Positive effects of moderate exercise on glycosaminoglycan content in knee cartilage: a four-month, randomized, controlled trial in patients at risk of osteoarthritis.

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Positive Effects of Moderate Exercise on Knee Cartilage Glycosaminoglycan Content

A Four-month Randomized Controlled Trial in Patients at Risk of Osteoarthritis

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Abstract

Objective. To evaluate the effects of moderate exercise on knee cartilage glycosaminoglycan content in subjects at high risk of knee osteoarthritis.

Methods. 45 subjects (16 women, mean age 46 years, mean BMI 26.6), treated with partial medial meniscus resection 3-5 years previously were randomized to supervised exercise 3 times weekly for four months or to a control group. Cartilage glycosaminoglycan content, important for cartilage biomechanical properties, was estimated by delayed Gadolinium Enhanced MRI of Cartilage (dGEMRIC) and reported as change in T_1(Gd).

Results. 30/45 patients were examined by dGEMRIC at baseline and follow-up. The exercise group (n=16) showed an improvement in T_1(Gd) compared to the control group (n=14) (15 vs. -15 ms, p=0.036). To study the dose response, change in T_1(Gd) was correlated to self-reported change in physical activity level. A strong correlation was found in the exercise group (n=16, r_S=0.70, 95%CI 0.31-0.89) and when all subjects were pooled (n=30, r_S=0.74, 95%CI 0.52-0.87).

Conclusions. This *in vivo* cartilage monitoring study in exercising patients at risk of osteoarthritis indicates that adult human articular cartilage has a potential to adapt to loading change. Moderate exercise may be a good treatment not only to improve joint symptoms and function, but also to improve the knee cartilage glycosaminoglycan content in patients at risk of osteoarthritis.

Osteoarthritis and other rheumatic conditions comprise the leading cause of disability among adults and the cost of this public health burden is expected to increase as the population ages. Increased intervention efforts, including early diagnosis and appropriate clinical and self-management (e.g., physical activity, education, and maintaining appropriate weight), are needed to reduce the impact of arthritis and chronic joint symptoms (1). Moderate exercise is effective in reducing pain and improving function in knee and hip osteoarthritis (2). However, exercise is underutilized as osteoarthritis treatment and more than 60% of US adults with arthritis do not meet the physical activity recommendations (3, 4). The hallmark of structural changes occurring in the osteoarthritic joint is cartilage loss. Since osteoarthritis is considered a wear and tear disease, one identified barrier to exercise is the belief that exercise will not improve or even be harmful for the joint cartilage (5, 6). In studies in exercising animals developing osteoarthritis, it has been shown that exercise may protect against cartilage degeneration (7-9). The effects of exercise on human cartilage are largely unknown due to the previous inability to interrogate the biochemical properties of cartilage tissue *in vivo*.

Radiography, currently used to define osteoarthritis, identifies only later stages when severe cartilage damage has occurred (10). To study cartilage alterations earlier in the disease process, MRI techniques have been developed (11). Delayed Gadolinium Enhanced MRI of Cartilage (dGEMRIC) estimates cartilage quality by measuring tissue fixed charged density comprised by the glycosaminoglycans (12-14). Glycosaminoglycans are building blocks of the proteoglycans and crucial for the important visco-elastic properties of the cartilage (15).

To test the hypothesis that moderate exercise improves knee cartilage quality in subjects with early joint disease, we designed a randomized trial including middle-aged subjects previously meniscectomized because of a degenerative meniscus tear, a group at high risk of developing

radiographic osteoarthritis (16). We used dGEMRIC to evaluate the effects of a four months exercise intervention on knee cartilage glycosaminoglycan content.

Methods

The ethics committee of the medical faculty of Lund University approved the study, and written informed consent was obtained from all subjects.

Study participants

To recruit subjects with high risk of knee osteoarthritis, middle-aged patients treated with partial medial meniscus resection were identified through the surgical code system at the Department of Orthopedics, Malmö University Hospital, Sweden. Inclusion criteria were: partial medial meniscectomy 3-5 years previously, both genders, current age between 35 and 50 years, willingness to participate in the study, and signed informed consent. Exclusion criteria were: misclassified in the surgical code system (not meniscectomized), known concomitant anterior cruciate ligament injury, cartilage changes defined as deep clefts or visible bone in the arthroscopy report, too high activity level (being a competitive athlete), too low activity level (only walking indoors), self-report of limiting co-morbid condition, not being in the geographic area during all of the study period. In a letter, patients were informed about the study and asked if they would agree to participate. Screening questions were used to ensure compliance with the above given inclusion and exclusion criteria. In a few cases with ambiguous replies an additional telephone interview was conducted. Letters of invitation and screening questionnaires were sent to 166 patients (Figure 1).

Randomization process

Randomization was performed sequentially as letters of acceptance of the invitation were received. Subjects were stratified according to high leisure physical activity level or low leisure physical activity level to assure similar response to exercise in both groups. High level was defined as recreational sports including e.g. golf, hiking, and biking. Low level was defined as yard work, shopping, etc. Since the total number of subjects in each stratum was

unknown when randomization begun, 52 opaque envelopes, organized in blocks, were prepared for each strata. The first 4 blocks for each strata contained 4 envelopes, the additional blocks contained 2 envelopes each. This strategy was chosen to avoid allocation of unequal numbers of subjects of the 2 strata to the treatment and control groups.

Exercise intervention

The objectives of the intervention were to improve neuromuscular control, muscle strength and aerobic capacity. The patients were offered exercise classes on every weekday for four months in a group-fashion led by one of five experienced and especially trained physical therapists. It was expected that each patient should attend three days a week. To tailor the program to each individual, all subjects in the exercise group underwent clinical examination and functional assessment by one physical therapist prior to study start. This physical therapist was also responsible for instructing the five physical therapists leading the exercise groups. The exercise program lasted for one hour. The warming up consisted of ergometer cycling, rope skipping and jogging on a trampoline. Examples of individually progressed weight bearing strengthening exercises are given in Figure 1. Neuromuscular control during the exercises was repeatedly emphasized. Most commonly four to six subjects attended each exercise session allowing the physical therapist to closely monitor each individual. The complete exercise program can be obtained from the first author.

Control group

No intervention was undertaken in the control group. Since changes in physical activity may occur naturally, or be induced by taking part in an exercise study, change in physical activity level during the study period was evaluated also in the control subjects as described below.

End points

The primary end point was change in T_1(Gd) relaxation time between baseline and follow-up as quantified by delayed Gadolinium Enhanced MRI of Cartilage (dGEMRIC) (12, 14, 17-19). dGEMRIC is an *in vivo* assessment method of cartilage glycosaminoglycan content that relies on the principle that the intravenously injected negatively charged contrast agent Gd-DTPA^{2-} distributes inversely to the negatively charged glycosaminoglycans in the cartilage (14, 20). Hence, a high cartilage glycosaminoglycan content yields low contrast agent content, resulting in a long T_1(Gd) relaxation time. In an intervention study, an increase in glycosaminoglycan content will be reflected by an increased T_1(Gd).

MRI was performed by a standard 1.5 T MRI-system (Magnetom Vision; Siemens Medical Systems, Erlangen, Germany) approximately two hours after injection of the contrast agent (Gd-DTPA^{2-}) (17). A dose of 0.3 mmol/kg was used (17, 19). To optimize the distribution of the contrast agent into the cartilage, and to assess aerobic capacity, the subjects underwent a standardized bicycle ergometer test lasting for fifteen minutes starting within 10 minutes of the injection of the contrast agent.

Sets of six sagittal turbo inversion recovery images with different inversion times (TR = 2000 ms, TE = 15 ms, turbo factor 7, FoV 120 x 120 mm^2, matrix=256 x 256, TI=50, 100, 200, 400, 800, 1600 ms, slice thickness = 3 mm) were acquired. In each set of images, a validated technique to draw a region of interest (ROI) in a centrally positioned slice in the weight bearing cartilage of the medial femoral condyle was used (21). The ROI was placed between the center of the tibia plateau and the rear insertion of the meniscus and included the full thickness of the cartilage (17), Figure 2. The assessor was blinded to the subject's group

allocation. Quantitative T_1(Gd) relaxation time calculations were performed using the mean signal intensity from each ROI as input to a three-parameter fit (22).

Clinical outcomes were assessed at baseline and follow-up by the Knee injury and Osteoarthritis Outcomes Score (KOOS, www.koos.nu). Scores are given on a 0-100, worst to best, scale. The KOOS has been validated for short- and long-term follow up of meniscectomized patients (16, 23, 24). The KOOS data was used to determine the correlation of change in T_1(Gd) with change in clinical outcomes. The study was not powered to determine differences between groups over time in clinical outcomes.

At follow-up, all subjects self-reported their change in physical activity level during the study period as increased, unchanged or reduced. The change of the index leg in three muscular performance tests, isokinetic strength of the index leg knee extensors and aerobic capacity were evaluated as objective measures of change in physical activity. The performance tests were one-leg jump (25), square hop (26) and one-leg rising (26, 27). Isokinetic peak torque, adjusted for body weight, during knee extension at 60 degrees/sec was obtained by a Biodex isokinetic testing system. Aerobic capacity was assessed by a bicycle ergometer test according to Astrand et al. (28).

Power calculation and statistics

Based on prior data from a cross-sectional study (18), we estimated 30 patients needed to, with 80% power, detect a difference of 40±40 ms between groups in T_1(Gd) relaxation time. We estimated a drop out rate of 30% and decided to randomize at least 40 subjects. Non-parametric statistics were used, Mann-Whitney U-test when comparing the exercise group to the control group and Spearman's Rho when comparing three ranked groups. A p-value of 0.05 or less was considered significant.

Results

Patients

A chart of the subject flow in the study is shown in Figure 3. Fifty-six patients who met the inclusion and exclusion criteria were randomized. Forty-five of these patients had baseline examinations, 22 in the exercise group and 23 in the control group. Nineteen subjects in the exercise group completed the follow-up questionnaire, and 16 underwent follow-up with dGEMRIC. The corresponding numbers in the control group were 18 and 14, respectively. The exercise and control groups did not differ significantly with regard to patient characteristics such as age, sex, activity level, BMI, and baseline pain, stiffness, functional limitations and awareness of knee problems, Table 1. Eighty-seven percent of the subjects were aware of their knee problems at least monthly, and the majority suffered from pain, stiffness and functional limitations. 11/30 subjects, equally distributed between the groups, fulfilled the clinical ACR criteria for knee OA. One subject in the exercise group reported the use of non-prescription painkillers and one subject in the control group used glucosamine. The subjects lost to follow-up MRI (n=15) did not significantly differ from the subjects that were available for follow-up with MRI (n=30) with regard to any of the baseline characteristics as shown in Table 1.

Exercise group vs. control group

In the exercise group, the 16 subjects with follow-up MRI attended on average 31 (±16), range 0-54, supervised exercise sessions during the trial. In addition, they self-reported, on a weekly basis, on average 22 (±19), range 0-53, exercise sessions such as running, biking or tennis. In total, the intervention group exercised on average three times weekly. At follow-up,

improvements in performance tests were noted in the exercise group compared to the controls, Table 2.

T_1(Gd) values did not differ between groups at baseline. However, at follow-up there was a significant improvement in T_1(Gd) in the exercise group compared to the control group (+15 vs. -15 ms, p=0.036), Table 2.

Dose response analyses

To study the dose response, the change in T_1(Gd) was correlated to self-reported change in physical activity level. In the exercise group, 68% reported an increased activity level and in the control group no one reported an increased activity level, (Figure 3). A strong correlation was found in the exercise group (n=16, r_S=0.70, 95%CI 0.31-0.89) and when all subjects were pooled (n=30, r_S=0.74, 95%CI 0.52-0.87), Figure 4.

To support the validity of self-reported change in physical activity, the mean improvements seen in aerobic capacity and isokinetic peak torque correlated positively with self-report of change in physical activity level (n=30, r_S=0.42, 95%CI 0.07-0.68 and r_S=0.39, 95%CI 0.04-0.66, respectively).

Last, to determine if improvement in cartilage glycosaminoglycan content correlated with improvement in self-report of clinical status, change in T_1(Gd) was correlated with change in KOOS scores. When both groups were analyzed together (n=30), improved cartilage glycosaminoglycan content correlated with improvement in all five KOOS subscales (r_S=0.38-0.52, 95%CI 0.02-0.70).

Discussion

This study shows compositional changes in adult joint cartilage from increased exercise, a result confirming prior animal studies (7, 8) but not previously shown in humans. The changes implies that human cartilage responds to physiological loading in a way similar to muscle and bone, and that previously established positive symptomatic effects of exercise in patients with osteoarthritis may parallel, or even be caused by improved cartilage properties.

The unpredictable and individually different progression rate of osteoarthritis may partly be explained by subject's differences in matrix integrity due to e.g. differences in physical stimulation. Animal and cartilage explant studies have shown increased cartilage glycosaminoglycan metabolism and content, and improved indentation stiffness by increased degree of dynamic joint loading (29-31). dGEMRIC, as an estimate of glycosaminoglycan content and assessment of cartilage quality, has in humans shown that subjects with high level of exercise have a higher T_1(Gd) relaxation time, likely as a means to withstand higher mechanical demands (18). Furthermore, recent dGEMRIC studies have shown a high correlation between glycosaminoglycan distribution and biomechanical properties {Nieminen, 2004 #455;Samosky, 2005 #456}. It is notable that dGEMRIC, presumably more sensitive to disease as it is sensitive to the biochemical changes in the tissue, allows for significance in outcomes to be determined with a smaller number of study participants than is feasible with clinical outcome measures.

A state of pre-stress, due to the balance between the swelling that arises from the proteoglycans and the rigid collagen network, is crucial for the function of the healthy cartilage (34). In the present study, the higher mean change in T_1(Gd) in the intervention group suggests that cartilage responded to exercise by increasing its glycosaminoglycan

content. It may be that increased cartilage glycosaminoglycan content improves the visco-elasticity to protect the collagen network to compressive forces as suggested in canine studies (35). In a cartilage matrix with low glycosaminoglycan content, as in cartilage disease, insufficient visco-elasticity may cause progressive denaturation of collagen molecules, collagen loss and subsequent osteoarthritis (36).

It is possible that the susceptibility of joint cartilage to develop osteoarthritis is related to its quality, specifically to its molecular content of highly fixed charged density glycosaminoglycans (37). In patients with joint disease, dGEMRIC indicates a decreased cartilage glycosaminoglycan content in patients with arthroscopic cartilage fibrillations, ligament injury, meniscus tear, and hip dysplasia (19, 38, 39). Furthermore, proteoglycan analysis of healthy and diseased human cartilage and joint synovial fluids indicate increased proteolytic activity in diseased joints and increased release of proteoglycan fragments that differ from those released in normal joints (40-43).

Limitations of the study

Potential limitations of the study include, but are not limited to, the following: Applicability of the results to other groups at risk of osteoarthritis, the loss to follow up, methodological issues related to dGEMRIC, clinical significance of the results and the short follow-up time.

The current results apply to middle-aged meniscectomized patients. Meniscectomized patients have an increased risk of knee OA (44). In addition, the radiographic and clinical outcome is worse in patients with a degenerative tear where the meniscus injury is suggested to be an early signal of OA (16). In our paper 25/30 patients had such a meniscal tear. The possible association with hand OA in meniscectomized patients suggests that our results may be

applicable also to other groups at risk of OA (45). The primary outcome in this trial was cartilage glycosaminoglycan content measured as T_1(Gd) relaxation time. An objective MRI parameter is not subjected to bias the way a patient-relevant outcome as pain would be, and thus the loss to follow up seem not likely to influence the results. Repeated dGEMRIC examinations or ROI drawings were not included in our protocol. However, the issues of T_1(Gd) reproducibility in repeated examinations and the T_1(Gd) variability between repeated drawings of the region of interest are not probable biases. First, these possible biases would likely occur in both groups. Second, dGEMRIC T_1(Gd) has shown to be reproducible with 10-15% variation in repeated examinations within patients and the intra-observer variation in T_1(Gd) in repeated ROI drawings is less than 2.5% (20, 21). The baseline T_1(Gd) values of the patients lost to follow-up did not differ from the patients available for follow-up. We suggest the difference of 40 ms found in T_1(Gd) values at follow-up between exercisers and controls is *clinically* significant. It is comparable to the T_1(Gd) differences of 52 and 40 ms, respectively, previously found between sedentary and moderately active healthy adults, and moderately active healthy adults and elite runners (18). It is not possible to extrapolate any long-term effects of exercise on cartilage from this study. Most likely, the effect is dependent on compliance in accordance with the effects of exercise on muscle and bone.

Conclusion

We conclude that moderate supervised exercise improves knee cartilage glycosaminoglycan content in patients at risk of osteoarthritis. Improvement in pain and function parallel the structural improvement. Exercise may have important preventive implications in patients at risk of knee osteoarthritis development.

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Tables

Table 1. Baseline characteristics of the 30 patients who were available for follow-up with MRI and for the 15 subjects lost to MRI follow-up.

	Total group n=30	Exercise group n=16	Control group n=14	Lost to follow-up n=15
Mean age (SD)	45.8 (3.3)	45.8 (3.1)	45.8 (3.6)	46.8 (2.6)
Men/Women, n	20/10	10/6	10/4	9/6
High/Low activity level, n	20/10	10/6	10/4	10/5
BMI (SD)	26.6 (3.2)	26.5 (3.6)	26.8 (2.6)	26.2 (3.6)
Knee pain[1] at least monthly/never, n	22/8	11/5	11/3	11/4
Knee joint stiffness[2] at least mild/none, n	21/9	9/7	12/2	11/6
Functional difficulty[3] at least mild/none, n	16/14	9/7	7/7	8/7
Awareness of knee problem[4] at least monthly/never, n	26/4	13/3	13/1	14/1

1 Assessed with KOOS question “How often do you experience knee pain? Never, Monthly, Weekly, Daily, Always”

2 Assessed with KOOS question “How severe is your knee stiffness after sitting, lying or resting later in the day? None, Mild, Moderate, Severe, Extreme”

3 Assessed with KOOS question “What difficulty have you experienced during the last week when descending stairs? None, Mild, Moderate, Severe, Extreme”

4 Assessed with KOOS question “How often are you aware of your knee problems? Never, Monthly, Weekly, Daily, Always”

Table 2. Mean (SD) baseline and change in T_1(Gd) (ms) BMI, KOOS scores and performance measures for the exercise group and the control group.

	Exercise group n=16	Control group n=14	P-value Mann-Whitney
dGEMRIC, T_1 (ms)			
baseline	367 (76)	357 (62)	0.7
change	15(54)	-15(32)	0.036
BMI			
baseline	26.5 (3.6)	26.8 (2.6)	0.5
change	-0.3 (0.8)	0.2 (0.6)	0.2
KOOS Pain			
baseline	85 (11)	80 (17)	0.5
change	1 (15)	4 (12)	0.7
KOOS Symptoms			
baseline	90 (9)	81 (12)	0.047
change	1 (10)	4 (5)	0.4
KOOS ADL			
baseline	91 (10)	83 (17)	0.2
change	2 (8)	5 (12)	0.4
KOOS Sport/Rec			
baseline	67 (25)	60 (26)	0.4
change	11 (27)	2 (17)	0.4
KOOS QOL			

baseline	66 (21)	68 (18)	0.6
change	8 (16)	4 (10)	0.6
Aerobic capacity, BW adj.			
baseline	32 (5)	33 (8)	0.6
change	3.2 (4.8)	1.9 (4.7)	0.4
Isokinetic peak torque 60 deg/sec BW adj. (Nm)			
baseline	192 (42)	201 (57)	0.7
change	6 (26)	3 (27)	0.6
Square jump (n)			
baseline	4.5 (2.8)	7.2 (5.8)	0.4
change	3.4 (3.6)	0.8 (4.2)	0.112
One leg jump (cm)			
baseline	104 (31)	110 (39)	0.6
change	17 (10)	7 (8)	0.009
One leg rise (n)			
baseline	16 (9)	14 (10)	0.5
change	6 (10)	4 (9)	0.4

Figure 1. Examples of weight-bearing exercises from the intervention program to improve strength and neuromuscular control in the lower extremity.

Figure 2. An illustration of the region of interest (ROI) (dark gray area shown by an arrow) in the weight-bearing femoral cartilage.

Figure 3. Subject flow in the study.

Figure 4. Change in T_1(Gd), reflective of change of glycosaminoglycan content in the medial femoral condyle of the meniscectomized (study) knee for both exercise and control groups (n=30) depending on self-reported change in physical activity level during the study period. The horizontal line denotes the mean T_1(Gd) for each of the three groups of self-reported change.

Figure 1.

Figure 2.

Figure 4.

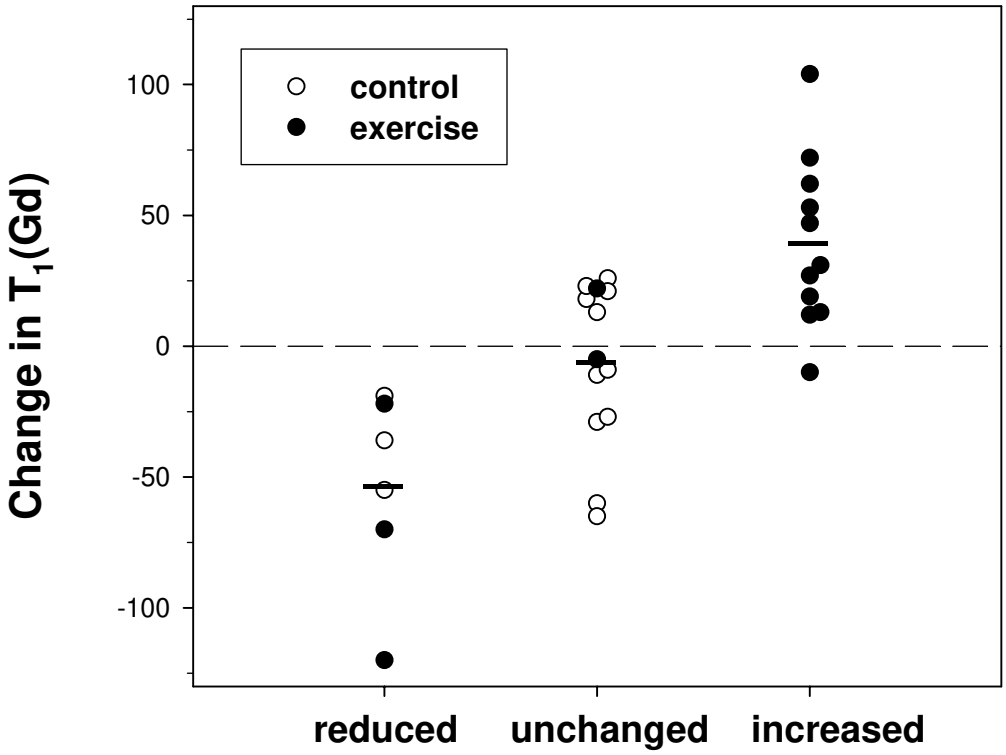
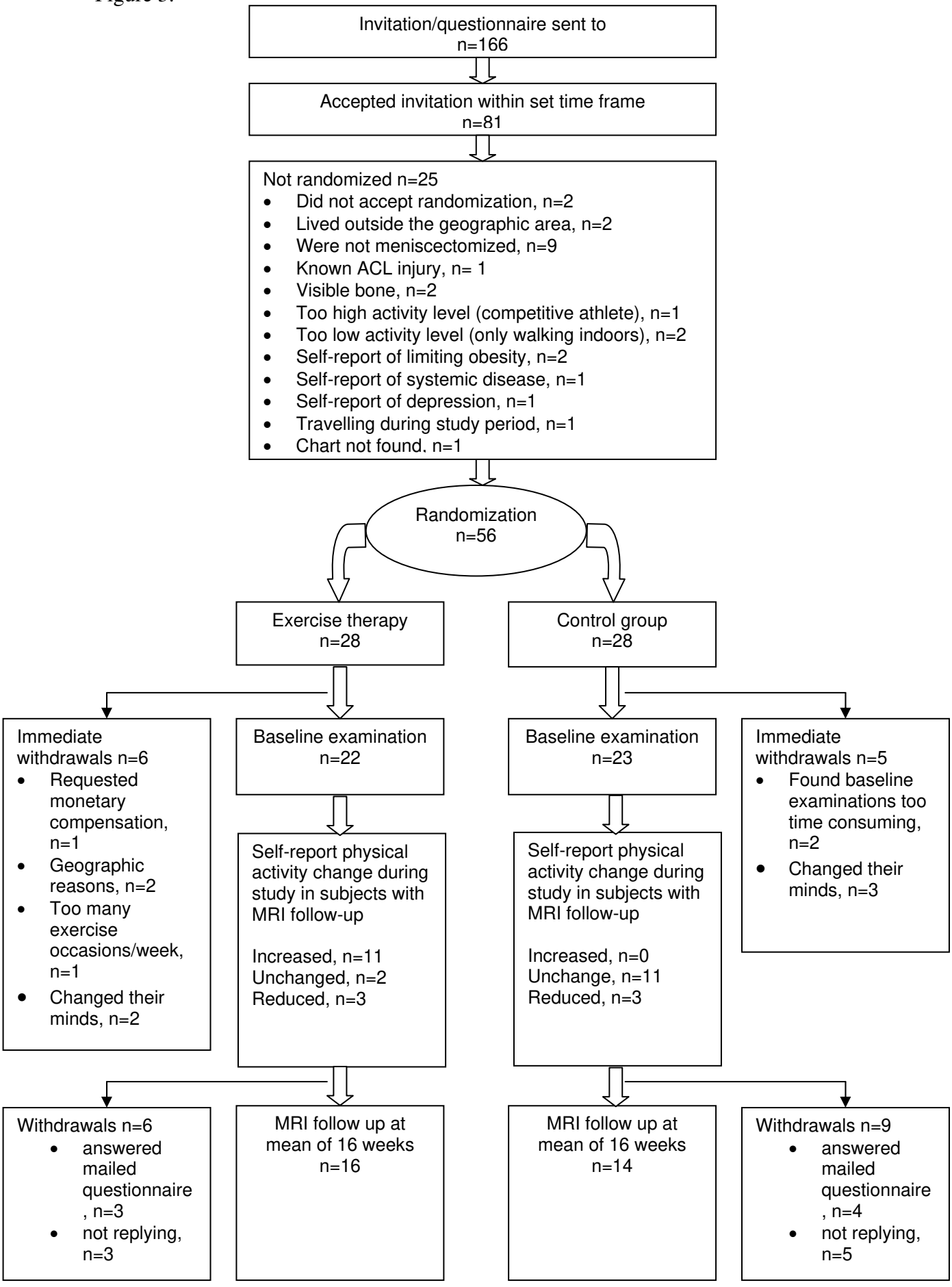

control
exercise
Change in T_1(Gd)
100
50
0
-50
-100
reduced
unchanged
increased

Figure 3.


Invitation/questionnaire sent to n=166
Accepted invitation within set time frame n=81
Not randomized n=25
Did not accept randomization, n=2
Lived outside the geographic area, n=2
Were not meniscectomized, n=9
Known ACL injury, n= 1
Visible bone, n=2
Too high activity level (competitive athlete), n=1
Too low activity level (only walking indoors), n=2
Self-report of limiting obesity, n=2
Self-report of systemic disease, n=1
Self-report of depression, n=1
Travelling during study period, n=1
Chart not found, n=1
Randomization n=56
Exercise therapy n=28
Control group n=28
Immediate withdrawals n=6
Requested monetary compensation, n=1
Geographic reasons, n=2
Too many exercise occasions/week, n=1
Changed their minds, n=2
Baseline examination n=22
Baseline examination n=23
Immediate withdrawals n=5
Found baseline examinations too time consuming, n=2
Changed their minds, n=3
Self-report physical activity change during study in subjects with MRI follow-up
Increased, n=11
Unchanged, n=2
Reduced, n=3
Self-report physical activity change during study in subjects with MRI follow-up
Increased, n=0
Unchange, n=11
Reduced, n=3
Withdrawals n=6
answered mailed questionnaire , n=3
not replying, n=3
MRI follow up at mean of 16 weeks n=16
MRI follow up at mean of 16 weeks n=14
Withdrawals n=9
answered mailed questionnaire , n=4
not replying, n=5