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Positive Effects of Moderate Exercise on Glycosaminoglycan Content in Knee Cartilage

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

Ewa M. Roos[1] and Leif Dahlberg[2]

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

Methods. **Forty-five subjects (16 women, mean age 46 years, mean body mass index 26.6 kg/m^2) who underwent partial medial meniscus resection 3–5 years previously were randomized to undergo a regimen of supervised exercise 3 times weekly for 4 months or to a nonintervention control group. Cartilage GAG content, an important aspect of the biomechanical properties of cartilage, was estimated by delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC), with results expressed as the change in the T1 relaxation time in the presence of Gd-DTPA (T1[Gd]).**

Results. **Thirty of 45 patients were examined by dGEMRIC at baseline and followup. The exercise group (n = 16) showed an improvement in the T1(Gd) compared with the control group (n = 14) (15 msec versus −15 msec; $P = 0.036$). To study the dose response, change in the T1(Gd) was assessed for correlation with self-reported change in physical activity level, and a strong correlation was found in the exercise group (n = 16, $r_S = 0.70$, 95% confidence interval [95% CI] 0.31–0.89) and in the pooled group of all subjects (n = 30, $r_S = 0.74$, 95% CI 0.52–0.87).**

Conclusion. **This in vivo cartilage monitoring study in patients at risk of knee OA who begin exercising 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 GAG content in patients at high risk of developing OA.**

Osteoarthritis (OA) and other rheumatic conditions comprise the leading cause of disability among adults. 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, patient 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 OA (2). However, exercise is underutilized as a therapy for OA, and more than 60% of US adults with arthritis do not satisfy the recommendations for physical activity (3,4).

The hallmark of structural changes occurring in the OA joint is cartilage loss. Since OA is considered a wear and tear disease, one identified barrier to exercise is the belief that exercise will not improve or may even be harmful to joint cartilage (5,6). In studies of exercise in animals that develop OA, it has been shown that exercise may protect against cartilage degeneration (7–9). The effects of exercise on human cartilage are largely unknown because, until recently, investigators have been unable to examine the biochemical properties of cartilage tissue in vivo.

Radiography, currently used to define the pres-

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[1]Ewa M. Roos, PT, PhD: Lund University, Lund, Sweden; [2]Leif Dahlberg, MD, PhD: Malmö University Hospital, Malmo, Sweden.

Address correspondence and reprint requests to Leif Dahlberg, MD, PhD, Department of Orthopedics, Malmö University Hospital, SE-205 02 Malmo, Sweden. E-mail: leif.dahlberg@med.lu.se.

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ence of OA in the joints, identifies disease only in the later stages, when severe cartilage damage has occurred (10). To study cartilage alterations earlier in the disease process, magnetic resonance imaging (MRI) techniques have been developed (11). Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) estimates cartilage quality by measuring the fixed-charge density of tissue, comprising glycosaminoglycans (GAGs) (12–14). GAGs are building blocks of proteoglycans and are crucial for the important viscoelastic properties of cartilage (15).

To test the hypothesis that moderate exercise improves the quality of knee cartilage in patients with early joint disease, we designed a randomized trial involving middle-age patients who previously underwent meniscectomy because of a degenerative meniscus tear, a group who are considered at high risk of developing radiographic OA (16). We used dGEMRIC to evaluate the effects of 4 months of exercise intervention on the GAG content of knee cartilage.

PATIENTS AND METHODS

Study participants. The ethics committee of the medical faculty of Lund University approved the study, and written informed consent was obtained from all subjects. To recruit subjects at high risk of knee OA, middle-age patients of both sexes who had been treated with partial medial meniscus resection were identified through the surgical code system at the Department of Orthopedics, Malmö University Hospital. Inclusion criteria were partial medial meniscectomy 3–5 years previously, a current age between 35 years and 50 years, willingness to participate in the study, and provision of signed informed consent. Exclusion criteria were misclassification in the surgical code system (no meniscectomy), 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), a self-reported limiting comorbid condition, and not being in the geographic area during all of the study period.

Patients were informed about the study by correspondence and were asked if they would agree to participate. Screening questions were used to ensure compliance with the 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 were received. Patients were stratified according to a self-reported high or low leisure physical activity level, to ensure a similar response to exercise in both groups. High-level activity was defined as recreational sports, e.g., golf, hiking, and biking. Low-level activity was defined as yard work, shopping, and similar activities. Since the total number of patients in each stratum was unknown when randomization began, 52 opaque envelopes, organized in blocks, were prepared for each stratum. The first 4 blocks for each stratum contained 4 envelopes, and the additional blocks contained 2 envelopes each. This strategy was chosen to avoid allocation of unequal numbers of patients of the 2 strata to the treatment and control groups.

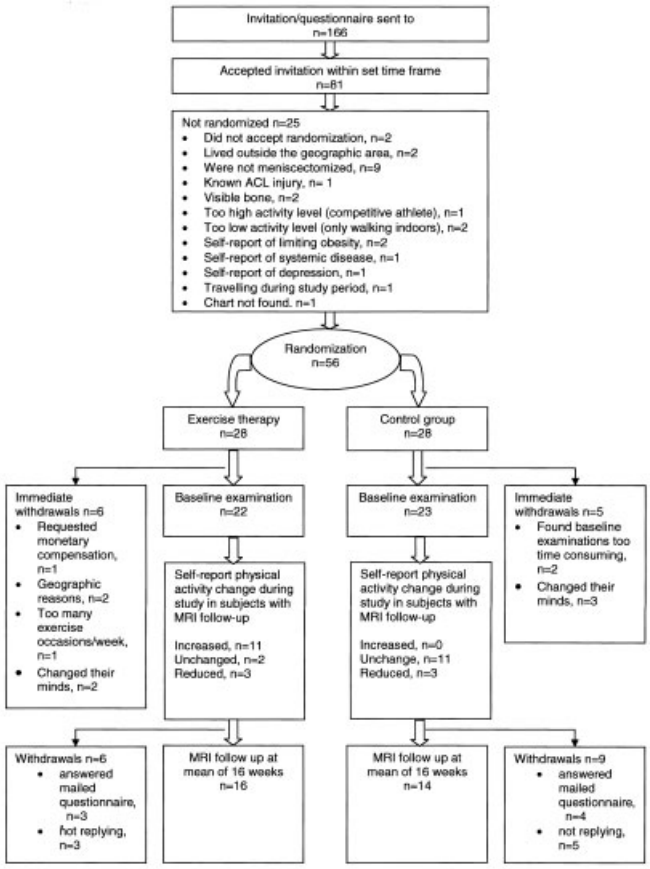

Figure 1. Distribution of patients in the trial. ACL = anterior cruciate ligament; MRI = magnetic resonance imaging.

Exercise intervention. The objectives of the intervention were to improve neuromuscular control, muscle strength, and aerobic capacity. The patients were offered group exercise classes on every weekday for 4 months, led by 1 of 5 experienced and specifically trained physical therapists. It was expected that each patient should attend the exercise sessions 3 days weekly. To tailor the program to each individual, all patients in the exercise group underwent a clinical examination and functional assessment by 1 physical therapist prior to study start. This physical therapist was also responsible for instructing the 5 physical therapists leading the exercise groups. The exercise program lasted for 1 hour. The warm-up period consisted of ergometer cycling, rope skipping, and jogging on a trampoline. Examples of individually pro-

Figure 2. Examples of weight-bearing exercises from the intervention program to improve strength and neuromuscular control in the lower extremity.

gressed weight-bearing strengthening exercises are given in Figure 2.

Neuromuscular control during the exercises was repeatedly emphasized. Most often, 4–6 patients attended each exercise session, thus allowing the physical therapist to closely monitor each individual. A description of the complete exercise program can be obtained from one of us (EMR).

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 also evaluated in the control subjects.

End points. The primary end point was change in the T1 relaxation time in the presence of Gd-DTPA (T1[Gd]) between baseline and followup, as quantified by dGEMRIC (12,14,17–19). The dGEMRIC method is an in vivo approach for the assessment of GAG content in cartilage that relies on the principle that the intravenously injected negatively charged contrast agent Gd-$DTPA^{2-}$ distributes inversely to the negatively charged GAGs in the cartilage (14,20). Therefore, a high GAG content in cartilage yields a low content of contrast agent, resulting in a long T1(Gd). In an intervention study, an increase in GAG content will be reflected by an increased T1(Gd).

The dGEMRIC was performed using a standard 1.5T MRI system (Magnetom Vision; Siemens Medical Systems, Erlangen, Germany) ~2 hours after injection of the contrast agent Gd-$DTPA^{2-}$ (17). A dose of 0.3 mmoles/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 15 minutes, starting within 10 minutes of the injection of the contrast agent.

Sets of 6 sagittal, turbo inversion recovery images with different inversion times (repetition time 2,000 msec, echo time 15 msec, turbo factor 7, field of view 120 $\times$ 120 mm^2, matrix size 256 $\times$ 256 pixels, inversion time 50, 100, 200, 400, 800, and 1,600 msec, 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 of the weight-bearing cartilage of the medial femoral condyle was used (21). The ROI was placed between the center of the tibial plateau and the rear insertion of the meniscus, and included the full thickness of the cartilage (17) (Figure 3). The assessor was blinded to the patient's group allocation. Calculations of the quantitative longitudinal T1(Gd) were performed with the use of the mean signal intensity from each ROI as the input data in a 3-parameter fit (22).

Clinical outcomes were assessed at baseline and followup using the Knee Injury and Osteoarthritis Outcomes Score (KOOS) (for details, see the Web site at www.koos.nu). Scores are given on a 0–100 (worst to best) scale. The KOOS has been validated for short- and long-term followup of patients with meniscectomized joints (16,23,24). The KOOS data were used to determine the correlation of change in the T1(Gd) with change in clinical outcomes. The study was not powered to determine differences between groups over time in clinical outcomes.

At followup, all subjects self-reported change in their physical activity level during the study period as increased, unchanged, or reduced. The change in the index leg was assessed according to the results of 3 muscular performance tests, a measure of isokinetic strength of the knee extensors of the index leg, and aerobic capacity, as objective measures of change in physical activity. The performance tests were the 1-leg jump (25), square hop (26), and 1-leg rising (26,27). Isokinetic peak torque, adjusted for body weight, during knee extension at 60°/second was obtained by a Biodex isokinetic testing system (Biodex, Shirley, NY). Aerobic capacity was assessed by a bicycle ergometer test according to the method described by Astrand (28).

Power calculation and statistical analysis. Based on prior data from a cross-sectional study (18), we estimated that 30 patients were needed, at 80% power, to detect a mean $\pm$ SD difference of 40 $\pm$ 40 msec in the T1(Gd) between groups. We estimated a dropout rate of 30% and decided to randomize at least 40 subjects. Nonparametric statistics were used; the Mann-Whitney U test was used when comparing the exercise

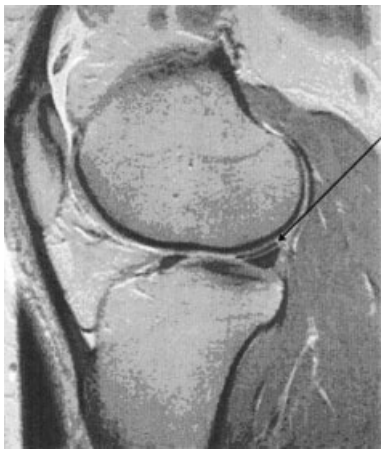

Figure 3. An illustration of the region of interest (ROI) (dark shaded area denoted by **arrow**) in the weight-bearing femoral cartilage.

Table 1. Baseline characteristics of the 30 patients who were available for followup with dGEMRIC and the 15 subjects lost to followup*

	Total group (n = 30)	Exercise group (n = 16)	Control group (n = 14)	Lost to followup (n = 15)
Age, mean ± SD years	45.8 ± 3.3	45.8 ± 3.1	45.8 ± 3.6	46.8 ± 2.6
Men/women	20/10	10/6	10/4	9/6
High/low physical activity level	20/10	10/6	10/4	10/5
BMI, mean ± SD kg/m^2	26.6 ± 3.2	26.5 ± 3.6	26.8 ± 2.6	26.2 ± 3.6
Knee pain, at least monthly/never†	22/8	11/5	11/3	11/4
Knee joint stiffness, at least mild/none‡	21/9	9/7	12/2	11/4
Functional difficulty, at least mild/none§	16/14	9/7	7/7	8/7
Awareness of knee problem, at least monthly/never¶	26/4	13/3	13/1	14/1

* Except where indicated otherwise, values are the number of patients. dGEMRIC = delayed gadolinium-enhanced magnetic resonace imaging of cartilage; BMI = body mass index.
† Assessed with the Knee Injury and Osteoarthritis Outcomes Score (KOOS) question, "How often do you experience knee pain?" Response options: never, monthly, weekly, daily, always.
‡ Assessed with the KOOS question, "How severe is your knee stiffness after sitting, lying or resting later in the day?" Response options: none, mild, moderate, severe, extreme.
§ Assessed with the KOOS question, "What difficulty have you experienced during the last week when descending stairs?" Response options: none, mild, moderate, severe, extreme.
¶ Assessed with the KOOS question, "How often are you aware of your knee problems?" Response options: never, monthly, weekly, daily, always.

group with the control group, and Spearman's rho was used when comparing 3 ranked groups. *P* values less than or equal to 0.05 were considered significant.

RESULTS

Patients. The distribution of the study participants is shown in Figure 1. Fifty-six patients who met the inclusion criteria were randomized. Among the 45 patients who were given baseline examinations, 22 were in the exercise group and 23 were in the control group. Nineteen patients in the exercise group and 18 control subjects completed the followup questionnaire. Sixteen patients in the exercise group and 14 control subjects underwent followup with dGEMRIC. The exercise and control groups did not differ significantly with regard to characteristics such as age, sex, physical activity level, body mass index, and baseline pain, stiffness, functional limitations, and awareness of knee problems (Table 1).

Eighty-seven percent of the patients were aware of their knee problems at least monthly, and the majority of patients had pain, stiffness, and functional limitations. Eleven of the 30 patients who were followed up with dGEMRIC, equally distributed between the groups, fulfilled the American College of Rheumatology clinical criteria for knee OA (29). One patient in the exercise group reported taking nonprescription painkillers and 1 subject in the control group was taking glucosamine. The subjects who were lost to followup with dGEMRIC (n = 15) did not significantly differ from the patients who were available for this followup (n = 30), with regard to any of the baseline characteristics shown in Table 1.

Exercise group versus control group. In the exercise group, the 16 patients who were followed up with dGEMRIC attended a mean ± SD 31 ± 16 (range 0–54) supervised exercise sessions during the trial. In addition, they self-reported attendance, on a weekly basis, of a mean ± SD 22 ± 19 exercise sessions (range 0–53), such as running, biking, or tennis. In total, the intervention group exercised an average of 3 times weekly. At followup, improvements in performance test results were noted in the exercise group compared with the control group (Table 2).

The T1(Gd) values did not differ between groups at baseline. However, at followup there was a significant improvement in the T1(Gd) in the exercise group compared with the control group (+15 msec versus −15 msec; $P = 0.036$) (Table 2).

Dose-response analyses. To study the dose response to the trial intervention, change in the T1(Gd) was assessed for a correlation with self-reported change in physical activity level. In the exercise group, 68% reported an increased activity level, whereas in the

Table 2. Change in the dGEMRIC results, clinical characteristics, and physical activity performance measures from baseline to followup in the exercise group and the control group*

	Exercise group (n = 16)	Control group (n = 14)	*P*, by Mann-Whitney U test
dGEMRIC, T1(Gd), msec			
Baseline	367 ± 76	357 ± 62	0.7
Change	15 ± 54	−15 ± 32	0.036
BMI, kg/m^2			
Baseline	26.5 ± 3.6	26.8 ± 2.6	0.5
Change	−0.3 ± 0.8	0.2 ± 0.6	0.2
KOOS (scale 0–100)			
Pain			
Baseline	85 ± 11	80 ± 17	0.5
Change	1 ± 15	4 ± 12	0.7
Symptoms			
Baseline	90 ± 9	81 ± 12	0.047
Change	1 ± 10	4 ± 5	0.4
ADL			
Baseline	91 ± 10	83 ± 17	0.2
Change	2 ± 8	5 ± 12	0.4
Sports/recreation level			
Baseline	67 ± 25	60 ± 26	0.4
Change	11 ± 27	2 ± 17	0.4
QOL			
Baseline	66 ± 21	68 ± 18	0.6
Change	8 ± 16	4 ± 10	0.6
Performance testing			
Aerobic capacity, V_{O_2} max, BW adjusted			
Baseline	32 ± 5	33 ± 8	0.6
Change	3.2 ± 4.8	1.9 ± 4.7	0.4
Isokinetic peak torque at 60°/seconds, Nm, BW adjusted			
Baseline	192 ± 42	201 ± 57	0.7
Change	6 ± 26	3 ± 27	0.6
No. of square hops			
Baseline	4.5 ± 2.8	7.2 ± 5.8	0.4
Change	3.4 ± 3.6	0.8 ± 4.2	0.112
1-leg jump, cm			
Baseline	104 ± 31	110 ± 39	0.6
Change	17 ± 10	7 ± 8	0.009
No. of 1-leg risings			
Baseline	16 ± 9	14 ± 10	0.5
Change	6 ± 10	4 ± 9	0.4

* Values are the mean ± SD baseline values and change from baseline to followup. T1(Gd) = T1 relaxation time in the presence of Gd-DTPA; ADL = activities of daily living; QOL = quality of life; BW = body weight (see Table 1 for other definitions).

control group, none of the subjects reported an increased activity level (Figure 4). A strong correlation between self-reported change in physical activity level and change in the T1(Gd) as quantified by dGEMRIC at followup was found in the exercise group (n = 16, r_S = 0.70, 95% confidence interval [95% CI] 0.31–0.89) and in the pooled group of all subjects (n = 30, r_S = 0.74, 95% CI 0.52–0.87) (Figure 4). In support of the validity of the self-reported change in physical activity, the mean improvements seen in aerobic capacity and isokinetic peak torque within the total group (n = 30) correlated positively with self-reported change in physical activity level (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 GAG content correlated with improvement in self-reported clinical status, the change in the T1(Gd) was assessed for a correlation with change in KOOS ratings. When both groups were analyzed together (n = 30), improved cartilage GAG content correlated with improvement in all 5 KOOS subscales (r_S = 0.38–0.52, 95% CI 0.02–0.70).

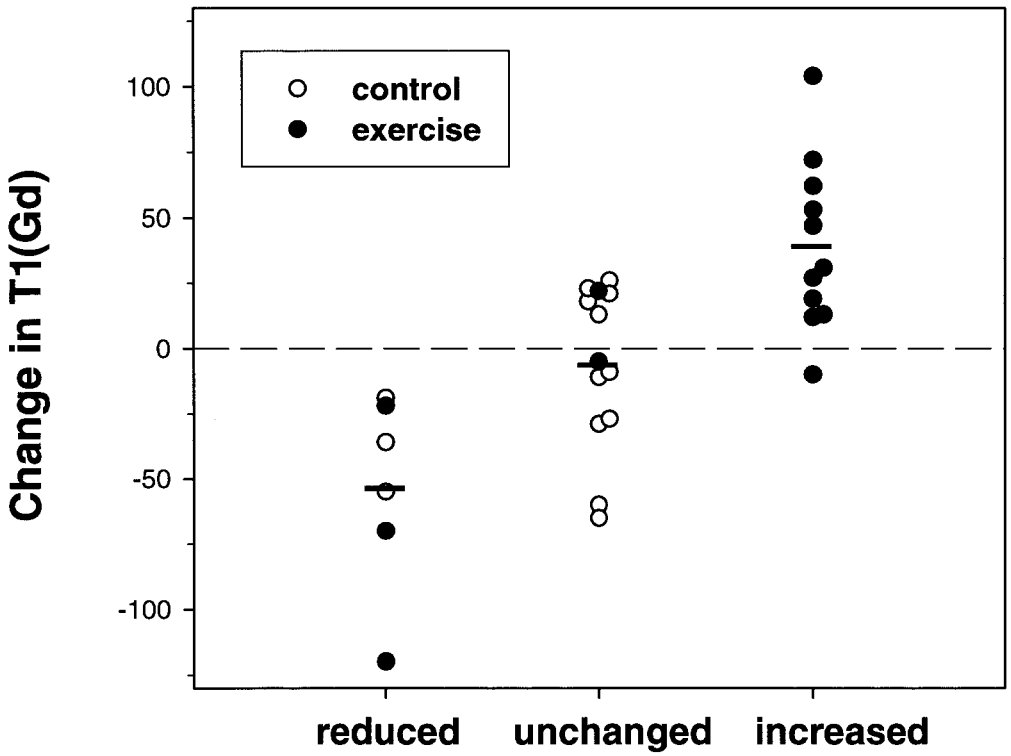

Figure 4. Change in the T1 relaxation time in the presence of Gd-DTPA (T1[Gd]) (in msec), reflecting change in the glycosaminoglycan content of the medial femoral condyle of the meniscectomized (study) knee, in both the exercise group and the control group (n = 30), as a function of self-reported change in physical activity level during the study period. Bars denote the mean T1(Gd) for each of the 3 groups of self-reported change.

DISCUSSION

This study shows compositional changes in adult joint cartilage as a result of increased exercise, which confirms the observations made in prior animal studies (7,8) but has not previously been shown in humans. The changes imply that human cartilage responds to physiologic loading in a way similar to that exhibited by muscle and bone, and that previously established positive symptomatic effects of exercise in patients with OA may occur in parallel to or even be caused by improved cartilage properties.

The unpredictable and individually different progression rate of OA may be explained partly by subjects' differences in matrix integrity, due to differences in, for example, physical stimulation. Animal and cartilage-explant studies have shown increased cartilage GAG metabolism and content and improved indentation stiffness according to increased degree of dynamic joint loading (30–32). The use of dGEMRIC as an estimate of GAG content and assessment of cartilage quality has shown in humans that those participating in a high level of exercise have a higher T1(Gd), and this is the likely means by which higher mechanical demands are withstood (18). Furthermore, recent dGEMRIC studies have shown a high correlation between GAG distribution and biomechanical properties of cartilage (33,34). It is notable that dGEMRIC, which is presumably more sensitive to disease because it is sensitive to biochemical changes in the tissue, allows the significance of the outcomes to be determined with a smaller number of study participants than is feasible with clinical outcome measures.

A state of prestress in the joint, due to the balance between the swelling that arises from the presence of proteoglycans and the rigid collagen network, is crucial for the function of healthy cartilage (35). In the present study, the higher mean change in the T1(Gd) in the intervention group suggests that cartilage responded to exercise by increasing its GAG content. It may be that increased cartilage GAG content improves the viscoelasticity, which, in turn, protects the collagen network from compressive forces, as has been suggested in canine studies (36). In a cartilage matrix with low GAG content,

as in cartilage disease, insufficient viscoelasticity may cause progressive denaturation of collagen molecules, collagen loss, and subsequent development of OA (37).

It is possible that the susceptibility of joint cartilage to OA is related to its quality, specifically to its molecular content of GAGs with high fixed-charge density (38). Among patients with joint disease, dGEMRIC indicates a decreased cartilage GAG content in those with arthroscopic cartilage fibrillations, ligament injury, meniscus tear, and hip dysplasia (19,39,40). Furthermore, analysis of proteoglycans from healthy and diseased human cartilage and joint synovial fluid indicates increased proteolytic activity in diseased joints and increased release of proteoglycan fragments that differ from those released in normal joints (41–44).

The potential limitations of this study include, but are not limited to, the limited applicability of the results to other groups at risk of OA, the loss to followup, the methodologic issues related to dGEMRIC, the clinical significance of the results, and the short followup time. The present results are applicable to middle-age patients who have undergone meniscectomy. Meniscectomized knee joints have an increased risk of developing OA (45). In addition, the radiographic and clinical outcome is worse in patients with a degenerative tear, in whom the meniscus injury is suggested to be an early signal of OA (16). In the present study, 25 of 30 patients had such a meniscal tear. The possible association of meniscectomy with hand OA suggests that our results may also be applicable to other groups at risk of developing OA (46).

The primary outcome in this trial was cartilage GAG content measured as the T1(Gd). An objective MRI parameter is not subject to bias in the way that a patient-relevant outcome such as pain would be, and thus the loss to followup does not seem likely to have any influence on the results. Repeated dGEMRIC examinations or ROI drawings were not included in our protocol. However, the issues of T1(Gd) reproducibility in repeated examinations and the T1(Gd) variability between repeated drawings of the ROI are not probable biases. First, these possible biases would likely occur in both groups. Second, dGEMRIC T1(Gd) has been shown to be reproducible with 10–15% variation in repeated examinations within patients, and the intraobserver variation in T1(Gd) in repeated ROI drawings is lower than 2.5% (20,21). The baseline T1(Gd) values of the patients lost to followup did not differ from those in the patients available for followup.

We suggest that the difference of 40 msec found in the T1(Gd) values at followup between the exercise group and the nonintervention control group is clinically significant. It is comparable with the T1(Gd) differences of 52 msec and 40 msec previously found between sedentary and moderately active healthy adults and between moderately active healthy adults and elite runners, respectively (18). It is not possible to extrapolate the results of this study to any long-term effects of exercise on cartilage. Most likely, the effect is dependent on compliance, in accordance with the effects of exercise on muscle and bone.

We conclude that moderate, supervised exercise improves knee-cartilage GAG content in patients at risk of OA. Improvements in pain and function are observed in parallel with the structural improvement. Exercise may have important implications for disease prevention in patients at risk of developing knee OA.

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REFERENCES

1. Prevalence of self-reported arthritis or chronic joint symptoms among adults: United States, 2001. MMWR Morb Mortal Wkly Rep 2002;51:948–50.
2. Fransen M, McConnell S, Bell M. Exercise for osteoarthritis of the hip or knee. Cochrane Database Syst Rev (CD004286); 2003.
3. Jordan KM, Sawyer S, Coakley P, Smith HE, Cooper C, Arden NK. The use of conventional and complementary treatments for knee osteoarthritis in the community. Rheumatology (Oxford) 2004;43:381–4.
4. Fontaine KR, Heo M, Bathon J. Are US adults with arthritis meeting public health recommendations for physical activity? Arthritis Rheum 2004;50:624–8.
5. Campbell R, Evans M, Tucker M, Quilty B, Dieppe P, Donovan JL. Why don't patients do their exercises? Understanding noncompliance with physiotherapy in patients with osteoarthritis of the knee. J Epidemiol Community Health 2001;55:132–8.
6. Thorstenson CA, Roos EM, Petersson IF, Arvidsson B. How do patients conceive exercise as treatment of knee osteoarthritis? Disabil Rehabil 2005. In press.
7. Otterness IG, Eskra JD, Bliven ML, Shay AK, Pelletier JP, Milici AJ. Exercise protects against articular cartilage degeneration in the hamster. Arthritis Rheum 1998;41:2068–76.
8. Galois L, Etienne S, Grossin L, Cournil C, Pinzano A, Netter P, et al. Moderate-impact exercise is associated with decreased severity of experimental osteoarthritis in rats. Rheumatology (Oxford) 2003;42:692–3.
9. Brismar BH, Lei W, Hjerpe A, Svensson O. The effect of body mass and physical activity on the development of guinea pig osteoarthrosis. Acta Orthop Scand 2003;74:442–8.
10. Boegard T, Rudling O, Petersson IF, Jonsson K. Correlation between radiographically diagnosed osteophytes and magnetic

resonance detected cartilage defects in the tibiofemoral joint. Ann Rheum Dis 1998;57:401–7.
11. Gray ML, Eckstein F, Peterfy C, Dahlberg L, Kim YJ, Sorensen AG. Towards imaging biomarkers for osteoarthritis. Clin Orthop Relat Res 2004;427:S175–81.
12. Bashir A, Gray ML, Burstein D. Gd-DTPA^{2-} as a measure of cartilage degradation. Magn Reson Med 1996;36:665–73.
13. Bashir A, Gray ML, Boutin RD, Burstein D. Glycosaminoglycan in articular cartilage: in vivo assessment with delayed Gd-(DTPA)(2−)-enhanced MR imaging. Radiology 1997;205:551–8.
14. Bashir A, Gray ML, Hartke J, Burstein D. Nondestructive imaging of human cartilage glycosaminoglycan concentration by MRI. Magn Reson Med 1999;41:857–65.
15. Lu XL, Sun DD, Guo XE, Chen FH, Lai WM, Mow VC. Indentation determined mechanoelectrochemical properties and fixed charge density of articular cartilage. Ann Biomed Eng 2004;32:370–9.
16. Englund M, Roos EM, Lohmander LS. Impact of type of meniscal tear on radiographic and symptomatic knee osteoarthritis: a sixteen-year followup of meniscectomy with matched controls. Arthritis Rheum 2003;48:2178–87.
17. Tiderius CJ, Olsson LE, de Verdier H, Leander P, Ekberg O, Dahlberg L. (Gd-DTPA2)-enhanced MRI of femoral knee cartilage: a dose-response study in healthy volunteers. Magn Reson Med 2001;46:1067–71.
18. Tiderius CJ, Svensson J, Leander P, Ola T, Dahlberg L. dGEMRIC (delayed gadolinium-enhanced MRI of cartilage) indicates adaptive capacity of human knee cartilage. Magn Reson Med 2004;51:286–90.
19. Tiderius CJ, Olsson LE, Leander P, Ekberg O, Dahlberg L. Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) in early knee osteoarthritis. Magn Reson Med 2003;49:488–92.
20. Burstein D, Velyvis J, Scott KT, Stock KW, Kim YJ, Jaramillo D, et al. Protocol issues for delayed Gd(DTPA)(2−)-enhanced MRI (dGEMRIC) for clinical evaluation of articular cartilage. Magn Reson Med 2001;45:36–41.
21. Tiderius CJ, Tjornstrand J, Akeson P, Sodersten K, Dahlberg L, Leander P. Delayed gadolinium enhanced MRI of cartilage (dGEMRIC): intra- and inter-observer variability in the standardized drawing of regions-of-interest. Acta Radiol 2004;45:628–34.
22. Kingsley PB, Ogg RJ, Reddick WE, Steen RG. Correction of errors caused by imperfect inversion pulses in MR imaging measurement of T1 relaxation times. Magn Reson Imaging 1998; 16:1049–55.
23. Roos EM, Roos HP, Ekdahl C, Lohmander LS. Knee injury and osteoarthritis outcome score (KOOS): validation of a Swedish version. Scand J Med Sci Sports 1998;8:439–48.
24. Roos EM, Roos HP, Ryd L, Lohmander LS. Substantial disability 3 months after arthroscopic partial meniscectomy: a prospective study of patient-relevant outcomes. Arthroscopy 2000;16:619–26.
25. Tegner Y, Lysholm J, Lysholm M, Gillquist J. A performance test to monitor rehabilitation and evaluate anterior cruciate ligament injuries. Am J Sports Med 1986;14:156–9.
26. Ostenberg A, Roos E, Ekdahl C, Roos H. Isokinetic knee extensor strength and functional performance in healthy female soccer players. Scand J Med Sci Sports 1998;8:257–64.
27. Roos EM, Ostenberg A, Roos H, Ekdahl C, Lohmander LS. Long-term outcome of meniscectomy: symptoms, function, and performance tests in patients with or without radiographic osteoarthritis compared to matched controls. Osteoarthritis Cartilage 2001;9:316–24.
28. Astrand PO. Measurement of maximal aerobic capacity. Can Med Assoc J 1967;96:732–5.
29. 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. Arthritis Rheum 1986;29:1039–49.
30. Grodzinsky AJ, Levenston ME, Jin M, Frank EH. Cartilage tissue remodeling in response to mechanical forces. Annu Rev Biomed Eng 2000;2:691–713.
31. Brandt KD, Palmoski MJ. Effects of salicylates and other nonsteroidal anti-inflammatory drugs on articular cartilage. Am J Med 1984;77:65–9.
32. Jurvelin J, Kiviranta I, Tammi M, Helminen HJ. Effect of physical exercise on indentation stiffness of articular cartilage in the canine knee. Int J Sports Med 1986;7:106–10.
33. Nieminen MT, Toyras J, Laasanen MS, Silvennoinen J, Helminen HJ, Jurvelin JS. Prediction of biomechanical properties of articular cartilage with quantitative magnetic resonance imaging. J Biomech 2004;37:321–8.
34. Samosky JT, Burstein D, Grimson WE, Howe R, Martin S, Gray ML. Spatially-localized correlation of dGEMRIC-measured GAG distribution and mechanical stiffness in the human tibia plateau. J Orthop Res 2005;23:93–101.
35. Mow VC, Hung CT. Mechanical properties of normal and osteoarthritic articular cartilage, and the mechanobiology of chondrocytes. In: Brandt K, Doherty M, Lohmander LS, editors. Osteoarthritis. 2nd ed. Oxford: Oxford University Press; 2003. p. 102–12.
36. Helminen HJ, Hyttinen MM, Lammi MJ, Arokoski JP, Lapvetelainen T, Jurvelin J, et al. Regular joint loading in youth assists in the establishment and strengthening of the collagen network of articular cartilage and contributes to the prevention of osteoarthrosis later in life: a hypothesis. J Bone Miner Metab 2000;18: 245–57.
37. Poole AR, Nelson F, Dahlberg L, Tchetina E, Kobayashi M, Yasuda T, et al. Proteolysis of the collagen fibril in osteoarthritis. Biochem Soc Symp 2003;70:115–23.
38. Tiderius CJ, Olsson LE, Nyquist F, Dahlberg L. Cartilage glycosaminoglycan loss in the acute phase after an anterior cruciate ligament injury: delayed gadolinium-enhanced magnetic resonance imaging of cartilage and synovial fluid analysis. Arthritis Rheum 2005;52:120–7.
39. Williams A, Gillis A, McKenzie C, Po B, Sharma L, Micheli L, et al. Glycosaminoglycan distribution in cartilage as determined by delayed gadolinium-enhanced MRI of cartilage (dGEMRIC): potential clinical applications. AJR Am J Roentgenol 2004;182: 167–72.
40. Kim YJ, Jaramillo D, Millis MB, Gray ML, Burstein D. Assessment of early osteoarthritis in hip dysplasia with delayed gadolinium-enhanced magnetic resonance imaging of cartilage. J Bone Joint Surg Am 2003;85:1987–92.
41. Sandy JD, Flannery CR, Neame PJ, Lohmander LS. The structure of aggrecan fragments in human synovial fluid: evidence for the involvement in osteoarthritis of a novel proteinase which cleaves the Glu 373-Ala 374 bond of the interglobular domain. J Clin Invest 1992;89:1512–6.
42. Lohmander LS, Neame PJ, Sandy JD. The structure of aggrecan fragments in human synovial fluid: evidence that aggrecanase mediates cartilage degradation in inflammatory joint disease, joint injury, and osteoarthritis. Arthritis Rheum 1993;36:1214–22.
43. Rizkalla G, Reiner A, Bogoch E, Poole AR. Studies of the articular cartilage proteoglycan aggrecan in health and osteoarthritis: evidence for molecular heterogeneity and extensive molecular changes in disease. J Clin Invest 1992;90:2268–77.
44. Dahlberg L, Roos H, Saxne T, Heinegard D, Lark MW, Hoerrner LA, et al. Cartilage metabolism in the injured and uninjured knee of the same patient. Ann Rheum Dis 1994;53:823–7.
45. Roos H, Lauren M, Adalberth T, Roos EM, Jonsson K, Lohmander LS. Knee osteoarthritis after meniscectomy: prevalence of radiographic changes after twenty-one years, compared with matched controls. Arthritis Rheum 1998;41:687–93.
46. Englund M, Paradowski PT, Lohmander LS. Association of radiographic hand osteoarthritis with radiographic knee osteoarthritis after meniscectomy. Arthritis Rheum 2004;50:469–75.