Chapter 5

The association between reduced knee joint proprioception and medial meniscus abnormalities using MRI in knee osteoarthritis: results from the Amsterdam Osteoarthritis cohort

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Abstract

Background. Osteoarthritis (OA) of the knee is characterized by pain and activity limitations. In knee OA, proprioceptive accuracy is reduced and might be associated with pain and activity limitations. Although causes of reduced proprioceptive accuracy are divergent, medial meniscal abnormalities, which are highly prevalent in knee OA, have been suggested to play an important role. No study has focussed on the association between proprioceptive accuracy and meniscal abnormalities in knee OA.

Objective. To explore the association between reduced proprioceptive accuracy and medial meniscal abnormalities in a clinical sample of knee OA subjects.

Methods. Cross-sectional study in 105 subjects with knee OA. Knee proprioceptive accuracy was assessed by determining the joint motion detection threshold in the knee extension direction. The knee was imaged with a 3.0 T magnetic resonance (MR) scanner. Number of regions with medial meniscal abnormalities and the extent of abnormality in the anterior and posterior horn and body were scored according to the Boston-Leeds Osteoarthritis Knee Score (BLOKS) method. Multiple regression analyses were used to examine whether reduced proprioceptive accuracy was associated with medial meniscal abnormalities in knee OA subjects.

Results. Mean proprioceptive accuracy was $2.9^o \pm 1.9^o$. Magnetic resonance imaging (MRI)-detected medial meniscal abnormalities were found in the anterior horn (78%), body (80%), and posterior horn (90%). Reduced proprioceptive accuracy was associated with both the number of regions with meniscal abnormalities ($P<0.01$) and the extent of abnormality ($P=0.02$). These associations were not confounded by muscle strength, joint laxity, pain, age, sex, body mass index (BMI), and duration of knee complaints.

Conclusion. This is the first study showing that reduced proprioceptive accuracy is associated with medial meniscal abnormalities in knee osteoarthritis. The study highlights the importance of meniscal abnormalities in understanding reduced proprioceptive accuracy in persons with knee OA.

Introduction

Osteoarthritis (OA) of the knee involves many tissues, such as cartilage, bone, menisci, and the synovial membrane (1-4). Clinical characteristics of the disease are joint pain and activity limitations (5). Reduced joint proprioceptive accuracy might be associated with pain and activity limitations (6-10). Although causes of reduced joint proprioceptive accuracy are divergent, meniscal abnormalities have been suggested to play an important role (11-13). As far as we are aware, the direct association between reduced knee joint proprioceptive accuracy and meniscal abnormalities has not yet been demonstrated in persons with knee OA.

Proprioceptive accuracy in knee OA is reduced and not well understood (9,10). Key factors that may affect proprioceptive accuracy in knee OA are: impaired articular mechanoreceptors, muscle weakness through reduced γ-motor neuron activation with reduced muscle spindle sensitivity, OA-related inflammation and effusion, and concomitant abnormalities to the anterior cruciate ligament or meniscus (9,10).

Meniscal abnormalities (i.e., tears or maceration) have been found in up to 80% of knees with OA (2-4). Meniscal abnormalities affect the load transmission of the knee in at least 2 ways: 1) through alteration of the morphology and anatomical structure of the meniscus, and 2) by impairing the mechanoreceptors of the knee (2,12). Studies focusing on the mechanical properties of the menisci have found that the most substantive strains and the highest load (70%) are in the medial meniscus (14-16). In the medial meniscus, the mechanoreceptors are located in the outer rim, which is firmly attached to the capsule and the coronary (collateral) ligaments, where mechanoreceptors are also found (17,18). In contrast, the lateral meniscus is only attached to the coronary ligaments, not to the capsule and contains less mechanoreceptors (19). Therefore, it could be expected that a medial meniscal abnormality might reduce the number of mechanoreceptors, as well as impair mechanoreceptor function, thereby affecting proprioceptive accuracy. This effect may be bi-directional. Reduced proprioceptive accuracy may lead to meniscal damage due to impaired neuromuscular control and thereby knee instability. Instability may increase the strains and load on the medial meniscus with a high risk for damage, leading to a self-perpetuating cycle (20). The first step in studying this self-perpetuating cycle is by examining the relationship between proprioceptive accuracy and meniscal abnormality, which will improve knowledge regarding reduced proprioceptive accuracy. Therefore, the aim of this study was to explore the association between reduced proprioceptive accuracy and medial meniscal abnormality in a clinical sample of persons with knee OA.

Methods

Subjects

For the present study, participants were recruited from a randomized controlled trial (STABILITY-trial) from January 2010 to August 2011(21,22). This trial was embedded in the Amsterdam Osteoarthritis (AMS-OA) cohort, a cohort of subjects with OA of the knee and/or hip who are referred to a specialized clinic (Reade, center for rehabilitation and rheumatology, Amsterdam, The Netherlands) (21,22). Inclusion criteria were clinical knee OA diagnosis according to the American College of Rheumatology criteria (23), age between 40 and 75 years, biomechanically assessed and/or self-reported knee instability, and written informed consent (21,22). Exclusion criteria were total knee arthroplasty, any form of arthritis other than OA, comorbidities affecting daily functioning, severe knee pain (numeric rating scale (NRS) > 8) and contra-indication for magnetic resonance imaging (MRI) (e.g., pacemaker, claustrophobia). The study was approved by the Slotervaart Hospital/ Reade, Institutional Review Board. All measurements were scheduled prior to the start of an exercise program.

Measures

Knee joint proprioception. Proprioception was assessed in a knee joint motion detection task, expressed as the joint motion detection threshold. A device was used that provided knee angular displacement in extension and precise measurement of the angular displacement with a resolution of 0.1^{o} (Fig. 1). This method of assessment has been described in previous studies (6,24). The angular displacement between the starting position and the position at the instant of pushing a stop button was recorded. The threshold for detection of knee joint movement was defined as the difference, in degrees, between the actual onset of motion and the subject's detection of knee joint position change or motion. High joint motion detection threshold meant a great difference between the actual onset of motion and the subject's detection and expressed poor proprioceptive accuracy. The mean joint motion detection threshold from 3 measurements was used for analyses. ICCs for intra-rater reliability for the assessment of participants with and without OA by a single experienced tester were 0.91 and 0.86, respectively (24). The within-rater minimal detectable difference (MDD) was 6.26^{o} and the between-rater MDD was 5.90^{o} respectively, in subjects with knee OA (24)

Fig. 1. Experimental setup for the assessment of knee joint proprioception, showing the measurement chair control mechanism, handheld button, air splints, and footrest (the moving component of the apparatus)

Magnetic resonance (MR) imaging. MRI scans were performed of the knee that was clinically diagnosed with knee OA (in unilateral knee OA) or of the knee with most severely affected daily activities (in bilateral knee OA). Knees were imaged by a 3.0 T whole body MR scanner (General Electric Medical Systems, Milwaukee, WI) using a phased array knee coil. The MRI examination included 5 sequences. The first sequence was a sagittal proton density-weighted turbo spin-echo with fat suppression (slice thickness 3 mm; interslice gap 0.3 mm; repetition time (TR) 3480 ms; echo time (TE) 42 ms; turbo factor 8; matrix 384x256). The second sequence was a sagittal T1-weighted turbo spin-echo (slice thickness 3 mm; interslice gap 0.3 mm; TR 760 ms; TE 14 ms; turbofactor 2; matrix 384x256). The third sequence was a coronal T2-weighted turbo spin-echo with fat suppression (slice thickness 3mm; interslice gap 0.3 mm; TR 5800 ms; TE 85 ms; turbo factor 15; matrix 384x256). The fourth sequence was a sagittal combined multi-echo gradient echo (MERGE; thickness 3.5 mm; interslice gap 0.3 mm; TR 973 ms; excitation angle 20 degrees; matrix 352x224). The last sequence was a coronal combined multi-echo gradient echo (MERGE; thickness 3.0 mm; interslice gap 0.5 mm; TR 854 ms; excitation angle 20 degrees; matrix 352x224). For meniscal scoring, all 5 sequences were used, particularly the second and third sequences.

MRI medial meniscal abnormality was assessed following a commonly used scoring method, the Boston-Leeds Osteoarthritis Knee Score (BLOKS) (25,26), by a radiologist (JPK) with 27 years of musculoskeletal radiology expertise who was blinded to the participants

clinical characteristics. Intra-observer reliability was found to be good in 15 participants (ICC=0.82).

The medial meniscus was divided into 3 regions: anterior horn, body and posterior horn. The extent of meniscal abnormality was scored as follows: normal, signal only, vertical tear, horizontal tear, complex tear, root tear, and maceration. A signal only was indicated as a signal within the meniscus which did not extend to an articular surface. A tear was indicated as high signal intensity within the meniscus that extended to 2 meniscal surfaces. Maceration indicated loss of overall normal morphological appearance of the meniscus as well as an associated increased diffuse signal in the meniscal tissue.

Two meniscal abnormality scores were used in statistical analyses. First, the number of regions (ranging from 0 to 3 regions) of the medial meniscus with an abnormality was scored. Second, meniscal abnormality extent was scored as follows: 0=no abnormality, 1=signal only, 2=tear (including vertical, horizontal, complex or root tear) and 3=maceration. The highest score of meniscal abnormality extent of the 3 regions was used in analyses.

In addition, medial meniscal extrusion relative to medial tibia margin and anterior extrusion were scored as follows: 0= <2mm, 1= 2-2.9 mm, 2= 3-4.9 mm and 3= >5 mm.

Other variables. Muscle strength. Muscle strength of the left and right leg was measured isokinetically (EnKnee, Enraf-Nonius, Rotterdam, Netherlands) at 60°/second (6,27). The mean muscle torque (i.e., extension and flexion) per leg was calculated to obtain a measure of overall leg muscle strength (Nm). For the analyses, individual mean muscle strength was divided by the subject's body weight for a normalized measure (Nm/kg).

Knee joint laxity. Joint varus-valgus laxity was measured as the total movement in the frontal plane during varus-valgus load in a non-weight bearing position (27). The mean of 3 measurements (degrees) was calculated for each knee.

Pain. Knee pain over the past week was assessed by an 11 point NRS (0-10), with higher scores representing more pain. Subjects were asked: what was your pain rating on average over the past week?

Radiography. Radiographs of the knee were scored in a blinded fashion by an experienced radiologist. The grading scale proposed by Kellgren & Lawrence (K/L) was used to determine Radiographic Osteoarthritis (ROA) (28). Weightbearing, anterior-posterior radiographs of the knee joints were obtained following the Buckland-Wright protocol (29).

Demographics. A series of demographic variables were obtained including age, sex, height, weight, body mass index (BMI), and duration of complaints. For the analyses, age, BMI, and duration of complaints were used as continuous variables.

Statistical analysis

Data of knee-specific variables were used from the index knee, which was the knee of which MRI had been obtained (i.e., knee diagnosed with clinical OA in unilateral knee OA or participant-reported knee most severely affecting daily activities in bilateral knee OA). First, descriptive statistics (mean±SD or *n*, %) of the index knee were obtained. Second, analysis of variance was used to check for linearity of the associations between proprioceptive acuity and the MRI detected number of regions with meniscal abnormality and the extent of meniscal abnormality. Third, in order to assess the relationship between proprioceptive accuracy (joint motion detection) and MRI meniscal abnormality in knee OA 2 simple linear regression analyses were performed. The dependent variable was proprioceptive accuracy in degrees. The independent variable was the meniscal abnormality score, which was in model 1: number of regions with an abnormality (ranging from 0-3 regions) and in model 2: abnormality extent (ranging from 0-3, with 0=none; 1=signal only; 2=meniscal tear; 3= macerated meniscus). Results of the regression analyses are expressed as unstandardized (B) regression coefficients that represent the associations between proprioceptive accuracy and the number of regions with a meniscal abnormality and the extent of meniscal abnormality. Fourth, in multiple regression analyses, the dependent variable was proprioception in degrees and the independent variables were the meniscal abnormalities (model 1: number of regions with an abnormality, model 2: extent of abnormality). In both models muscle strength, joint laxity, pain, age, sex, BMI, and duration of complaints were included as covariates. Background knowledge identified these covariates as potential confounders, according to the confounder selection method by Greenland (30). When with stepwise addition of covariates the regression coefficient of the number of regions with an abnormality or the regression coefficient of the extent of abnormality was not changed by 10%, these covariates were deemed insignificant to the outcome and were excluded from the final model. All analyses were performed using SPSS software, version 19.0 (SPSS, Chicago, IL, USA).

Results

From a total of 112 potential candidates that participated a randomized controlled trial (21) from January 2010, 7 persons were excluded (reason: MRI could not be scheduled before start of trial). Table 1 shows the characteristics of participants.

The number of regions with a medial meniscal abnormality and the extent of abnormality are shown in Table 2. In 77% of the knees, an abnormality was found in the medial meniscus, with overall the highest prevalence of abnormalities in the posterior horn (89%). Maceration was present mostly in the body of the meniscus (44%). Tears were found most frequently in the posterior horn (29%) and signal only most frequently in the anterior

Table 1: Characteristics of participants (*n*=105)

	Value
Age, mean ± SD years	61.4 ± 6.9
Women, no. (%)	73 (70%)
Body mass index, mean ± SD kg/m^2	29.1 ± 4.7
Duration of complaints, mean ± SD years	11.3 ± 9.2
Joint proprioception, mean ± SD degrees	2.93 ± 1.86
Joint laxity, mean ± SD degrees	6.9 ± 2.8
Isokinetic muscle strength (extension), mean ± SD Nm/kg	0.89 ± 0.47
NRS for pain intensity during the past week, mean ± SD (range 0-10)	5.1±2.1
K/L knee score, no. (%)	
0	1 (1%)
1	31 (29%)
2	28 (27%)
3	26 (25%)
4	19 (18%)

SD=standard deviation; NRS=numeric rating scale; K/L=Kellgren/Lawrence.

Table 2: Prevalence of MRI medial meniscal abnormality* by region (*n*=105)

	Anterior horn	Body	Posterior horn
Normal (no signal or tear)	23 (21.9%)	21 (20.0%)	11 (10.5%)
Signal	49 (46.7%)	24 (22.9%)	26 (24.7%)
Tears	5 (4.8%)	13 (12.5%)	30 (28.6%)
Maceration	28 (26.7%)	47 (44.8%)	38 (36.2%)

* Meniscal abnormalities were scored using the BLOKS meniscus score (one option per region).

Table 3: Distribution of proprioceptive accuracy in degrees over the number of regions with an abnormality and the extent of abnormality of the medial meniscus (*n*=105)

Number of regions with an abnormality	Proprioceptive accuracy mean (SD)	Extent of abnormality	Proprioceptive accuracy mean (SD)
No region	1.83 (1.06)	No abnormality	1.83 (1.06)
One region	2.09 (0.79)	Signal	2.70 (1.74)
Two regions	2.57 (0.93)	Tears	2.85 (1.83)
Three regions	3.20 (2.02)	Maceration	3.19 (1.80)

SD=standard deviation.

Table 4: Results of the regression analyses of the number of regions and the extent of MRI abnormality in the medial meniscus on knee joint proprioception

Model 1: Number of regions				Model 2: Extent of abnormality			
	B	*P*	95% CI		B	*P*	95% CI
Unadjusted*	0.45	0.009	0.12, 0.79	Unadjusted*	0.37	0.023	0.05, 0.69
Adjusted†	0.48	0.006	0.14, 0.83	Adjusted†	0.39	0.023	0.05, 0.72

B=unstandardized regression coefficient; CI=confidence interval; * simple regression: unadjusted; † multiple regression: adjusted for muscle strength, joint laxity, NRS pain, age, sex, BMI, and duration of complaints.

horn (47%).

In Table 3 it is shown that the proprioceptive accuracy decreased when the number of regions with a medial meniscus abnormality increased. For those with 3 regions of the meniscus affected, the proprioceptive accuracy was reduced by 3.2 degrees. It is also shown that the proprioceptive accuracy reduced when the extent of a meniscal abnormality increased. For those with a macerated medial meniscus the proprioceptive accuracy was reduced by 3.2 degrees.

To identify cases that were outlying with respect to their values we used Cook's distance and leverage values to assess the influence on the regression model (31). We identified one case as an outlier with extreme proprioceptive inaccuracy and high laxity values and that case was excluded from further regression analyses.

Linear regression analyses (Table 4) showed that the number of regions with a meniscal abnormality was significantly associated with proprioceptive accuracy. This association was not confounded by any of the covariates (muscle strength, joint laxity, pain, duration of complaints, and demographic factors). The regression coefficient (B) indicates that with every increase in the number of regions with an abnormality in the medial meniscus, the accuracy of proprioception decreased by 0.48 degrees. Linear regression analyses also showed that the extent of meniscal abnormality was also significantly associated with proprioceptive accuracy (Table 4). This association was not substantively confounded by the covariates. The regression coefficient (B) indicates that any unit of increase in extent of abnormality in the medial meniscus, ranging from normal to maceration, decreased the accuracy of proprioception by 0.39 degrees.

No associations between medial and anterior medial meniscal extrusion and accuracy of proprioception were found.

Discussion

In a cross-sectional study of persons with established knee OA, we explored the association between reduced proprioceptive accuracy and medial meniscal abnormalities. Abnormalities were present in the anterior horn (78%), body (80%) and posterior horn (90%) of the medial meniscus. A significant association was found between reduced proprioceptive accuracy and the number of regions with an abnormal medial meniscus, as well as with the extent of medial meniscus abnormality. Our results confirm the hypothesis that proprioceptive accuracy and meniscal abnormality are associated (2,3). A meniscal abnormality may predispose to reduced proprioceptive accuracy. Alternatively, reduced proprioceptive accuracy might itself add to an overloading of the medial meniscus through its reduced neuromuscular reflex responses, leading to knee joint instability and therefore to a self-

perpetuating cycle. The cause and effect relationship need to be confirmed in longitudinal studies.

In proprioception, different active and passive key factors of the knee are integrated and related to each other (9,10). Via neuromuscular reflex responses, proprioception controls muscle activity and as a result protects the knee from excessive and possible injurious loads (9). In cases of injurious loads, meniscal abnormality is indirectly the result of reduced proprioceptive accuracy, but conversely, the meniscal abnormality will alter proprioceptive accuracy. Reduced proprioceptive accuracy, next to muscle weakness, is an important factor of the neuromuscular reflex system in the facilitation of joint stabilization. Knee instability is a highly prevalent characteristic in knee OA subjects (20,21,32-34). Therefore, our results suggest that persons with knee OA with reduced proprioceptive accuracy and meniscal abnormality will suffer from more knee instability. Future studies are needed to explore the associations between knee joint instability, reduced proprioceptive accuracy, and meniscal abnormality. Consequently, reduced proprioceptive accuracy and meniscal abnormality necessitate a change in exercise regimens. Neuromuscular exercises might be of great importance in persons with reduced proprioceptive accuracy and meniscal abnormality with the aim to affect the self-perpetuating cycle and improve knee joint stability.

Several scoring methods have been developed over the last few years (25,26,35). We used the scoring of meniscal abnormality as has been described by the BLOKS (25,26). This scoring method provided the radiologist with a clear method to identify and classify the abnormal features of the medial meniscus. An MRI-detected meniscal abnormality was defined as a loss of overall normal morphological appearance of the medial meniscus and scored as signal only, vertical tear, horizontal tear, complex tear, root tear, or maceration of the anterior horn, body or posterior horn (25). Maceration of the meniscus was highly prevalent, which has also been found in other studies (2,11), indicating that our sample had severe knee OA. Tears were less frequently present (range from 4.7% to 28.6%) when compared to other studies (36-40). In those studies, more than 50% of subjects with knee OA showed tears, particularly in the early stages of knee OA. The prevalence of meniscal changes in the anterior horn was high compared to other knee OA studies (39,40). However, we could not find a clear explanation for this high prevalence. A possible reason could be the severity of OA in our sample, with complaints duration of 11.3 ± 9.2 years and radiographic damage in 70% of the knees (K&L score ≥2).

Meniscal signal only, can be presumed as the first MRI meniscal feature showing an abnormal integrity of the meniscus (13). Some authors suggest that a signal is an MRI feature indicating normal integrity, while other authors define it as the first feature of a loss of integrity and therefore as an abnormality (13). We scored signal only as a non-severe abnormality, which we interpreted as the first characteristic of the medial meniscus in knee OA with a loss of integrity. A further reason to classify a meniscal signal as an abnormality is

to be able to distinguish more precisely between normal morphology of the meniscus and the presence of a tear in the meniscus with high signal.

Several limitations to our study bear attention. Firstly, no control-group was included in the study. It is necessary to control for meniscal abnormalities in a 'healthy' population of comparable age and sex. It has been shown that meniscal abnormality is highly prevalent in healthy older subjects (2,3) and that proprioceptive accuracy decreases in the elderly (7,9). The present study is the first exploratory study that has shown an association between proprioceptive accuracy and meniscal abnormality in persons with established knee OA. This needs to be replicated in future studies, including early and severe knee OA, matched with healthy controls. Secondly, we assessed maceration as a severe extent of a meniscal abnormality. Maceration could be the result of destruction of the meniscus as part of the osteoarthritic process, but also the result of a former resection of the meniscus. In scoring MRI features, it is difficult to distinguish between maceration due to destruction or to a resection of the meniscus. History-taking could give additional information about the cause behind maceration. Thirdly, the BLOKS scoring system does not provide a scoring of tears in the 'red' zone, i.e., in the high-vascularization region of the insertional ligaments of the meniscus, while this region is of particular interest as it contains a higher density of mechanoreceptors. Future studies on the relation between meniscal damage and proprioceptive accuracy may need to focus on this particular region. Fourthly, subjects were included when biomechanically assessed and/or self-reported knee instability was present. Therefore, our results cannot be generalized to all subjects with knee OA. Finally, this study confirms former speculations about the relationship between proprioceptive accuracy and meniscal abnormality (2,3), however, it does not prove a causal relationship. Future studies need to focus on MRI-detected meniscal features and proprioception in a longitudinal design, to clarify the interaction between meniscal abnormality and reduced proprioceptive accuracy in a self-perpetuating cycle.

To conclude, this is the first study showing that reduced proprioceptive accuracy is associated with medial meniscal abnormality in knee osteoarthritis. The study highlights the importance of meniscal abnormality in understanding reduced proprioceptive accuracy in persons with knee OA.

References

(1) Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. Lancet 2011;377(9783):2115-2126.

(2) Englund M, Guermazi A, Lohmander SL. The role of the meniscus in knee osteoarthritis: a cause or consequence? Radiol Clin North Am 2009;47(4):703-12.

(3) Englund M, Guermazi A, Lohmander LS. The meniscus in knee osteoarthritis. Rheum Dis Clin North Am 2009;35(3):579-90.

(4) Lo GH, Hunter DJ, Nevitt M, Lynch J, McAlindon TE; OAI Investigators Group. Strong association of MRI meniscal derangement and bone marrow lesions in knee osteoarthritis: data from the osteoarthritis initiative. Osteoarthritis Cartilage 2009;17(6):743-7.

(5) Dekker J, van Dijk GM, Veenhof C. Risk factors for functional decline in osteoarthritis of the hip or knee. Curr Opin Rheumatol 2009;21(5):520-4.

(6) van der Esch M, Steultjens M, Harlaar J, Knol D, Lems W, Dekker J. Joint proprioception, muscle strength, and functional ability in patients with osteoarthritis of the knee. Arthritis Rheum 2007;57(5):787-793.

(7) Sharma L, Cahue S, Song J, Hayes K, Pai YC, Dunlop D. Physical functioning over three years in knee osteoarthritis: role of psychosocial, local mechanical, and neuromuscular factors. Arthritis Rheum 2003; 48(12):3359-3370.

(8) Felson DT, Gross KD, Nevitt MC, Yang M, Lane NE, Torner JC et al. The effects of impaired joint position sense on the development and progression of pain and structural damage in knee osteoarthritis. Arthritis Rheum 2009;61(8):1070-1076.

(9) Knoop J, Steultjens MP, van der Leeden M, van der Esch M, Thorstensson CA, Roorda LD et al. Proprioception in knee osteoarthritis: a narrative review. Osteoarthritis Cartilage 2011;19(4):381-388.

(10) Smith TO, King JJ, Hing CB. The effectiveness of proprioceptive-based exercise for osteoarthritis of the knee: a systematic review and meta-analysis. Rheumatol Int 2012;32(11):3339-51.

(11) Englund M, Felson DT, Guermazi A, Roemer FW, Wang K, Crema MD, et al. Risk factors for medial meniscal pathology on knee MRI in older US adults: a multicentre prospective cohort study. Ann Rheum Dis 2011;70(10):1733-9.

(12) Englund M. The role of the meniscus in osteoarthritis genesis. Med Clin North Am 2009;93(1):37-43.

(13) Englund M, Niu J, Guermazi A, Roemer FW, Hunter DJ, Lynch JA, et al. Effect of meniscal damage on the development of frequent knee pain, aching, or stiffness. Arthritis Rheum 2007;56(12):4048-54.

(14) Andriacchi TP, Dyrby CO, Johnson TS. The use of functional analysis in evaluating knee kinematics. Clin Orthop Relat Res 2003;410:44-53.

(15) Schipplein OD, Andriacchi TP. Interaction between active and passive knee stabilizers during level walking. J Orthop Res 1991;9:113-9.

(16) Netravali NA, Koo S, Giori NJ, Andriacchi TP. The effect of kinematic and kinetic changes on meniscal strains during gait. J Biomech Eng 2011;133(1):011006.

(17) Aagaard H, Verdonk R. Function of the normal meniscus and consequences of meniscal resection. Scand J Med Sci Sports 1999;9(3):134-40

(18) Messner K, Gao J. The menisci of the knee joint. Anatomical and functional characteristics, and a rationale for clinical treatment. J Anat 1998;193:161-78.

(19) Assimakopoulos AP, Katonis PG, Agapitos MV, Exarchou EI. The innervation of the human meniscus. Clin Orthrop 1992;275:232-6.1992.

(20) Sharma L, Eckstein F, Song J, Guermazi A, Prasad P, Kapoor D, et al Relationship of meniscal damage, meniscal extrusion, malalignment, and joint laxity to subsequent cartilage loss in osteoarthritic knees. Arthritis Rheum 2008;58:1716-26.

(21) Knoop J, van der Leeden M, van der Esch M, Thorstensson C, Gerritsen M, Voorneman R, et al. Association of lower muscle strength with self-reported knee instability in osteoarthritis of the knee: results from the Amsterdam Osteoarthritis cohort. Arthritis Care Res (Hoboken) 2012;64(1):38-45.

(22) Knoop J, Dekker J, van der Leeden M, van der Esch M, Thorstensson CA, Gerritsen M et al. Knee joint stabilization therapy in patients with osteoarthritis of the knee: a randomized, controlled trial. Osteoarthritis Cartilage 2013;21(8):1025-34.

(23) Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29(8): 1039-1049.

(24) Hurkmans EJ, van der Esch M, Ostelo RW, Knol D, Dekker J, Steultjens MP. Reproducibility of the measurement of knee joint proprioception in patients with osteoarthritis of the knee. Arthritis Rheum 2007;57(8):1398-403.

(25) Hunter DJ, Guermazi A, Lo GH, Grainger AJ, Conaghan PG, Boudreau RM, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthritis Cartilage 2011;19(8):990-1002.

(26) Hunter DJ, Lo GH, Gale D, Grainger AJ, Guermazi A, Conaghan PG. The reliability of a new scoring system for knee osteoarthritis MRI and the validity of bone marrow lesion assessment: BLOKS (Boston Leeds Osteoarthritis Knee Score). Ann Rheum Dis 2008;67(2):206-211.

(27) van der Esch M, Steultjens MPM, Knol D, Dinant H, Dekker J. Joint laxity modifies the relationship between muscle strength and disability in patients with osteoarthritis of the knee. Arthritis Rheum 2006; 55:953-9.

(28) Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage 2007;15 Suppl A:A1-56.

(29) Buckland-Wright C. Protocols for precise radio-anatomical positioning of the tibiofemoral and patellofemoral compartments of the knee. Osteoarthritis Cartilage 1995;3 Suppl A:71-80.

(30) Greenland S. Invited commentary: variable selection versus shrinkage in the control of multiple confounders. A J Epidemiolog 2008;167:523-29

(31) Kutner MH, Nachtsheim CJ, Neter J, Li W. Applied Linear Statistical Models; 5th ed. McGraw-Hill: New York, 2005;398-405

(32) van der Esch M, Knoop J, van der Leeden M, Voorneman R, Gerritsen M, Reiding D,et al. Self-reported knee instability and activity limitations in patients with knee osteoarthritis: results of the Amsterdam osteoarthritis cohort. Clin Rheumatol 2012;31(10):1505-10.

(33) Felson DT, Niu J, McClennan C, Sack B, Aliabadi P, Hunter DJ et al. Knee buckling: prevalence, risk factors, and associated limitations in function. Ann Intern Med 2007;147:534-40.

(34) Fitzgerald GK, Piva SR, Irrgang JJ. Reports of joint instability in knee osteoarthritis: its prevalence and relationship to physical function. Arthritis Rheum 2004;51:941-6.

(35) Hayashi D, Guermazi A, Hunter DJ. Osteoarthritis year 2010 in review: imaging. Osteoarthritis Cartilage 2011;19(4):354-60.

(36) Bhattacharyya T, Gale D, Dewire P, Totterman S, Gale E, McLaughlin S et al. The clinical importance of meniscal tears demonstrated by magnetic resonance imaging in osteoarthritis of the knee. J Bone Joint Surg Am 2003;85(1):4-9.

(37) Davies-Tuck ML, Martel-Pelletier J, Wluka AE, Pelletier JP, Ding C, Jones G, et al. Meniscal tear and increased tibial plateau bone area in healthy post-menopausal women. Osteoarthritis Cartilage 2008; 16(2):268-71.

(38) Hunter DJ. Imaging insights on the epidemiology and pathophysiology of osteoarthritis. Rheum Dis Clin North Am 2009;35(3):447-63.

(39) Crema MD, Hunter DJ, Roemer FW, Li L, Marra MD, Nogueira-Barbosa MH, et al. The relationship between prevalent medial meniscal intrasubstance signal changes and incident medial meniscal tears in women over a 1-year period assessed with 3.0 T MRI. Skeletal Radiol 2011;40(8):1017-23.

(40) Roemer FW, Guermazi A, Hunter DJ, Niu J, Zhang Y, Englund M, et al. The association of meniscal damage with joint effusion in persons without radiographic osteoarthritis: the Framingham and MOST osteoarthritis studies. Osteoarthritis Cartilage 2009;17(6):748-53.