAI, and KFM are reliable variables to measure the medial knee load.

Previous studies have investigated the relationship of knee load and biomarkers with pain and physical function (Garnero et al. 2001; Ishijima et al. 2011; O'Connell,

Farrokhi, and Fitzgerald 2016). This is necessary given pain and physical function are commonly used to measure the result of an intervention (Hunt et al. 2013; Bennell et al. 2010) added to which, these measures can be used to identify high risk subjects for symptomatic KOA (Wang et al. 2014; Sharma et al. 1998). It is important to highlight that there is no clear association between these measures in the current literature. For instance, a study (Garnero et al. 2001) found no association of uCTX-II level with pain, stiffness, physical function or total WOMAC score in patients with KOA, while another study (Ishijima et al. 2011) showed an association between pain and uCTX-II in patients with early KOA (Grade II – Kellgren and Lawrence(Kellgren and Lawrence 1957)). In the same way, only a few studies have explored the relationship between knee load and pain and physical function, however, these associations remain unclear. Recently, a study (O'Connell, Farrokhi, and Fitzgerald 2016) found that the level of pain (WOMAC score) influences the KFM but not the KAM. Similarly, another study(Maly, Costigan, and Olney 2006a) found no association between KAM and pain and physical function in subjects with KOA. On the other hand, pain, stiffness, and physical function were pointed out as associated with KAAI during the stance duration, initial double stance interval, and single limb support interval in patients with KOA(Kito et al. 2010). At the present time, there is no clear association of knee load and biomarkers with pain and physical function. A better understanding of these relationships would help in the development of new strategies of treatment as well as in defining which measures should be considered to identify high risk subjects for symptomatic KOA.

Finally, given the association of knee load and biomarkers with cartilage degradation, some studies have explored the relationship between these measures. However, to our knowledge, only one study has investigated the relationship between

uCTX-II and knee load (Hunt et al. 2013). Although they did not find any association between uCTX-II level and KAM and KAAI, they did not investigate the association of uCTX-II with KFM, pain, and physical function. Investigating these relationships would contribute to understanding the mechanism of onset, progression, and intervention response of the disease in patients with KOA. Therefore, the aim of this study was to investigate the association between uCTX-II, knee moments (KAM, KFM, and KAAI), pain, and physical function in subjects with medial KOA. We hypothesized that uCTX-II level is associated with pain, physical function, and knee moments (KAM, KFM, and KAAI). We also hypothesized that knee moments (KAM, KFM, and KAAI) have no association with pain or physical function.

Methods

Subjects

Twenty five subjects radiographically diagnosed with KOA (Table 1). All participants underwent anteroposterior semiflexed weight-bearing, lateral view, and skyline view radiographs and were then classified according to the Kellgren and Lawrence (KL) criteria (Kellgren and Lawrence 1957). Only subjects with predominantly medial KOA and medial knee pain were included, therefore subjects were excluded if they presented KL grades in the lateral or patellofemoral compartment greater than the medial compartment (Zeni, Rudolph, and Higginson 2010). In addition, participants were excluded for any of the following criteria: body mass index greater than 35kg/m^2, history of hip or knee arthroplasty or osteotomy, had undergone knee surgery or other nonpharmacological treatment in the 6 months prior to the study (Kean et al. 2015). For bilateral KOA participants the most symptomatic knee was evaluated. All participants provided written informed consent and the present study was approved

by the Ethics committee for Human Investigations at the Federal University of São Carlos.

WOMAC (*The Western Ontario and McMaster Universities Osteoarthritis Index*)

The WOMAC index is a disease-specific, tri-dimensional, self-administered questionnaire used to assess health status and health outcomes in subjects with KOA. The WOMAC contains 24 questions and consists of three subscales: pain, stiffness, and physical function with five, two, and seventeen questions, respectively. Answers for each of the 24 questions are scored on five-point Likert scales (none=0, slight=1, moderate=2, severe=3, extreme=4) with total scores ranging from 0 to 96. Higher scores indicate greater disease severity. The WOMAC questionnaire is well recognized for its adequate validity, reliability, and responsiveness for individuals with knee OA (Bellamy et al. 1988).

40-m walk test

The 40-m self-paced walk test was developed to evaluate the ability to walk quickly over short distances, which is an important activity for a good quality of life and in subjects with KOA this activity is usually limited. Two marks on the ground were placed 10m apart and a cone was placed 2 meters beyond each end of the 10m walkway. Participants, wearing comfortable clothes and shoes, were instructed to walk as fast as possible, without running, along the walkway between the two cones, turn around the cone at the end, return, and repeat for a total of 40 m. Participants were timed for this test and based on this time, we calculated the speed as suggested by previous studies (Dobson et al. 2013; Wright et al. 2011; Kennedy et al. 2005).

Urinary C-Telopeptide fragments of type II collagen (uCTX-II)

Fasting urine was collected in the early morning (within 2 hours of waking), second void, and all samples were stored frozen at -80°C until analysis. The uCTX-II level was determined using an enzyme linked immunosorbent assay (ELISA) based on a monoclonal antibody raised against a linear six amino acid epitope of human type II collagen C telopeptide (Urine CartiLaps®ELISA)(Christgau et al. 2001). The uCTX-II level was corrected with creatinine concentration (mmol/L) in the sample using an enzymatic colorimetric routine method. For this correction we used the formula: corrected CTX-II Value = 1000xUrine CartiLaps (µg/L)/Creatinine (mmol/L). The intra- and inter-assay coefficients of variation are ≤7.8% and ≤12.2%, respectively (according to the package insert). All analyses were conducted in duplicate and blinded regarding group (control or KOA).

Gait evaluation

Gait of the participants was evaluated using an eight-camera Qualisys Oqus 300 motion analysis system (Qualisys, Gothenburg, Sweden) and a force plate (Bertec Corporation, OH, USA) to record kinematic and kinetic data at sampling frequencies of 120 and 1200 Hz, respectively. Participants walked barefoot at a self-selected speed along an 8 m walkway. For each subject, a static calibration trial followed by five successful trials were collected for kinetic and kinematic analysis. The following reflective markers were located on anatomical landmarks bilaterally (Goncalves et al. 2017; Selistre et al. 2017): acromia, iliac crests, anterior and posterior superior iliac spines, greater trochanters of the femur, medial and lateral femoral epicondyles, medial and lateral malleoli, first, second and fifth metatarsal heads, base of the fifth metatarsal, and calcaneus. A single marker was placed on the sternal notch and spinous process of

C7. Four clusters built with 4 noncollinear markers were placed over the lateral side of the right and left thigh and shank. Two additional clusters built with 3 noncollinear markers were positioned on the spinous process of T4 and T12. Medial and lateral malleoli, femoral epicondyles, seventh cervical vertebrae, greater trochanters, and acromia were removed after the static standing calibration trial was performed. These markers were used to construct the anatomical coordinate system for the trunk, pelvis, thigh, shank, and foot segments.

The ankle and knee joint centres were calculated as midpoints between the malleoli and femoral epicondyles, respectively (Chapman et al. 2015). The hip joint centre was measured using the regression model based on the anterior and posterior superior iliac spine markers(Bell, Brand, and Pedersen 1989). The pelvic coordinate system was built from markers on the anterior and posterior superior iliac spines and then contralateral pelvic drop was measured using a laboratory coordinate system as the reference. The trunk coordinate system was built from markers on the acromia and iliac crest (bilaterally) and the ipsilateral trunk lean was measured using a laboratory coordinate system as the reference. The angular motion of all assessed joints was defined using Cardan angles in accordance with the recommendations of the International Society of Biomechanics (Wu et al. 2002).

The kinetic and kinematic data were processed using Qualisys Track Manager (Qualisys AB) and Visual3D software (C-motion Inc., Rockville, MD, USA). The data were filtered using a fourth-order, zero-lag, low-pass Butterworth filter at cut-off frequencies of 6 and 25 Hz, respectively. The stance phase was determined using a force plate, where the initial contact (IC) and toe-off (TO) were identified as adopting a force threshold of 20N. The kinetic and kinematic data were normalized to 101 points. KFM,

KAM, and KAAI were calculated using three-dimensional inverse dynamics. KFM and KAM were normalized by the body mass and height (%Bw*Ht), while KAAI was normalized by the body mass, height, and time (%Bw*Ht*s). The peak of each variable throughout the stance phase was used for analysis.

Statistical Analyses

All statistical analyses were performed using SPSS software (Version 20, SPSS Inc., Chicago, IL, USA). The normality of distribution of all variables was analysed using the Shapiro-Wilk test. Pearson's product-moment correlation coefficient was used to examine the relationship between uCTX-II level, knee moments, symptoms, and physical function. For all significant correlations (uCTX-II with pain, physical function, and the walk test – 40m) we processed a hierarchical linear regression. Based on previous studies, we controlled our analysis for severity (Karsdal et al. 2010; Reijman et al. 2004) and BMI (Mouritzen et al. 2003), using these variables as the first step of the hierarchical linear regression. The second step was composed of uCTX-II levels. An alpha level of 0.05 was set for all statistical tests.

Results

Group characteristics and descriptive values are presented in table 1. A significant correlation of uCTX-II level and pain, physical function, and the walk test (40m) was found (Table 2) while no significant correlation was found with the other measures.

Table 1. Demographic and subject gait characteristics.

	KOA group (n=25) Mean (SD)
Female (%)	48
Age (years)	58.2 (4.7)
Height (m)	1.67 (0.09)
Mass (kg)	79.5 (13.6)
BMI (kg/m^2)	28.4 (3.9)
WOMAC Score	
Pain	8.2 (3.8)
Stiffness	3.4 (1.9)
Physical Function	24 (13.5)
Walk test – 40m (m/s)	1.71 (0.28)
Severity (KL)	
Grade 2	15
Grade 3	10
Gait speed (m/s)	1.18 (0.16)
uCTX-II (ng/mmol crea)	266.1 (148.7)
Peak KAM (Nm/kg.Ht)	3.02 (0.82)
Peak KFM (Nm/kg.Ht)	2.56 (1.48)
KAAI (Nm/kg.s.Ht)	1.19 (0.46)

KOA: knee osteoarthritis, SD: standard deviation, m: meters, kg: kilograms, BMI: body mass index, m^2: square mater, WOMAC: Western Ontario & McMaster Universities Osteoarthritis Index, s: seconds, KL: Kellgren and Lawrence classification, uCTX-II: urinary C-Telopeptide fragments of type II collagen, ng: nanogram, mmol: millimole, crea: creatinine, Nm: newton meter, Ht: height, KAM: knee adduction moment, KFM: knee flexion moment, KAAI: knee adduction angular impulse.

Table 2. Measures with a significant correlation presented as Pearson correlation coefficient (r).

	uCTX-II Level r
WOMAC Pain score	0.49 *
WOMAC Physical Function score	0.53 *
Walk test (40m)	-0.48 *

*Significant correlation ($p<0.05$).

uCTX-II: urinary C-Telopeptide fragments of type II collagen, WOMAC: Western Ontario & McMaster Universities Osteoarthritis Index, m: meters.

After controlling for severity and BMI through a hierarchical linear regression we found: 1) severity and BMI explained 35% of the variance of the WOMAC pain score, while uCTX-II level explained an additional 9% of this variance; 2) severity and BMI explained 19% of the variance in the WOMAC physical function score but was not significant, while uCTX-II level explained an additional 27% of this variance; finally 3)

severity and BMI explained 39% of the variance in the walk test (40m), while uCTX-II level explained an additional 7% of this variance (Table 3).

Table 3. Hierarchical Linear Regression Predicting pain and physical function.

Dependent variable	Step	Independent variable	R	R^2	ΔR^2
WOMAC Pain score	1	Severity and BMI	0.59	0.35*	0.35
	2	uCTX-II	0.67	0.44*	0.09
WOMAC Physical Function Score	1	Severity and BMI	0.43	0.19	0.19
	2	uCTX-II	0.67	0.45*	0.27
Walk test (40m)	1	Severity and BMI	0.62	0.39*	0.39
	2	uCTX-II	0.68	0.46*	0.07

*Significant difference ($p<0.05$)

WOMAC: Western Ontario & McMaster Universities Osteoarthritis Index, m: meters, BMI: body mass index, uCTX-II: urinary C-Telopeptide fragments of type II collagen.

Discussion

The present study confirmed the hypothesis that uCTX-II level is associated with pain and physical function as a significant correlation was demonstrated of uCTX-II with the WOMAC pain and physical function scores (r=0.49 and r=0.53 respectively), and also a negative correlation with the walk test – 40m (r=-0.48). The present study also hypothesized that uCTX-II level has a relationship with knee moments (KAM, KFM, and KAAI) and this was not confirmed as we did not find a significant correlation between these measures. Finally, it was hypothesized that knee moments have no association with pain and physical function which was also confirmed as the correlation test showed no influence of knee moments on pain and physical function. This cross-sectional study provides new information regarding the relationship between biological, mechanical, and structural components of the disease.

The main question of this study was regarding the relationship between uCTX-II level and knee moments. Despite it being well established that both measures are

associated with the onset and progression of the disease, we did not find an association between these measures. To our knowledge, only one study has investigated the relationship between uCTX-II level and knee moments (Hunt et al. 2013). Using only KAM and KAAI, they found no association with uCTX-II through a linear regression model (Hunt et al. 2013). The present study investigated this relationship not only using the KAM and KAAI but also KFM as an important measure to improve the ability to measure the medial knee load (Manal et al. 2015). For instance, the flexion knee angle at heel strike is associated with the thickest region of the cartilage on the medial femoral condyle (Koo, Rylander, and Andriacchi 2011). Considering that previous studies have shown an influence of kinetic and kinematic measures on the cartilage structure (Koo, Rylander, and Andriacchi 2011; Andriacchi, Koo, and Scanlan 2009), we expected to find an association between uCTX-II and knee moments. This expectation was also based on the osteoarthritis system model, where the biological, mechanical, and structural components work together to maintain the cartilage in homeostasis (Andriacchi et al. 2004). Consequently, when one of these components moves out of the normal range, the other components tend to alter their normal behaviour as a compensatory strategy (Andriacchi et al. 2015). There are many reasons why we did not find an association between uCTX-II and knee moments. First, although we used three reliable (KAM, KFM, and KAAI) measures to calculate the knee load, they do not represent the total knee load. However, as we studied subjects with medial KOA, the medial knee load was the focus of our analysis. Second, we measured the fasting level of uCTX-II through a sample of the second void of morning urine, which means that our volunteers had limited physical effort in the hours prior to the sample collection. This may have influenced our findings given that the biomarker response to a mechanical stimulus has been shown to be more sensitive to understand the relationship between

cartilage metabolism and knee load than only resting levels (Erhart-Hledik et al. 2012). For this reason, future studies should explore the stimulus-response approach (Andriacchi et al. 2004) to better understand the relationship between uCTX-II level and knee moments. Third, as a systemic biomarker, perhaps uCTX-II level was not sensitive enough to correlate with specific medial knee load measures. For this reason, future studies may consider using synovial fluid to investigate this relationship, given specific regions of the cartilage have shown specific responses to a mechanical stimulus (Bevill et al. 2009; Andriacchi, Koo, and Scanlan 2009) that are also associated with kinematic measures (Koo, Rylander, and Andriacchi 2011). Based on our findings, this may represent that the influence mechanisms of uCTX-II and knee joint load on cartilage degradation are different from each other; however, as this is a cross-sectional study we cannot make this conclusion. Future studies may investigate this relationship in the longer-term to establish a causal association between medial knee load and uCTX-II.

The present study showed that uCTX-II level explained only a small portion of the variance in WOMAC pain score (9%), WOMAC physical function score (27%), and the walk test-40m (7%). In addition, the influence of BMI and disease severity were controlled as both measures explained 35% of the WOMAC pain score and 39% of the variance in the walk test (40m). In contrast to these findings, Garnero et al. (Garnero et al. 2001) found no correlation of uCTX-II levels with the WOMAC total score or subscales (pain, stiffness, and physical function). The difference between the present study and Garnero's study (Garnero et al. 2001) may be related to the age of the participants given that uCTX-II tends to increase during aging (Tanishi et al. 2009b), and also our sample was younger than that in Garnero's study (Garnero et al. 2001). It is important to take into account that uCTX-II represents the cartilage destruction

(Christgau et al. 2001), and this is only one of the factors that influence knee pain in subjects with KOA (Kittelson et al. 2014). In addition, uCTX-II seems to be more sensitive to the presence of knee pain than the severity of the disease (Ishijima et al. 2011). As articular cartilage is an aneural tissue, knee pain has been attributed to the osteochondral junction, which reinforces our findings given CTX-II was found predominantly at the bone-cartilage interface (Bay-Jensen et al. 2008). Although the present study cannot establish a causal relationship between uCTX-II level and pain, studies have shown that uCTX-II can be used to predict knee pain in patients with KOA (Wang et al. 2014; Henrotin et al. 2007). In the same way, uCTX-II predicted 27% of the variance in WOMAC physical function score and 7% in the walk test-40m. Although a causal relationship is not possible, our findings advocate using uCTX-II to predict worsening physical function. Considering that radiographic KOA severity is positively associated with physical function (Riddle, Makowski, and Kong 2015), it may suggest that the higher the uCTX-II level the worse the physical function. Further investigation is necessary to clarify the mechanism of the influence of uCTX-II on pain and physical function in subjects with medial KOA. Moreover, longitudinal studies would clarify the causal relationship of uCTX-II with pain and physical function.

Consistent with other studies (Maly, Costigan, and Olney 2008; Teichtahl et al. 2006), we did not find any association of WOMAC pain and physical function score with KAM, KFM, and KAAI. Although knee pain and disability are considered as a consequence of abnormal joint mechanics (Ishijima et al. 2011), our findings are consistent with a previous study showing that WOMAC pain and physical function scores are not the main determinants of knee moments (Maly, Costigan, and Olney 2008; Teichtahl et al. 2006; Hurwitz et al. 2002). However, it is noteworthy that

changes in knee pain may influence the behaviour of knee moments. For instance, decreasing knee pain after an intervention with analgesic drugs was associated with increasing KAM (Hurwitz et al. 2000). In the same way, increasing pain experimentally is associated with decreasing knee moments (KAM and KFM) (Henriksen et al. 2010). Some authors have suggested that pain can provoke body compensatory strategies to decrease the medial knee load and improve physical function (Henriksen et al. 2010; O'Connell, Farrokhi, and Fitzgerald 2016; Hurwitz et al. 2000; Maly, Costigan, and Olney 2008). Although these compensatory strategies can decrease KAM (Favre et al. 2016; Simic et al. 2011), some of these strategies may increase KFM, which means that even when KAM is decreased it does not guarantee that the knee load is reduced (Walter et al. 2010). More recently, patients with medial KOA were divided into three groups according to their pain during walking (no pain, mild pain, and moderate/severe pain) using the first question of the WOMAC pain score (O'Connell, Farrokhi, and Fitzgerald 2016). Subjects with moderate/severe pain displayed a higher KFM, which likely suggests that these subjects used compensatory strategies, given that no difference was found in KAM between the groups. In addition, patients with moderate/severe pain presented more disability in comparison with the other groups, which was expected given pain is one of the main determinants of physical function in subjects with KOA (Creamer, Lethbridge-Cejku, and Hochberg 2000; Maly, Costigan, and Olney 2006b). Therefore, as pain and physical function have no association with KAM, KFM, or KAAI, interventional studies should investigate strategies to decrease not only pain and disability but also knee moments, controlling for possible compensatory strategies.

The present study has some limitations that have to be considered. First, we did not control the menstrual cycle of our female participants, and postmenopausal women

usually present high levels of uCTX-II (Reijman et al. 2004). Second, as participants collected their own urine at home, we did not control the collection time. Considering the diurnal variation in uCTX-II previously found, we believe that future studies should consider controlling the time of collection (Kong et al. 2006). Finally, we did not evaluate the level of physical activity (Henrotin et al. 2007), although it may have influenced our findings, as urine samples were collected in the morning, our subjects had limited physical effort before the collection. In conclusion, as no relationship was found between uCTX-II and knee moments, our findings suggest that the influence mechanisms of uCTX-II and knee moments for the onset and progression of the disease may be different. In addition, knee moments may not be one of the main determinant factors of pain and physical function in patients with medial KOA as we did not find any association between these measures. Finally, as uCTX-II explained a portion of pain and physical function, interventional studies should consider the use of this biomarker to investigate the effects of interventions on cartilage health, which may influence the onset and progression of the disease.

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CONSIDERAÇÕES FINAIS

Considerando os achados desta tese alguns pontos devem ser destacados:

- A relação da força dos abdutores do quadril com a queda contralateral da pelve, ângulo de adução do quadril e função física, nos apontam que propostas de intervenção devem enfatizar o fortalecimento desses músculos, o que provavelmente levará melhorara na qualidade dos movimentos da pelve e do quadril, bem como melhora da função física.

- Por outro lado, considerando que não houve relação entre a força dos abdutores com o MAJ, o fortalecimento desse grupo muscular não deve ter como objetivo a redução da carga no compartimento medial.

- O mecanismo de ação dos componentes mecânicos e biológicos é diferente, visto que nenhuma relação foi encontrada entre as variáveis utilizadas para avaliação destes componentes.

- O biomarcador uCTX-II explica uma pequena parte da dor (9%), função física pelo WOMAC (27%) e teste de caminhada de 40m (7%). Por esta razão, estudos de intervenção devem considerar esse biomarcador para melhor entendimento do seu papel nas medidas clínicas.

ATIVIDADES RELACIONADAS À TESE

Durante o desenvolvimento dos estudos da presente tese, outras atividades foram desempenhadas paralelamente que visaram contribuir para o amadurecimento e aperfeiçoamento do trabalho final:

Doutorado Sanduíche

- Bolsa de Estágio de Pesquisa no Exterior (BEPE) na Universidade de Salford (Manchester – Reino Unido), por 12 meses, sob a supervisão do Professor Richard K. Jones. Neste período, foi realizado um estudo intitulado "*The relationship of foot kinematics on medial load in individuals with medial compartment osteoarthritis: Implications for biomechanical response of interventions*".

Participação em projetos do Laboratório de Análise da Função Articular (LAFAr) - DFisio

Projetos de Doutorado

GONÇALVES GH. Análise cinemática dos membros inferiores e pelve na subida de degraus e avaliação da força dos músculos do tornozelo em indivíduos com osteoartrite de joelho em graus leves e moderados.

PETRELLA M. Análise cinemática e do padrão de ativação muscular das tarefas de sentar e levantar e mini-agachamento em indivíduos com osteoartrite de joelho.

Artigo aceito para publicação

- **Selistre LFA**, Mattiello SM, Nakagawa TH, Gonçalves GH, Petrella M, Jones RK. The relationship between external knee moments and muscle co-activation in subjects with medial knee osteoarthritis. J. Electromyogr Kinesiol, 2017 Jan 18;33:64-72. doi: 10.1016/j.jelekin.2017.01.007. [Epub ahead of print].
- **Selistre LFA**, Gonçalves GH, Petrella M, Mattiello SM. The effects of strengthening, neuromuscular and lumbopelvic stabilization exercises on strength, physical function and symptoms in men with mild knee osteoarthritis: A Pilot Study. Isokinetics and Exercise Science -1 (2017) 1–9 1 DOI 10.3233/IES-218161.

- Gonçalves GH, **Selistre LF**, Petrella M, Mattiello SM. Kinematic alterations of the lower limbs and pelvis during an ascending stairs task are associated with the degree of knee osteoarthritis severity. Knee. 2017 Jan 30. pii: S0968-0160(17)30028-5. doi: 10.1016/j.knee.2017.01.007. [Epub ahead of print].

Autor de capítulo de livro

- Selistre LFA, Serrão PRMS, Lessi GC. *Therapeutic Exercises in the Rehabilitation of Knee Osteoarthritis*. Chapter 7, pp. 129-156. ISBN: 978-1-63483-131-4. Series: Physical Medicine and Rehabilitation. Título do livro: Physical Exercises: An Important Tool for Physical Therapy.

Resumos publicados em anais de congressos

- 2016 World Congress on Osteoarthritis, Amsterdam (Osteoarthritis and Cartilage):

1. **SELISTRE LFA**, MATTIELLO SM, NAKAGAWA TH, GONÇALVES GH, PETRELLA M, JONES RK. A comparison of the composition of the knee index between subjects with mild and moderate knee osteoarthritis.
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4. PEDROSO MG, ALMEIDA AC, AILY JB, GONÇALVES GH, PETRELLA M, **SELISTRE LFA**, LIBERATORI JR RM, MATTIELLO SM. "The influences of different categories of body mass index (BMI) in the stair climbing function in patients with knee osteoarthritis and healthy people";
5. **SELISTRE LFA**, MATTIELLO SM, NAKAGAWA TH, GONÇALVES GH, PETRELLA M, JONES RK. A comparison of the composition of the knee index between subjects with mild and moderate knee osteoarthritis";
6. PETRELLA M, SERRAO PR, **SELISTRE LFA**, GONÇALVES GH, MATTIELLO SM. "Muscle imbalance and physical function in different knee

osteoarthritis degrees."

- 67ª REUNIÃO annual da SBPC:

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- Annual European Congress of Rheumatology - European League Against

Rheumatism, 2014, Paris (Annals of the Rheumatic Diseases The Eular Journal):
PETRELLA M, SERRAO PRS, GRAMANY-SAY K, **SELISTRE LFA**, GONCALVES GH, MATTIELLO SM. Correlation between Self-Reported Physical Function and Isokinetic Total Muscle Work in Early Degrees of Knee Osteoarthritis.

- XX Simpósio de Fisioterapia da UFSCar, 2013, São Carlos:
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GONÇALVES GH, **SELISTRE LFA**, PETRELLA M, MATTIELLO SM. Correlação entre o Torque Extensor e Função Física em homens com Osteoartrite garu II do joelho. 2013. (8° Congresso Paulista de Geriatria e Gerontologia (GERP.13) e o 7° Simpósio das Ligas de Geriatria e Gerontologia).

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APÊNDICE I – Termo de Consentimento Livre e Esclarecido.

UNIVERSIDADE FEDERAL DE SÃO CARLOS
DEPARTAMENTO DE FISIOTERAPIA/ PROGRAMA DE PÓS-GRADUAÇÃO EM FISIOTERAPIA

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

1. Você está sendo convidado para participar da pesquisa "**Momento adutor do joelho durante a marcha, torque abdutor do quadril e biomarcadores: estudo na progressão da osteoartrite do joelho**".
2. Objetivo desta pesquisa: investigar o momento adutor do joelho, inclinação do tronco e ângulo de progressão do pé durante a marcha, assim como torque abdutor do quadril e o nível de uCTX-II e sCOMP em indivíduos com diferentes graus de osteoartrite do joelho.
3. Justificativa: Essa pesquisa ajudará no entendimento do desgaste no joelho, por meio de medidas importantes, para que novos tratamentos sejam desenvolvidos.
4. Procedimentos (Sua participação nesta pesquisa envolverá os seguintes procedimentos):

- Avaliação física: será feita uma investigação do seu histórico de doenças e histórico de um possível problema nas pernas, principalmente joelho (Duração de 30 minutos). Local: Departamento de Fisioterapia da UFSCar.

- Questionário WOMAC: trata-se de um conjunto de perguntas sobre o seu joelho que servirão para avaliar sua capacidade de realizar atividade do dia-a-dia e presença de dor no joelho (Duração de 15 minutos). Local: Departamento de Fisioterapia da UFSCar;

- Exame radiográfico: para avaliar se você tem ou não desgaste no joelho, caso você tenha o exame verificará ainda a quantidade de desgaste (Duração de 20 minutos). Local de realização: Centro Integrado de Diagnóstico por Imagem (CIDI), Rua Paulino Botelho de Abreu Sampaio, 573, Vila Pureza;

- Exame de urina: será utilizado para verificar a quantidade de uma substância chamada CTX-II, trata-se de uma molécula presente na urina que mostra a quantidade de desgaste da cartilagem você tem (Duração de 10 minutos). Local: Laboratório Maricondi, rua Major José Inácio, 2392, centro;

- Exame de sangue: utilizado para verificar a concentração de uma substância chamada COMP, trata-se de uma molécula presente na urina que mostra a quantidade de desgaste da cartilagem você tem (Duração de 15 minutos). Local: Laboratório Maricondi, rua Major José Inácio, 2392, centro;

- Avaliação da força muscular: realizada por meio de um equipamento que irá avaliar a quantidade de força que você consegue fazer para abrir as pernas, afastar uma coxa da outra com joelhos esticados, na posição deitado de lado. (Duração de uma hora). Local: Departamento de Fisioterapia da UFSCar;

- Avaliação da caminhada, realizada por meio de um equipamento que irá filmar você caminhando por um tapete, com várias bolinhas grudadas no seu corpo. A partir dessa avaliação será possível avaliar como você caminha (Duração de duas horas). Local: Departamento de Fisioterapia da UFSCar.

Tempo estimado para realização de todas as avaliações: 4 horas e 30 minutos, divididos em 3 dias. No 1° dia você será submetido(a) a uma avaliação física, responderá algumas perguntas sobre seu joelho e será encaminhado para realização dos exames de urina, sangue e radiográfico; no 2° dia você irá realizar avaliação da força muscular (duração de uma hora); e no 3° dia você irá realizar uma avaliação de sua caminhada (duração de duas horas). Os exames de sangue, urina e radiográfico são realizados fora do Departamento de Fisioterapia da UFSCar e embora não tenham custos para realização o transporte até o local dos exames ficará por sua conta.

Após esclarecimento das dúvidas e do seu consentimento será realizada a avaliação inicial (composta por avaliação física e questionário sobre seu joelho). Você será encaminhado(a) para realização da radiografia dos joelhos, exame de sangue e urina. Em seguida, serão agendadas as avaliações de força e de caminhada, com intervalo entre elas de pelo menos 48 horas, de acordo com sua disponibilidade. Dessa forma, sua

participação nesta pesquisa terá uma duração de aproximadamente uma semana, variando de acordo com sua disponibilidade para a realização dos exames e avaliações.

Sua identidade será preservada em todas as situações que envolvam discussão, apresentação ou publicação dos resultados da pesquisa, a menos que haja uma manifestação da sua parte por escrito, autorizando tal procedimento. No entanto, as informações obtidas a partir de suas avaliações poderão ser utilizadas para fins científicos, desde que resguarda a sua privacidade.

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 não 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.

5. Riscos (A sua participação nesta pesquisa irá expor você à alguns riscos), são eles:
   - Dor muscular após a avaliação de força, pois essa avaliação exige um esforço muscular grande e comumente vem acompanhado de dor muscular. Entretanto trata-se de uma avaliação no qual você fará somente cinco movimentos de abrir e fechar as pernas contra a resistência da máquina. Além disso, é um teste comum para pessoas com desgaste no joelho e idosos, comumente causa somente um cansaço muscular após essa avaliação da força.

- Dor no joelho por caminhar várias vezes sobre uma passarela ou pelo esforço durante o teste de força muscular. Entretanto caso isso ocorra você será orientado(a) quanto ao uso de recursos para diminuir sua dor (gelo ou bolsa com água quente). Caso a dor persista, os pesquisadores responsáveis realizarão o seu tratamento até que sua dor diminua. Apesar desse risco, trata-se de uma atividade que você provavelmente está habituado(a) a fazer e provavelmente não terá dificuldades para realizá-la.

- Dor pela perfuração da agulha na pele, durante a coleta de sangue, entretanto você não será obrigado(a) a participar desse procedimento e sua recusa não impedirá sua participação nesta pesquisa, bem como no recebimento dos resultados. Além disso, trata-se de um procedimento que provavelmente você já conhece e já deve ter sido submetido(a), será realizado por profissionais treinados, experientes e com materiais adequados de modo a proporcionar o menor desconforto possível durante o procedimento.

- Infecção ou irritação da pele, pela perfuração da coleta de sangue, entretanto seu sangue será coletado em um laboratório especializado neste tipo de procedimento, por profissionais treinados, experientes e com materiais descartáveis e adequadamente esterilizados.

- Exposição a radiação, durante o exame radiográfico, entretanto a exposição será pequena pois somente os joelhos serão radiografados e por isso, não deverá trazer prejuízos a você. Além disso, trata-se de um exame bastante comum e amplamente utilizado no mundo inteiro. Você deve estar ciente que os equipamentos de radiografia recebem regularmente manutenção e calibração, impedindo a emissão de radiação desnecessária ou acima do que você pode receber.

6. Benefícios (A sua participação nesta pesquisa irá trazer alguns benefícios), são eles:

- Força muscular, você terá conhecimento da sua atual condição em relação a sua força muscular do quadril. Atualmente os músculos do quadril têm uma importância muito grande para que você realize suas atividades no dia-a-dia com boa qualidade. Além disso, iremos utilizar o melhor e mais confiável equipamento que existe para avaliação da sua força muscular. A partir dessa avaliação você saberá se precisa fortalecer esses músculos ou não.

- Capacidade de realizar atividades no dia-a-dia e dor no joelho, por meio de um questionário que você irá responder, saberá quais atividades você tem mais dificuldade para fazer no dia-a-dia e a partir dessas informações, receberei orientações e exercícios específicos para melhora dessas atividades;

- Presença ou não de desgaste nos joelhos, pois a partir da radiografia você saberá se você tem ou não desgaste nos joelhos. Caso você tenha desgaste, o exame permitirá saber o quanto de desgaste você tem no joelho, ou seja, se a doença está no começo numa fase mais avançada.

- Como você caminha, pois após a filmagem de você caminhando iremos lhe informar sobre a presença de alterações na sua caminhada. Essas alterações podem prejudicar seu joelho e nem sempre você consegue perceber que está caminhando de forma errada. Dessa forma, a partir dessa avaliação você receberá informações sobre sua caminhada, bem como orientações e exercícios específicos para correção dessas alterações. Caso você tenha desgaste no(s) joelho(s), você provavelmente terá alterações na caminhada e dessa forma, após corrigir essas alterações poderá sentir alívio das dores, maior segurança na realização de atividades do dia-a-dia e melhor cansaço físico durante suas caminhadas.

- Quantidade de desgaste no seu corpo, pois os exames de sangue e urina servirão para medir a quantidade de desgaste que você tem no corpo. As substâncias que serão medidas, nos exames de sangue e urina, são eliminadas pela cartilagem desgastada e assim, quanto maior o desgaste maior a quantidade dessas substâncias no sangue e na urina. É importante você saber ainda que esses exames são muitas vezes utilizados para identificar o desgaste antes que você sinta dor nos joelho e por isso, o resultado desses exames poderá te ajudar na prevenção do desgaste.

Como benefícios indiretos da sua participação, os dados obtidos nessa pesquisa poderão servir para podermos compreender melhor como essa doença aparece, progride e como poderemos tratá-la de forma melhor. Além disso, você terá a oportunidade de conversar com especialista no assunto e esclarecer dúvidas que ainda tenha sobre a sua doença.

7. Você será previamente informado verbalmente de todos esses procedimentos, será esclarecido quanto a possíveis dúvidas antes, durante e depois da pesquisa. Embora esse projeto de pesquisa não envolva o tratamento do seu joelho, você receberá uma lista de exercícios que poderão ser realizados em sua casa e que servirão para tratamento e prevenção do desgaste no joelho.
8. A sua recusa em participar desta pesquisa ou retirar seu consentimento poderá ser realizada em qualquer momento da pesquisa, sem penalização ou prejuízo algum. Além disso, sua recusa não trará prejuízo em sua relação com o pesquisador, departamento de Fisioterapia ou instituição UFSCar.
9. Você receberá uma cópia deste termo onde consta o telefone e o endereço do pesquisador principal, podendo tirar suas dúvidas sobre o projeto e sua participação, agora ou a qualquer momento.

Se você tiver qualquer problema ou dúvida durante a sua participação na pesquisa poderá comunicar-se pelo telefone (016)3351-9579 ou vir neste ambulatório de 2ª. ou 6ª. das 8:00 às 12:00 h e procurar o fisioterapeuta Luiz Fernando A. Selistre. Você receberá uma cópia deste termo onde consta o telefone e o endereço do pesquisador principal, podendo tirar suas dúvidas sobre o projeto e sua participação, agora ou a qualquer momento.

_____

Ms. Luiz Fernando A. Selistre
(pesquisador principal)
Rod. Washington Luís, km 235, São Carlos / SP
Fone: (16) 99104-8574
email: lfselistre@yahoo.com.br

_____

Dr. Stela Márcia Mattiello
(Orientadora do pesquisador principal)
Rod. Washington Luís, km 235, São Carlos / SP
Fone: (16) 3351-8031
email: stela@ufscar.br

_____

Dr. Theresa Helissa Nakagawa
(colaboradora)
Rod. Washington Luís, km 235, São Carlos / SP
Fone: (16) 3351-8031, email:
helissa8@gmail.com

Declaro que entendi os objetivos, riscos e benefícios de minha participação na pesquisa e concordo em participar. O pesquisador me informou que o projeto foi aprovado pelo Comitê de Ética em Pesquisa em Seres Humanos da UFSCar que funciona na Pró-Reitoria de Pós-Graduação e Pesquisa da

Universidade Federal de São Carlos, localizada na Rodovia Washington Luiz, Km. 235 - Caixa Postal 676 - CEP 13.565-905 - São Carlos - SP – Brasil. Fone (16) 3351-8110. Endereço eletrônico: cephumanos@ufscar.br

Local e data: _____

Nome do Sujeito da pesquisa: _____
Número e tipo de documento de identificação_____
Assinatura do Sujeito da pesquisa:_____

ANEXO I – Aprovação do Comitê de Ética em Pesquisa.

UNIVERSIDADE FEDERAL DE SÃO CARLOS/UFSCAR

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: MOMENTO ADUTOR DO JOELHO DURANTE A MARCHA, TORQUE ABDUTOR DO QUADRIL E BIOMARCADORES: ESTUDO NA PROGRESSÃO DA OSTEOARTRITE DO JOELHO

Pesquisador: Luiz Fernando Approbato Selistre

Área Temática:

Versão: 3

CAAE: 41716015.0.0000.5504

Instituição Proponente: Departamento de Fisioterapia

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.038.864

Data da Relatoria: 12/05/2015

Apresentação do Projeto:

Trata-se de estudo experimental, transversal, com avaliação quanti-qualitativa. Homens e mulheres com idade entre 40 e 60 anos serão convidados a participarem desta pesquisa. Deverão ter, ainda, alinhamento em valgo menor que 5°, com dor predominante no compartimento medial do joelho. Serão excluídos os sujeitos incapazes de caminhar 20 minutos sem auxílio, com artrites sistêmicas, relato de dor no tendão (quadricipital, patelar ou calcâneo), cirurgia prévia nos últimos 6 meses, fisioterapia e/ou uso de corticosteróides nos últimos 6 meses, presença de prótese (parcial ou total) de quadril ou joelho, déficit cognitivo que comprometa o entendimento do teste, índice de massa corporal (IMC) >40, qualquer outra restrição médica que impossibilite a participação nesse estudo. Os voluntários deverão responder um questionário antes e após a intervenção fisioterapêutica e serão submetidos à avaliação radiológica do joelho, exames sanguíneo e urinário para dosagem, respectivamente, de Collagen Oligomeric Matrix Protein (sCOMP) e C-terminal telopeptide of collagen (uCTX-II). Também serão realizadas a avaliação isocinética do joelho e a avaliação cinemática da marcha.

Objetivo da Pesquisa:

Primariamente, irá investigar o momento adutor do joelho, inclinação do tronco e ângulo de progressão do pé durante a marcha, assim como torque abdutor do quadril e o nível de uCTX-II

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

urinário e sCOMP sérico em indivíduos com diferentes graus de osteoartrite (OA) do joelho. Como objetivos secundários, o pesquisador pretende comparar: o movimento adutor do joelho (MAJ) entre os grupos controle, OA grau II e OA grau III, a variável ângulo de progressão do pé, inclinação do tronco entre os grupos controle, OA grau II e OA grau III e correlacionar o MAJ com o ângulo de progressão do pé, inclinação lateral do tronco, torque abdutor do quadril, nível de uCTX-II e sCOMP de pacientes com OA de joelho graus II e III.

Avaliação dos Riscos e Benefícios:

O aponta os seguintes riscos para os participantes: sentir dor muscular após a avaliação de força (avaliação isocinética), sentir dor no joelho por caminhar várias vezes sobre a passarela, sentir dor pela perfuração da agulha na pele, ou infecção ou irritação pela coleta de sangue. Acrescenta que a exposição à radiação será pequena e que não trará prejuízo. Em relação aos benefícios diretos aos voluntários, o pesquisador assinala os seguintes: conhecimento sobre sua condição física, conhecimento sobre a presença ou não de osteoartrite do joelho, conhecimento sobre sua forma de caminhar, por meio de um equipamento considerado padrão ouro em análise do movimento humano, possibilitando ao voluntário uma correção, objetivando a redução da dor ou a prevenção de alguma lesão por meio de orientações do avaliador, conhecimento sobre sua condição de desgaste da cartilagem no corpo em geral (sistêmico) a partir das informações fornecidas pelos biomarcadores.

Comentários e Considerações sobre a Pesquisa:

O projeto de pesquisa possui relevância à área em questão. O pesquisador corrigiu quanto ao desenho deste estudo e apresentou novo cronograma.

Considerações sobre os Termos de apresentação obrigatória:

A Folha de Rosto foi preenchida corretamente e está assinada. O TCLE foi reapresentado e encontra-se adequado segundo a Resolução CNS 466/12.

Recomendações:

Conclusões ou Pendências e Lista de Inadequações:

As pendências foram resolvidas.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

Projeto Aprovado.

SAO CARLOS, 28 de Abril 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

ANEXO II – Questionário para Avaliação da dor, rigidez e função física (WOMAC).

ÍNDICE WOMAC PARA OSTEOARTRITE

Nome: _____ Data: _____/_____/201_____

As perguntas a seguir se referem à INTENSIDADE DA DOR que você está atualmente sentindo devido a artrite de seu joelho. Para cada situação, por favor, coloque a intensidade da dor que sentiu nas últimas 72 horas (3 dias)

Pergunta: Qual a intensidade da sua dor?

1-Caminhando em um lugar plano

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

2- Subindo ou descendo escadas

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

3- A noite deitado na cama

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

4-Sentando-se ou deitando-se

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

5-Ficando em pé

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

TOTAL: _____

As perguntas a seguir se referem a intensidade de RIGIDEZ nas junta (não dor), que você está atualmente sentindo devido a artrite em seu joelho nas últimas 72 horas. Rigidez é uma sensação de restrição ou dificuldade para movimentar suas juntas.

1- Qual é a intensidade de sua rigidez logo após acordar de manhã?

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

2- Qual é a intensidade de sua rigidez após se sentar, se deitar ou repousar no decorrer do dia?

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

TOTAL: _____

As perguntas a seguir se referem a sua ATIVIDADE FÍSICA. Nós chamamos atividade física, sua capacidade de se movimentar e cuidar de você mesmo(a). Para cada uma das atividades a seguir, por favor, indique o grau de dificuldade que você está tendo devido à artrite em seu joelho durante as últimas 72 horas.

Pergunta: Qual o grau de dificuldade que você tem ao:

1 - Descer escadas

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

2- Subir escadas

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

3- Levantar-se estando sentada

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

4- Ficar em pé

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

5- Abaixar-se para pegar algo

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

6- Abaixar-se para pegar algo

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

7- Abaixar-se para pegar algo

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

8- Abaixar-se para pegar algo

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

9- Abaixar-se para pegar algo

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

10- Abaixar-se para pegar algo

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

11- Abaixar-se para pegar algo

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

12- Abaixar-se para pegar algo

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

13- Abaixar-se para pegar algo

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

14- Abaixar-se para pegar algo

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

15- Abaixar-se para pegar algo

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

16- Abaixar-se para pegar algo

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

17- Abaixar-se para pegar algo

( )Nenhuma ( )Pouca ( )Moderada ( )Intensa ( )Muito intensa

TOTAL: _____