Chapter 8

Knee joint stabilization therapy in patients with osteoarthritis of the knee and knee joint instability: subgroup-analyses in a randomized, controlled trial

J. Knoop

M. van der Leeden

L.D. Roorda

C.A. Thorstensson

M. van der Esch

W.F. Peter

M. de Rooij

W.F. Lems

J. Dekker

M.P.M. Steultjens

Journal of Rehabilitation Medicine (accepted for publication)

Abstract

Objective. To test whether knee stabilization therapy, prior to strength/functional training, may only have added value in reducing activity limitations in knee osteoarthritis (OA) patients with knee instability and (i) low upper leg muscle strength, (ii) impaired knee proprioception, (iii) high knee laxity, or (iv) frequent episodes of knee instability.

Design. Subgroup-analyses in a randomized, controlled trial comparing 2 exercise programs (with/without knee stabilization therapy) (STABILITY; NTR1475).

Patients. Participants from the STABILITY-trial with clinical knee OA and knee instability (*n*=159).

Methods. Effect modification by upper leg muscle strength, knee proprioception, knee laxity, and patient-reported knee instability was determined using interaction terms of 'treatment group*subgroup factor', with outcome measures WOMAC physical function (primary), NRS pain and the Get up and Go test (secondary).

Results. Effect modification by muscle strength was found for the primary outcome (*P*=0.01), indicating that patients with higher muscle strength tend to benefit more from the experimental program with additional knee stabilization training, while patients with lower muscle strength more from the control program.

Conclusion. Knee stabilization therapy may have added value in patients with instability and strong muscles. This may imply that exercises should target muscle strength prior to knee stabilization.

Introduction

The majority (>60%) of knee OA patients reports knee instability (i.e. buckling, shifting or giving way) (1;2), which has been associated to pain and activity limitations (1-3). The knee joint is presumed to be stabilized by active neuromuscular control, provided by muscles and proprioceptive stimuli, and passive restraint, provided by ligaments and capsule (4).

We previously conducted a randomized, controlled trial (STABILITY) (5) to test our hypothesis that knee OA patients suffering from knee joint instability benefit more from a tailored exercise program that initially focuses on knee stability, prior to muscle strength and performance of daily activities, compared to a control program focusing on muscle strength and performance of daily activities only. Unexpectedly, the 2 programs were found to be similarly effective in reducing activity limitations (~30% improvement), pain (~40%) and knee instability (~30%). Possibly, initial knee stabilization therapy may only be effective in patients in whom knee instability is most severe (i.e., those with lowest muscle strength, worst proprioception, highest laxity, or most frequent episodes of instability).

Therefore, the aim of the study was to test whether knee stabilization therapy, prior to strength/functional training may only have added value in reducing activity limitations in knee OA patients with knee instability and (i) low upper leg muscle strength, (ii) impaired knee joint proprioception, (iii) high knee joint laxity, or (iv) frequent episodes of knee instability.

Methods

Design

A single-blind, randomized, controlled trial (STABILITY; Dutch Trial Registry NTR1475) (5) to compare 2 exercise programs had been conducted in an outpatient rehabilitation centre (Reade, the Netherlands). Participants were measured at baseline and 6-week (i.e., mid-treatment), 12-week (i.e., directly post-treatment) and 38-week follow-up (FU) (i.e., 6 months post-treatment), by a trained research assistant blinded for group allocation. This study was approved by the Medical Ethical Review Board (Reade/Slotervaart Hospital). For the present study, pre-planned subgroup-analyses were performed.

Participants

Inclusion criteria were (i) diagnosis of knee OA according to the clinical ACR criteria, (ii) age between 40 and 75 years, and (iii) presence of self-reported knee instability in past three months and/or biomechanically assessed knee instability (using cut-off points for upper leg muscle weakness, and proprioceptive accuracy and varus-valgus laxity of the knee joint (5)).

Exclusion criteria for the trial have been described in our previous publication (5). All participants provided written informed consent.

Experimental and control intervention

A detailed description of the interventions has been provided previously (5). In summary, both the experimental and control intervention comprised a supervised exercise program of 12 weeks with 2 sessions of 60 minutes weekly, in groups of approximately 8 participants. In addition, home exercises were provided for 5 days weekly (on non-treatment days only). Each group was supervised by 2 physical therapists, who were specifically trained to supervise only one of both treatments. Training intensity, which gradually increased during the program, and amount of attention from the physical therapists were similar in both groups (5).

The experimental program consisted of three phases: (i) week 1-4, focusing on knee stabilization, (ii) week 5-8, focusing on muscle strengthening, in addition to knee stabilization, and (iii) week 9-12, focusing on performance of daily activities, in addition to muscle strengthening and knee stabilization. During the entire program, but explicitly in the first four weeks, patients in the experimental group received instructions during exercising to focus on their knee position (i.e., proprioception) and to control this position (i.e., neuromuscular control). For this purpose, verbal and tactile feedback from physical therapists and visual feedback from mirrors were provided. Furthermore, patients received specific exercises challenging them to maintain adequate knee position.

The control program consisted of only two phases: (i) week 1-8, focusing on muscle strengthening, and (ii) week 9-12, focusing on performance of daily activities, in addition to muscle strengthening. Physical therapists in the control group were not allowed to give instructions and feedback on knee position.

Measurements

Outcome measures. Primary outcome. Self-reported activity limitations were assessed by the Dutch translation of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscale physical function, with a total score ranging from 0 (no limitations) to 68 (maximally limited) (6;7).

Secondary outcomes. Self-reported knee pain severity was assessed on a numeric rating scale (NRS), ranging from 0 (no pain) to 10 (worst imaginable pain), by the question ‘What was your average knee pain during the last week?’ (8). The Get Up and Go (GUG) test was used as a measure for observed activity limitations. The GUG-test is a performance-

based test in which a patient is asked to rise up from a chair and walk as fast as possible over a distance of 15 meters (9).

Subgroup factors. Baseline values of upper leg muscle strength, proprioceptive accuracy of the knee joint, varus-valgus knee joint laxity and patient-reported knee instability were used as subgroup factors.

Upper leg muscle strength. Muscle strength was assessed for knee flexion and extension using an isokinetic dynamometer (EnKnee, Enraf-Nonius). Patients performed 3 maximal test repetitions, which were averaged per leg and then divided by patient's weight. This normalized measure (in Nm/kg) was used for the analyses (10). Excellent intrarater reliability (intraclass correlation coefficient [ICC] 0.93) has been reported in knee OA patients (11).

Proprioceptive accuracy. Proprioceptive accuracy (motion sense) was assessed using a knee joint motion detection task (with motion at 0.3°/second in the extension direction). The mean of 3 measurements was calculated for each knee (10). Intra- and interrater reliability (ICC) in knee OA patients is 0.88 and 0.91, respectively (12).

Varus-valgus laxity. Laxity was operationalized as the total amount of passive movement in the frontal plane after fixed varus and valgus load of 7.7 Nm. The mean of 3 measurements was calculated for each knee (10). Intra- and interrater reliability (ICC) in healthy persons is 0.80 and 0.88, respectively (13).

Patient-reported instability. The number of episodes of buckling, shifting, or giving way of the knee in the past 6 weeks was assessed on an ordinal scale (i.e., 'none', 'seldom' [1-2 episodes], 'regularly' [3-5], and 'very often' [>5]), as part of a questionnaire (10) based on literature (1;3). This scale was dichotomized as follows: none/seldom vs. regularly/very often.

Other measures. In addition, multiple other variables were measured at baseline, including demographics (e.g., sex, age, body mass index [BMI]), radiographic knee OA severity [Kellgren/Lawrence grade], knee joint alignment as measured by goniometer in standing position) (5).

Statistical analysis

Data were analyzed using PASW Statistics 18.0 (SPSS Inc, Chicago, IL). Generalized Estimating Equation (GEE) analyses, based on intention-to-treat (ITT) approach, were performed to compare the effectiveness of experimental with control intervention over the 38-week study period (14). Effect modification by each of the subgroup factors was estimated by including

treatment group (0=control; 1=experimental), the subgroup factor, and an interaction term of 'treatment group*subgroup factor' into the GEE model, where a significant interaction term indicates effect modification (15). Outcome measures were WOMAC physical function (primary), NRS pain, and the GUG-test (secondary). We adjusted for the outcome measure at baseline, relevant baseline characteristics that were different between treatment groups (i.e., proprioceptive accuracy, instability affecting daily functioning (yes/no), and varus malalignment [yes/no] (5)), as well as for demographics (i.e., age, gender, BMI, and radiographic knee OA severity). Unstandardized regression coefficients (B) with adjunctive 95% confidence intervals (CI) and *P* values were estimated. Statistical significance was accepted at $P < 0.05$.

Results

Descriptives of the study sample (*n*=159) are shown in Table 1. During the study period, 5 participants (1 from experimental and 4 from control group) were lost to follow-up before the first follow-up measurement and could therefore not be analyzed. In addition, 2 participants discontinued the intervention (both from experimental group) and 4 underwent knee surgery after treatment (2 from each group). Participants attended on average 21 out of 24 sessions and performed home exercises for on average 4 days a week, similarly in the 2 treatment groups. As reported previously (5), no overall difference in effectiveness between experimental and control intervention could be demonstrated.

Table 1. Baseline characteristics of experimental and control group

	Experimental group (*n*=80)		**Control group (*n*=79)**	
	mean ± SD	***n* (%)**	**mean ± SD**	***n* (%)**
Demographics:				
Age (years)	62.1 ± 7.6		61.8 ± 6.6	
Gender (female)		53 (66)		44 (56)
BMI (kg/m^2)	28.8 ± 4.8		28.3 ± 4.5	
Radiographic severity of knee (K/L grade≥2)*		59 (61)		54 (68)
Outcome measures:				
WOMAC (physical function, 0-68)	25.2 ± 11.8		27.1 ± 12.7	
NRS (knee pain severity, 0-10)	4.8 ± 2.2		5.2 ± 2.0	
Get Up and Go test (seconds)	10.6 ± 1.8		10.8 ± 2.5	
Subgroup factors:				
Upper leg muscle strength (Nm/kg)*	0.83 ± 0.35		0.85 ± 0.43	
Proprioceptive accuracy of knee (degrees)*	2.7 ± 2.2		3.7 ± 2.6	
Varus-valgus laxity of knee (degrees)*	7.0 ± 3.1		7.1 ± 4.5	
Patient-reported knee instability in past 6 weeks (yes)		24 (30)		24 (30)

SD=Standard Deviation; BMI=Body Mass Index; K/L=Kellgren/ Lawrence; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index; NRS=Numeric Rating Scale; * data from index knee.

For the primary outcome WOMAC physical function, a significant interaction term of 'treatment group*upper leg muscle strength' (*P*=0.01) was found (Table 2). This indicates that in persons with higher muscle strength at baseline, the experimental intervention may be more effective than the control intervention (illustrated by Figure 1a, right handed side), while the control intervention may be more effective in persons with lower muscle strength (illustrated by Figure 1a, left handed side).

For the secondary outcome measures only, we found significant interactions with laxity (*P*<0.001 for pain) and patient-reported knee instability (*P*=0.05 for pain and 0.04 for the GUG-test). These interactions suggest that the experimental intervention may be more effective than the control intervention in those persons with lower laxity (as illustrated by Figure 1b, right handed side) or more frequent knee instability (as illustrated by Figure 1c, left handed side). Per-protocol analyses excluding protocol violators yielded similar results. Furthermore, similar results were yielded in analyses of data from the 12-week treatment period only.

Table 2. Interaction terms of treatment (experimental vs. control) x subgroup factor in association with outcome measure (*n*=154)

	Primary outcome		**Secondary outcomes**			
	WOMAC, physical function*		**NRS, pain***		**GUG-test***	
	B (95% CI)	***P***	**B (95% CI)**	***P***	**B (95% CI)**	***P***
Interaction with baseline value of:						
Upper leg muscle strength	-7.07 (-12.39, -1.75)	0.01	-0.67 (-1.82, 0.49)	0.26	-0.04 (-0.70, 0.62)	0.90
Knee joint proprioception	-0.25 (-1.35, 0.86)	0.66	-0.03 (-0.23, 0.16)	0.74	-0.08 (-0.21, 0.06)	0.25
Varus-valgus knee joint laxity	0.66 (-0.09, 1.40)	0.09	0.18 (0.07, 0.29)	<0.001	0.00 (-0.08, 0.08)	0.97
Patient-reported knee instability	0.73 (-5.76, 7.22)	0.83	-0.95 (-1.92, 0.01)	0.05	-0.58 (-1.13, -0.02)	0.04

ITT = intention-to-treat; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; NRS = Numeric Rating Scale; GUG = Get up and Go; * adjusted for relevant baseline characteristics that were different between groups (i.e., proprioceptive accuracy, instability affecting daily functioning, and varus malalignment) in addition to demographics (i.e., age, gender, body mass index, radiographic severity of knee OA) and baseline score of outcome measure.

Discussion

Main finding of this study is that initial knee stabilization training may have added value over standard exercises (i.e., strength/functional training) in patients with strong muscles, while not in patients with weak muscles. This was based on a significant interaction between treatment group and baseline upper leg muscle strength for the primary outcome WOMAC physical function. Stratified analyses showed that in the 'high muscle strength subgroup', the experimental program was on average 2.0 points more effective, whereas in the 'low muscle strength subgroup', the control program was on average 2.8 points more effective. This total difference of 4.8 points, which is 18% of the average baseline WOMAC score, can be considered a clinically important difference (16). Therefore, adequately allocating patients over the exercise groups based on baseline muscle strength could optimize treatment outcome. Although this main finding was in contrast to our hypothesis, it does confirm our explanation for the negative finding from our trial (5), as well as from others (17;18). We proposed that muscle strengthening exercises are highly effective for the majority of knee OA patients with knee instability, without necessarily adding specific knee stabilization training. The present subgroup-analysis further indicates that in patients with knee instability, and especially those with weak muscles, exercises should focus on muscle strengthening, whereas in patients with knee instability and (already) strong muscles, initial knee stabilization training can be additionally beneficial. This may imply that for optimal treatment effects, strength training needs to be provided first, prior to knee stabilization training.

Secondly, knee stabilization training may also have added value over strength/ functional training in patients with knee instability but having adequate passive restraint (i.e., minimal laxity). This was based on a significant interaction between treatment group and laxity for pain. Possibly, in patients with high laxity, interventions like knee bracing (19) to support the passive restraint system may need to be added to enable patients with high laxity to benefit from knee stabilization training.

Finally, we found significant interactions between treatment group and patient-reported knee instability for pain and the GUG-test. This result confirmed our hypothesis that initial knee stabilization training has added value over strength/functional training in patients reporting episodes of knee instability more frequently. This effect seems to apply mainly to the first half of the exercise program (as shown by Figure 1c, left handed side), which is exactly the period in which the experimental group received knee stabilization training most extensively. For patients reporting knee instability only occasionally, standard exercises seem to be sufficient.

We need to emphasize that our findings should be interpreted cautiously, as our study was not powered to perform subgroup-analyses. On the other hand, the subgroup-analyses were pre-planned and executed by using the interaction term-method, which

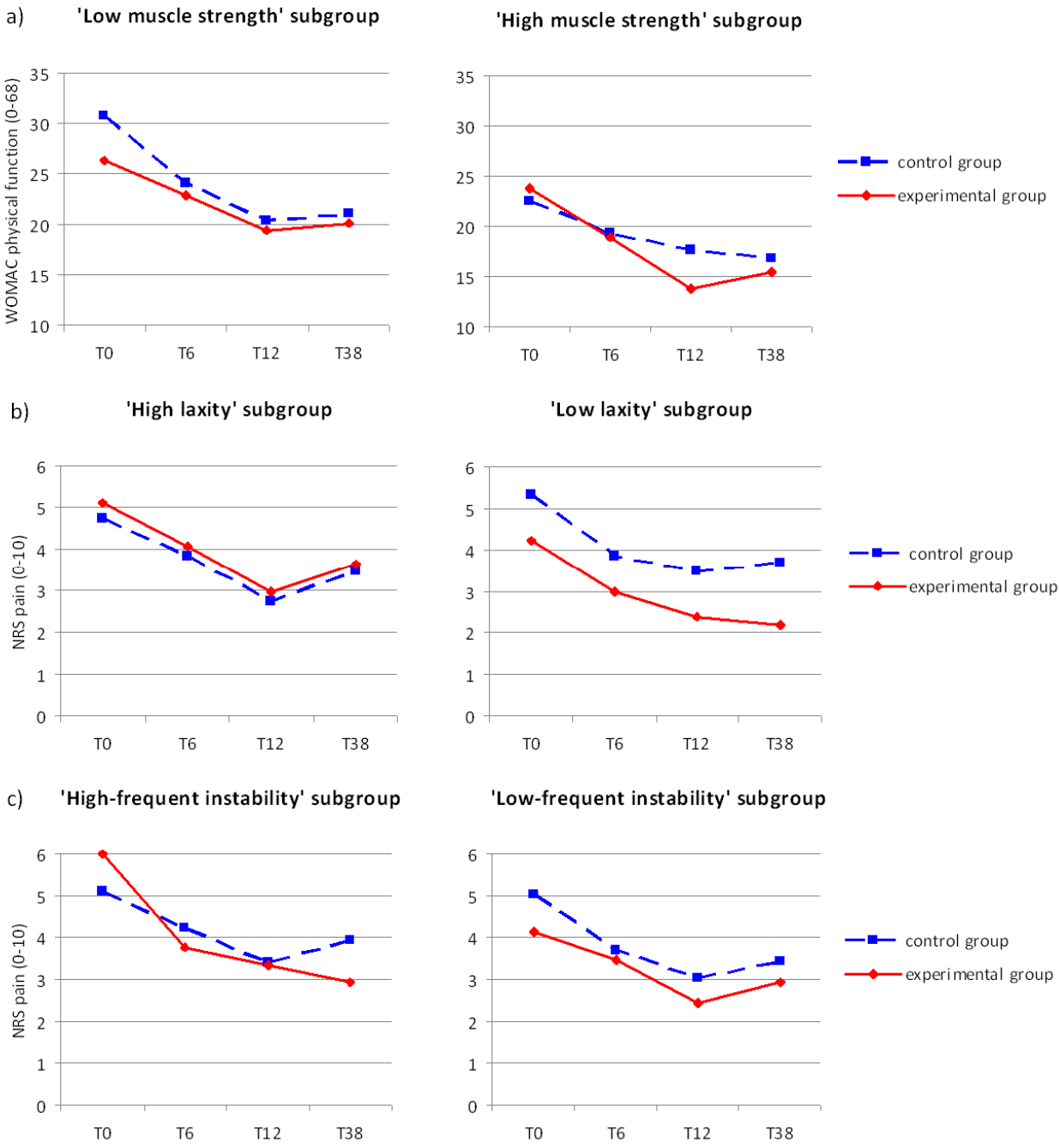

Fig. 1. Outcomes of control and experimental group during study period, stratified for subgroups which were based on baseline value of (a) upper leg muscle strength, (b) knee joint laxity, and (c) number of patient-reported episodes of knee instability, with higher scores meaning more severe activity limitations/pain. Subgroups were formed using gender-specific medians for upper leg muscle strength and knee joint laxity, or a cut-off of 3 episodes for knee instability.

carries a much smaller risk of false-positive results compared to stratified analyses (15). Furthermore, we used only a minimal number of subgroup factors, as recommended (15).

To conclude, initial knee stabilization therapy may have added value in patients with knee instability and strong muscles. This may imply that exercises should target muscle strength prior to knee stabilization. In addition, knee stabilization therapy could also have added value in patients with knee instability and minimal laxity, or reporting episodes of knee instability more frequently.

Acknowledgements

We gratefully acknowledge dr. Gerritsen and dr. Voorneman for examining patients, S. Romviel for assessing patients, and physical therapists for supervising treatment groups. The study was funded by the Dutch Arthritis Foundation, which had no role in project implementation, analysis, interpretation, or manuscript writing.

References

(1) Fitzgerald GK, Piva SR, Irrgang JJ. Reports of joint instability in knee osteoarthritis: its prevalence and relationship to physical function. Arthritis Rheum 2004;51(6):941-946.

(2) van der Esch M, Knoop J, van der LM, 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):1505-1510.

(3) 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(8):534-540.

(4) Schipplein OD, Andriacchi TP. Interaction between active and passive knee stabilizers during level walking. J Orthop Res 1991;9(1):113-119.

(5) 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.

(6) Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15(12):1833-1840.

(7) Roorda LD, Jones CA, Waltz M, Lankhorst GJ, Bouter LM, van der Eijken JW et al. Satisfactory cross cultural equivalence of the Dutch WOMAC in patients with hip osteoarthritis waiting for arthroplasty. Ann Rheum Dis 2004;63(1):36-42.

(8) Turk DC, Melzack R. Handbook of pain assessment. 2nd ed. New York: Guilford Press, 2001.

(9) Piva SR, Fitzgerald GK, Irrgang JJ, Bouzubar F, Starz TW. Get up and go test in patients with knee osteoarthritis. Arch Phys Med Rehabil 2004;85(2):284-289.

(10) Knoop J, van der Leeden M, van der Esch M, Thorstensson CA, Gerritsen M, Voorneman RE 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.

(11) Kean CO, Birmingham TB, Garland SJ, Bryant DM, Giffin JR. Minimal detectable change in quadriceps strength and voluntary muscle activation in patients with knee osteoarthritis. Arch Phys Med Rehabil 2010;91(9):1447-1451.

(12) 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):1398-1403.

(13) van der Esch M, Steultjens M, Ostelo RW, Harlaar J, Dekker J. Reproducibility of instrumented knee joint laxity measurement in healthy subjects. Rheumatology (Oxford) 2006;45(5):595-599.

(14) Twisk JWR. Applied longitudinal data analysis for epidemiology; a practical guide. 1st ed. Cambridge, UK: Cambridge University Press, 2003.

(15) Bierma-Zeinstra SM, Verhagen AP. Osteoarthritis subpopulations and implications for clinical trial design. Arthritis Res Ther 2011;13(2):213.

(16) Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities. Arthritis Rheum 2001;45(4):384-391.

(17) Fitzgerald GK, Piva SR, Gil AB, Wisniewski SR, Oddis CV, Irrgang JJ. Agility and perturbation training techniques in exercise therapy for reducing pain and improving function in people with knee osteoarthritis: a randomized clinical trial. Phys Ther 2011;91(4):452-469.

(18) Diracoglu D, Aydin R, Baskent A, Celik A. Effects of kinesthesia and balance exercises in knee osteoarthritis. J Clin Rheumatol 2005;11(6):303-310.

(19) Ramsey DK, Briem K, Axe MJ, Snyder-Mackler L. A mechanical theory for the effectiveness of bracing for medial compartment osteoarthritis of the knee. J Bone Joint Surg Am 2007;89(11):2398-2407.