Chapter 10

Is the severity of knee osteoarthritis on magnetic resonance imaging associated with outcome of exercise therapy?

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Abstract

Objective. To evaluate associations between severity of knee osteoarthritis (OA) on magnetic resonance imaging (MRI) and treatment outcome in knee OA patients treated with exercise therapy in an explorative study.

Method. Ninety-five participants with knee OA in a 12-week exercise program had obtained 3.0T MRI scans of the knee joint, prior to treatment. MRI data were systematically assessed for OA severity of multiple features (cartilage integrity, bone marrow lesions, osteophyte formation, effusion/synovitis, and meniscal abnormalities) according to the Boston-Leeds Osteoarthritis Knee Score (BLOKS) method. Regression analyses were performed to analyze associations between OA severity on MRI (for the tibiofemoral [TF] and patellafemoral [PF] compartment) and outcome of exercise therapy, i.e., changes in activity limitations (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] physical function; primary outcome), pain and upper leg muscle strength, and treatment response (Outcome Measures in Rheumatology/Osteoarthritis Research Society International [OMERACT/OARSI] criteria).

Results. Improvements of 24%, 34% and 21% on average in activity limitations, pain and muscle strength, respectively, after 12-week exercise therapy were found (P<0.001). Severity of abnormalities in PF cartilage integrity was significantly associated with fewer improvements in both activity limitations (P=0.01) and muscle strength (P=0.04). Severity of PF osteophyte formation was significantly associated with fewer improvements in muscle strength (P<0.01). All other features on MRI were not associated with treatment outcome.

Conclusion. Effectiveness of exercise therapy seems to be independent of OA severity on MRI, except for abnormalities in cartilage integrity and osteophyte formation, both in the PF compartment. Our study suggests that all grades of OA severity on MRI can benefit from professionally supervised exercise therapy, although effects might be reduced in patients with advanced PF OA.

Introduction

Exercise therapy is considered an effective treatment in patients with knee osteoarthritis (OA) for reducing pain and activity limitations (1,2). However, these effects are only small to moderate and vary widely among patients (2). Treatment effects might be optimized through identifying subgroups of patients that may not benefit optimally from exercise therapy, for instance patients with severe knee joint damage, in which exercise therapy has been suggested to be too painful or even potentially harmful (1;3;4).

Recently, we conducted a randomized, controlled trial (5) on the effectiveness of a newly developed, supervised exercise program in 159 knee OA patients (ranging from mild to severe radiographic OA), in which large and clinically relevant improvements in pain and activity limitations, and treatment response in 71% of participants were found. In a random subsample (*n*=95), we additionally obtained baseline magnetic resonance imaging (MRI) scans, enabling us to determine whether effectiveness of exercise therapy depends on OA severity on MRI. Therefore, the aim of this exploratory study was to evaluate associations between severity of knee OA on MRI and treatment outcome in knee OA patients treated with exercise therapy.

Patients and methods

Design

We previously conducted a single-blind, randomized, controlled trial (STABILITY-trial; Dutch Trial Registry NTR1475) (5) in 159 knee OA patients suffering from knee instability, in an outpatient rehabilitation center (Reade, Amsterdam, The Netherlands). In this trial, 2 exercise programs were compared to evaluate effectiveness of specific knee joint stabilization training. A research assistant who performed measurements was blinded for group allocation. For the present study, we additionally obtained MRI scans at baseline (i.e., prior to exercise therapy) in 95 consecutive participants. This study was approved by the Medical Ethical Review Board (Reade/Slotervaart Hospital).

Participants

Inclusion criteria for the STABILITY-trial were (i) diagnosis of knee OA according to the clinical ACR criteria (6), (ii) age between 40 and 75 years, and (iii) presence of self-reported knee instability (i.e., occurrence of episode of knee instability in past 3 months, as reported by the patient (5)) and/or biomechanically assessed knee instability (using cut-off points for upper leg muscle weakness, proprioceptive accuracy, and varus-valgus laxity of the knee joint (5)). Exclusion criteria for the trial are described in our previous publication (5); for the present study, contra-indications for MRI (e.g., pacemaker, claustrophobia) were added. All participants provided written informed consent.

Intervention

Both the experimental and control intervention comprised a 12-week exercise program with sessions of 60 minutes twice weekly in groups of approximately 8 participants, supervised by 2 physical therapists, specifically trained to supervise only one of both treatments, and a home-exercise program.

A detailed description of the exercise protocol is included in our previous publication (5). In summary, the experimental program focused on knee joint stabilization, muscle strengthening, and performance of daily activities, while the control program focused only on muscle strengthening and performance of daily activities. Training intensity and amount of attention from the physical therapists were similar in both groups.

Measurements

Detailed information on measurements is included in our previous publication (5). For the present study, we used measurements from baseline and 12-week follow-up (FU).

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, consisting of 17 items, with a total score ranging from 0-68, where 0=no limitations and 68=maximally limited.

Secondary outcomes. Knee pain severity was assessed on a NRS (range 0-10, where 0=no pain and 10=worst imaginable pain) by the question ‘What was your average knee pain during the last week?’. Upper leg muscle strength was assessed for knee flexion and extension using an isokinetic dynamometer (EnKnee, Enraf-Nonius) in Nm divided by bodyweight. The Outcome Measures in Rheumatology/Osteoarthritis Research Society International (OMERACT/OARSI) set of responder criteria was used as a dichotomous measure for treatment response, operationalized as follows: (i) improvement of ≥50% and absolute change of ≥20 points in pain (NRS) or function (WOMAC), or (ii) at least 2 of the 3 following items: (a) improvement of ≥20% and absolute change of ≥10 points in pain, (b) improvement of ≥20% and absolute change of ≥10 points in function, (c) improvement of ≥20% and absolute change of ≥10% in patient’s global assessment (PGA) (6). For these criteria, NRS pain and WOMAC physical function were rescaled into a 100-point scale. A global perceived effect score ≥5 (i.e., ‘symptoms slightly improved’ or better) (5) was regarded as an improvement in PGA.

MRI. Detailed information on MRI assessment in included in our previous publication (8). In summary, 3.0T MRI scans (General Electric Medical Systems, 5 sequences) of the most affected knee (index knee) were obtained at baseline (i.e., 1-3 weeks prior to start of intervention). MRIs were assessed for cartilage integrity, bone marrow lesions (BMLs), osteophyte formation, effusion, synovitis and meniscal abnormalities, according to the Boston-Leeds Osteoarthritis Knee Score (BLOKS) system (9) by a radiologist (JPK) with 27 years of musculoskeletal expertise, blinded for patient's clinical characteristics and radiographic assessment.

Potential baseline confounders. Potential baseline confounders that were included are sex, age and duration of knee symptoms (in years), use of pain medication, presence of obesity (i.e., body mass index [BMI] ≥30 kg/m^2), presence of knee malalignment (i.e., varus/valgus malalignment ≥10^o, measured by a goniometer), upper leg muscle strength (mean of knee extension and flexion isokinetic strength, in Nm divided by bodyweight), proprioceptive accuracy and varus-valgus knee joint laxity (in degrees), and presence of symptoms of anxiety and/or depression (measured by Hospital Anxiety Depression Scale [HADS]) (5).

Statistical analyses

Because both interventions were found to be similarly effective (5), data from both exercise groups were combined in the present study. Descriptive statistics (mean ± SD or percentages) for baseline patient characteristics and outcome measures (i.e., change between baseline and 12-week FU on WOMAC physical function, NRS pain, and upper leg muscle strength, where positive scores indicate improvement) were calculated. For severity of MRI features, region-specific grades (range 0-3) were combined in tibiofemoral (TF) and patellofemoral (PF) compartmental grades (for cartilage integrity, BMLs and osteophyte formation) or in knee-specific grades (for meniscal abnormalities), using the highest regional grade approach. Subsequently, grades were dichotomized as grade 0/1 (none-to-mild) versus grade 2/3 (moderate-to-severe). Effusion grade (range 0-3) and synovitis (presence/absence) were combined in a single feature for inflammation and dichotomized as effusion grade 0/1 in the absence of synovitis versus effusion grade 2/3 and/or presence of synovitis.

Linear and logistic regression analyses were performed with change scores on primary outcome WOMAC physical function, NRS pain, and upper leg muscle strength (all adjusted for baseline score) or with treatment response (yes/no) as dependent variables. Independent variables were each of the (dichotomized) MRI features. Crude models and adjusted models, in which relevant baseline confounders were added, were estimated. Standardized (β) and unstandardized (B) regression coefficients and odds ratios (OR), for linear and logistic regression analyses, respectively, with adjunctive 95% confidence intervals (95% CIs) and *P* values were estimated. Statistical significance was accepted at *P* values less than 0.05. Data analyses were performed using PASW Statistics 18.0 (SPSS Inc, Chicago, IL).

Results

From 112 consecutive, potential participants of the STABILITY-trial from January 2010, baseline MRIs could be obtained in 105 persons, of which 10 could not be included in the trial (reasons include not fulfilling inclusion criteria [*n*=6]) and withdrawal [*n*=4]), while 7 participants could not be planned for MRI prior to treatment. Therefore, 95 patient were included. Because 4 persons dropped out during the intervention (reasons: lack of time [*n*=1], health conditions unrelated to OA or to intervention [*n*=3]), regression analyses could be performed in 91 participants.

As shown in Table 1, baseline characteristics of the total trial sample (*n*=159) and the present subsample (*n*=95) are comparable. Our sample represents a severe knee OA group on average, with highest grade of severity on MRI found in 54%, 31%, and 58% of the participants for cartilage integrity, BMLs, and meniscal abnormalities, respectively. Participants followed a mean ± SD of 20.8 ± 4.1 of 24 treatment sessions. Improvements of 24%, 34% and 21% were found in activity limitations (WOMAC physical function), pain (NRS) and upper leg muscle strength, respectively, after 12-week exercise therapy ($P<0.001$ for all), with two-thirds (67%) of participants fulfilling OMERACT/OARSI criteria for treatment response.

Results from the regression analyses of OA severity on MRI and outcome of exercise therapy (*n*=91) are shown in Table 2. Severity of abnormalities in cartilage integrity in the PF compartment (i.e., grade 2 and 3) was significantly associated with fewer improvements in both the primary outcome WOMAC physical function and upper leg muscle strength (adjusted B= -5.0 (95% CI -8.8, 1.2) and -0.08 (95% CI -0.16, -0.01), respectively). Severity of PF osteophyte formation (i.e., grade 2 and 3) was significantly associated with fewer improvements in upper leg muscle strength (adjusted B= -0.12 (95% CI -0.20, -0.04)). No associations were found for OA severity of any other MRI features in crude or adjusted models.

Table 1. Patient characteristics of total study sample and subsample from the present study*

	Total sample (*n*=159)	Subsample (*n*=95)		
Baseline demographics:				
Female sex	97 (61)	64 (67)		
Age, mean ± SD years	61.9 ± 7.1	61.5 ± 7.0		
Duration of knee symptoms, mean ± SD years	10.6 ± 9.3	11.2 ± 9.5		
BMI, mean ± SD kg/m^2	29.0 ± 4.6	29.2 ± 4.8		
Radiographic severity				
K/L grade 0/1	56 (36)	27 (28)		
K/L grade 2	44 (28)	26 (27)		
K/L grade 3	41 (26)	27 (28)		
K/L grade 4	18 (11)	15 (16)		
WOMAC physical function (range 0-68), mean ± SD	26.2 ± 12.2	27.2 ± 12.3		
NRS pain (0-10), mean ± SD	5.0 ± 2.1	5.1 ± 2.1		
Upper leg muscle strength, mean ± SD Nm/kg	0.84 ± 0.39	0.75 ± 0.36		
Baseline MRI feature:		**knee†**	**TF†**	**PF†**
Cartilage integrity‡				
Grade 0	n/a	7 (7)	12 (13)	31 (33)
Grade 1		8 (8)	12 (13)	33 (35)
Grade 2		29 (31)	28 (30)	18 (19)
Grade 3		51 (54)	43 (45)	13 (14)
BMLs§				
Grade 0	n/a	16 (17)	28 (30)	66 (70)
Grade 1		24 (25)	21 (22)	17 (18)
Grade 2		26 (27)	20 (21)	9 (10)
Grade 3		29 (31)	26 (27)	3 (3)
Osteophyte formation¶				
Grade 0	n/a	14 (15)	18 (19)	18 (19)
Grade 1		36 (38)	36 (38)	44 (46)
Grade 2		31 (33)	31 (33)	27 (28)
Grade 3		14 (15)	10 (11)	6 (6)
Effusion#				
Grade 0	n/a	32 (34)	n/a	n/a
Grade 1		29 (30)		
Grade 2		22 (23)		
Grade 3		12 (13)		
Synovitis				
Absent	n/a	63 (66)	n/a	n/a
Present		32 (34)		
Meniscal abnormalities†				
Grade 0	n/a	7 (7)	n/a	n/a
Grade 1		12 (13)		
Grade 2		21 (22)		
Grade 3		55 (58)		

Table 1. (*Cont'd*)

	Total sample (*n*=159)	Subsample (*n*=95)
Outcome of exercise therapy:		
WOMAC physical function (range 0-68)		
ΔT0-T12, mean ± SD††	7.6 ± 10.2	6.4 ± 9.5
T0-T12, % change††	29	24
NRS pain (range 0-10)		
ΔT0-T12, mean ± SD††	1.9 ± 2.1	1.7 ± 2.2
T0-T12, % change††	39	34
Upper leg muscle strength (Nm/kg)		
ΔT0-T12, mean ± SD††	0.16 ± 0.21	0.16 ± 0.19
T0-T12, % change††	19	21
Treatment response, n (%)‡‡	113 (71)	64 (67)

SD=standard deviation; TF=tibiofemoral; PF=patellofemoral; BMI=body mass index; K/L=Kellgren/Lawrence; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index; NRS=numeric rating scale; MRI=magnetic resonance imaging; BML=bone marrow lesion; T0=baseline; T12=12-week follow-up; n/a=not applicable; * values are the number (percentages) unless otherwise stated; † highest regional grade per knee or per compartment; ‡ 0=none, 1= <10% of surface area, 2=10-75% of surface area, 3= >75% of surface area; § 0=none, 1= <10% of bone volume, 2=10-25% of bone volume, 3= >25% of bone volume; ¶ 0=none, 1=mild, 2=moderate, 3= severe; # 0=physiological amount (in supra-patellar bursa only), 1=small (fluid continuous in retropatellar space), 2=medium (with slight convexity of suprapatellar bursa), 3=large (evidence of capsular distention); ** 0=none, 1=signal only, 2=tear (horizontal, vertical or complex), 3=maceration; †† a positive score indicates improvement; ‡‡ according to the OMERACT/OARSI set of responder criteria (7).

Table 2. Results of regression analyses of outcome of exercise therapy and severity of knee OA on multiple MRI features (*n*=91) (significant associations [*P*<0.05] in bold)

	Change in WOMAC physical function (range 0-68), β (*P*)*	Change in NRS pain (range 0-10), β (*P*)*	Change in upper leg muscle strength (Nm/kg), β (*P*)*	Treatment response, OR (*P*)†
MRI feature:				
Cartilage integrity‡				
TF	-0.01 (0.92)	0.04 (0.69)	-0.03 (0.77)	2.0 (0.16)
PF	**-0.25 (0.01)**	-0.13 (0.16)	**-0.21 (0.04)**	0.5 (0.11)
BMLs‡				
TF	-0.10 (0.28)	-0.02 (0.86)	0.07 (0.50)	1.1 (0.81)
PF	-0.08 (0.45)	-0.11 (0.24)	-0.12 (0.24)	1.1 (0.89)
Osteophyte formation‡				
TF	0.02 (0.88)	-0.03 (0.75)	-0.11 (0.27)	1.2 (0.70)
PF	0.02 (0.83)	-0.08 (0.43)	**-0.30 (0.002)**	0.9 (0.92)
Inflammation§	-0.07 (0.45)	-0.10 (0.28)	0.01 (0.94)	0.6 (0.27)
Meniscal abnormalities‡	0.06 (0.51)	0.13 (0.16)	0.06 (0.54)	1.5 (0.50)

Negative β indicating less improvement, positive β indicating more improvement (compared to reference group). OR < 1 indicating lower odds for treatment response, OR > 1 indicating higher odds for treatment response (compared to reference group). MRI=magnetic resonance imaging; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index; NRS=numeric rating scale; OR=odds ratio; BML=bone marrow lesion; TF=tibiofemoral; PF patellofemoral; β=standardized b-coefficient; * adjusted for baseline value of outcome measure and relevant confounding (i.e., >10% change in B-coefficient of independent variable after addition of potential confounder, i.e., age, sex, duration of knee symptoms, use of pain medication, obesity, malalignment, upper leg muscle strength, proprioceptive accuracy, varus-valgus laxity and symptoms of anxiety/depression); † adjusted for relevant confounding (i.e., >10% change in B-coefficient of independent variable after addition of potential confounder i.e., age, sex, duration of knee symptoms, use of pain medication, obesity, malalignment, upper leg muscle strength, proprioceptive accuracy, varus-valgus laxity and symptoms of anxiety/ depression); ‡ grade 2/3 versus 0/1; § effusion grade 2/3 and/or presence of synovitis versus effusion grade 0/1 and absence of synovitis.

Discussion

This exploratory study is the first to evaluate the role of OA severity on MRI in effectiveness of exercise therapy in patients with knee OA. We demonstrated that outcome of exercise therapy was not affected by severity of OA on MRI in any feature (including BMLs and inflammation), except for abnormalities in cartilage integrity and osteophyte formation, both in the PF compartment. This suggests that all grades of OA severity on MRI can benefit from exercise therapy, although effects might be reduced in patients with advanced PF OA.

Severity of abnormalities in PF cartilage integrity (i.e., moderate-to-severe loss of cartilage thickness) was significantly associated with poor outcome of exercise therapy, i.e., fewer improvements in WOMAC physical function (P=0.01) and upper leg muscle strength (P=0.04). Furthermore, a trend towards less improvement in NRS pain (P=0.16) and lower odds for treatment response (P=0.11) was found as well (Table 2). Moderate to severe PF osteophyte formation was significantly associated with fewer improvements in upper leg muscle strength (P<0.01). These findings are in line with a recent study (10) in which PF pain predicted nonresponse to exercise therapy plus manual physiotherapy. As shown in Figure 1, patients with the highest grade of severity for abnormalities in PF cartilage integrity specifically do not seem to benefit optimally from exercise therapy. This trend was similar for PF osteophyte formation. Possibly, exercising is too painful for the subtype of patients with advanced PF OA. These patents may not be able to perform exercises at a level that can be expected to be effective, concordant with our clinical experience. As stated by Bennell et al (11), patients with PF joint symptoms may need to exercise '*in positions that minimize PF contact forces and knee loading (for example, in lesser degrees of knee flexion and in non-weightbearing positions)*'. Through these adaptations, as well as by cointerventions aimed to reduce PF pain (e.g., PF taping), effectiveness of exercise therapy might be optimized in this specific subgroup.

Except for PF defects in cartilage integrity and osteophyte formation, effectiveness of exercise therapy was found to be independent of OA severity of any other feature in each compartment on MRI. This indicates that referral to exercise therapy, supervised by professionally trained physical therapists, can be considered in patients from all grades of OA severity on MRI. This result is in line with a recent study (12) in which exercise therapy showed to be feasible and safe in patients with end-stage knee or hip OA waiting for total joint replacement. Our study also supports an expert opinion-based recommendation (13), proposing that exercise effects do not depend on (radiographic) OA severity, with evidence. On the other hand, our findings contrast existing beliefs from some physicians and patients that exercise may be too painful and possibly harmful, especially for severe knee OA patients (1;3;4). A longitudinal study using MRIs before and after exercise therapy may unravel the controversy on the impact of exercise therapy on knee joint structures, which may be protective (through improved shock absorption (14), improved cartilage quality (15), and

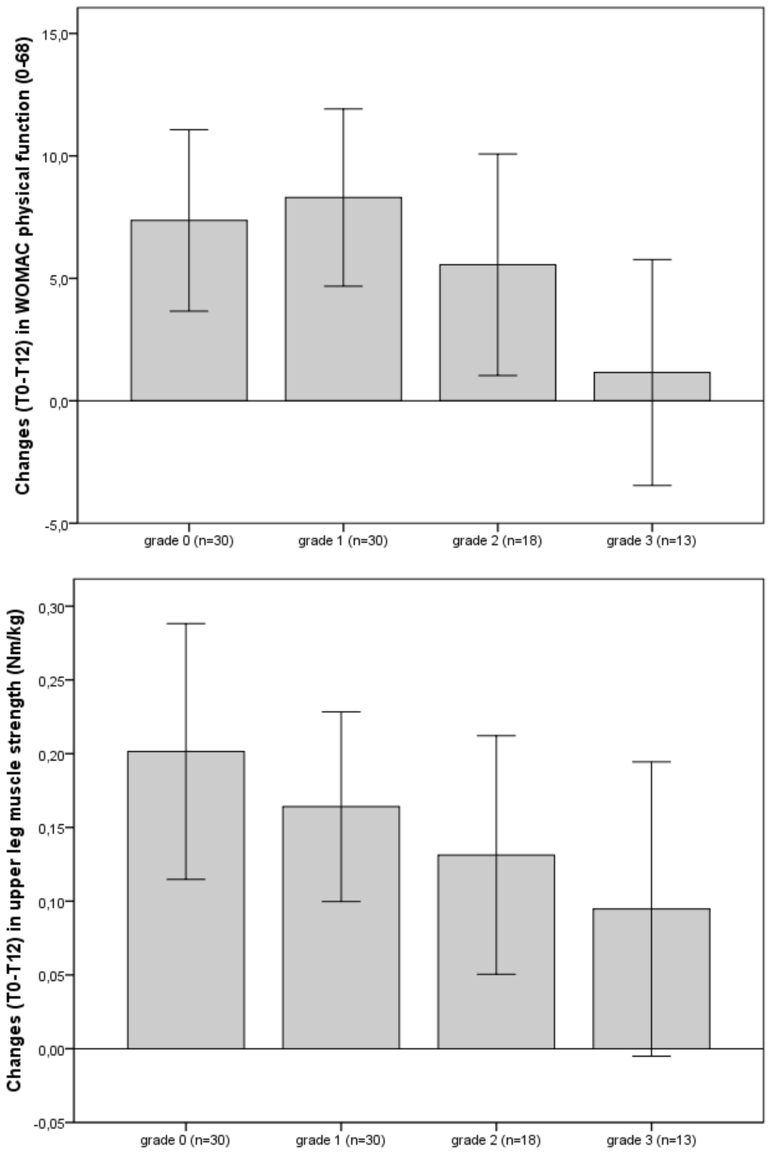

Fig. 1. Outcome of exercise therapy (changes between baseline [T0] and 12-week FU [T12], where a positive score indicates improvement and a negative score indicates worsening) on WOMAC subscale physical function (upper figure) and upper leg muscle strength (lower figure) for each grade of severity of abnormalities in cartilage integrity in the PF compartment (*n*=91). Bars show the mean scores and lines show the 95% confidence intervals.

reduced inflammation (16)) or destructive (through persistent overloading (4)).

Major strengths of this study are the use of 3.0T MRIs, which were systematically assessed according to the BLOKS scoring system (9), a low drop-out rate (4%), and high patient adherence. Study limitations include the absence of a ‘no exercise’ control group, the large number of analyzed associations (*n*=32) and the lack of contrast used for assessing effusion/synovitis.

To conclude, effectiveness of exercise therapy seems to be independent of OA severity on MRI, except for severity of abnormalities in cartilage integrity and osteophyte formation, both in the PF compartment. Our study suggests that all grades of OA severity on MRI can benefit from exercise therapy, which was shown to be highly effective, although effects might be reduced in patients with advanced PF OA.

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