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Relationship between cartilage glycosaminoglycan content (assessed with dGEMRIC) and OA risk factors in meniscectomized patients

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Summary

Objective: To study the relationship between cartilage integrity, assessed with [delayed Gadolinium-Enhanced Magnetic Resonance Imaging of Cartilage (dGEMRIC)] and epidemiologic risk factors for knee osteoarthritis (OA) in meniscectomized patients.

Methods: Body mass index (BMI) was calculated in 45 patients (16 women), mean age 46, who underwent an arthroscopic medial meniscectomy 1–6 years earlier. The cartilage glycosaminoglycan (GAG) content was estimated by dGEMRIC Index and tests of isokinetic muscle strength and functional performance (one-leg hop test) were conducted.

Results: BMI ranged from 20.0 to 34.3 (mean: 26.5). The dGEMRIC Index was 14.4% lower in the medial index compartment (374 ± 61 ms, mean ± SD) than in the lateral reference compartment (437 ± 59 ms, mean ± SD) ($P < 0.001$).
The dGEMRIC Index of the medial diseased compartment correlated positively with both knee flexor ($r = 0.50$, $P = 0.001$) and knee extensor strength ($r = 0.47$, $P = 0.001$) relative to body weight and with the one-leg hop test ($r = 0.42$, $P = 0.004$). Furthermore, a negative correlation was found between the dGEMRIC Index of the medial compartment and BMI ($r = -0.35$, $P = 0.019$).
No significant correlations were found in the lateral reference compartment.

Conclusion: The lower dGEMRIC Index of the medial compartment suggests decreased cartilage GAG content after medial meniscectomy, indicating an early stage OA. Furthermore, results suggest that overweight is a factor that deteriorates cartilage, whereas strong and co-ordinated thigh muscles may have a protective effect on the cartilage integrity.

Key words: Knee joint, Muscle strength, Body mass index, Middle-aged.

Introduction

Knee osteoarthritis (OA) is a painful, disabling condition with a prevalence of 10% in people older than 55 years and 30% in people older than 65 years[1,2]. The etiology and pathogenesis are not clear, but knee OA is associated with several risk factors, such as previous injury and meniscectomy[3,4] and obesity[5,6]. In addition, two recent longitudinal studies suggest that reduced knee extensor strength precedes radiographic knee OA[7,8].

By weight, the main cartilage matrix molecules are type II collagen and aggrecan. Aggrecan consists of a protein core to which negatively charged glycosaminoglycans (GAGs) are attached. The negative charge of the GAG attracts sodium and water, creating a strong osmotic pressure that is counterbalanced by the high tensile properties of the collagen II fibers. This composition provides joint cartilage with its necessary biomechanical properties, such as load distribution and a high resistance to compression and shear stress.

New imaging techniques have been focusing on the charge density of articular cartilage, which is essentially reflected by the sulfated GAG molecules. Delayed Gadolinium-Enhanced Magnetic Resonance Imaging of Cartilage (dGEMRIC) is a well-documented and validated technique to estimate cartilage GAG content and thus matrix quality[9–11]. In dGEMRIC, the clinical MRI contrast agent Gd-DTPA^{2-} is injected intravenously and, after given time to penetrate the cartilage ("delay") distributes in an inverse relationship to the likewise negatively charged GAG. Because Gd-DTPA^{2-} shortens the MRI parameter T1, the GAG content can be estimated by T1 calculations within a cartilage region, usually referred to as the dGEMRIC Index[10]. dGEMRIC studies have suggested that decreased cartilage GAG content is a significant factor in earlier phases of knee and hip OA development. Accordingly, patients with cartilage fibrillations detected at knee arthroscopy have a lower dGEMRIC Index than healthy individuals despite the absence of radiographic OA[12]. Similarly, patients with unilateral hip dysplasia but no or minimal radiographic signs of OA showed a lower dGEMRIC Index in the affected compared with the contralateral hip[13,14]. With respect to joint disease progression, dGEMRIC Index may have a prognostic value. A low dGEMRIC Index has been associated with an increased risk of developing radiographic knee OA as well as having a hip joint replacement after periacetabular osteotomy[15,16]. Experimental studies of cartilage degradation suggest a temporal pattern in the loss of cartilage molecules, where damage to the fiber-network has been considered a point of no return[17]. With respect to replacing lost or damaged molecules, dGEMRIC has indicated increased cartilage GAG content after exercise in meniscectomized patients[18].

Recently, we showed that meniscectomized subjects without radiographic OA changes demonstrate similar

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functional deficiencies as OA patients[19]. Meniscectomized subjects may thus serve as a model to study matrix-related molecular pathology before radiographic joint space narrowing (JSN) occurs.

The purpose of the present study was to examine the relationship between cartilage quality and potential risk factors for knee OA. We therefore correlated the knee cartilage GAG content using the dGEMRIC technique with body mass index (BMI), thigh muscle strength and functional performance in a group of subjects with a previous medial meniscectomy. We also compared the cartilage GAG content of the medial index compartment and the lateral reference compartment in this group of patients.

Patients and methods

PATIENTS

Patients that had an arthroscopic medial meniscectomy at the age of 35−45 were identified through the surgical code system at Malmo University Hospital. An invitation letter with a questionnaire comprising co-morbid conditions, current activity level of work and leisure time, current walking ability and knee-related problems was sent to 166 patients. To be eligible for the study, patients should be able and willing to participate in an exercise intervention during 4 months with dGEMRIC and physical tests before and after the intervention. This study reports patients at baseline. Patients were excluded if they had a cruciate ligament injury of the index knee, severe cartilage changes at the arthroscopy, steroid medication, depression, sick leave/sick pension caused by knee dysfunction, lack of outdoor walking ability or were competitive athletes. Eighty-one patients accepted the invitation and 56 that fulfilled the inclusion criteria were invited to participate in the study.

Forty-five of these patients completed the baseline tests and were included in the present study. Thirty of these 45 patients also fulfilled the exercise intervention program and the follow-up criteria. The result of the intervention in this subset of patients has been presented previously[18].

SURGERY

The meniscectomy was performed at a median of 4.4 years prior to investigation (range 1.2−5.8 years) by 19 surgeons, both staff and residents. All meniscus injuries were reported to be of degenerative nature. Only the ruptured and degenerated parts of the meniscus were excised, i.e., a partial meniscectomy. The status of the cartilage on the medial femoral condyle was stated as normal in 23 cases, shallow lesions were found in 19 cases and 4 cases were stated as localized full thickness lesions. All lateral compartments were reported as normal.

The study was approved by the Regional Ethical Review Board in Lund.

EVALUATION METHODS

The evaluation included dGEMRIC, isokinetic tests of muscle strength, a functional performance test and calculation of BMI.

dGEMRIC

A 1.5 T MRI system (Magnetom Vision; Siemens Medical Systems, Erlangen, Germany) with a dedicated knee coil was used for the examinations as previously described[12,20]. Briefly, 3 mm thick sagittal slices were positioned in the central parts of the medial and lateral femoral condyles, respectively. In these slices, T1-maps were generated, using sets of six inversion recovery images with different inversion times; repetition time (TR) = 2000 ms, echo time (TE) = 15 ms, turbo factor 11, field of view (FOV) 120 × 120 mm^2, matrix 256 × 256, inversion time (TI) = 50−1600 ms. In the T1 images, a Region of Interest (ROI) was drawn manually, by one of the authors (JT), in the medial and lateral weight-bearing femoral cartilage where OA lesions usually first appear[22,23]. Results are presented as the mean T1 of each ROI, the dGEMRIC Index.

Approximately 2 h prior to the dGEMRIC investigation[20], Gd-$DTPA^{2-}$ (Magnevist®, Schering AG, Berlin, Germany) was given intravenously at 0.3 mmol/kg body weight (triple dose). In order to increase the contrast distribution to the articular cartilage, the patient performed knee exercise during approximately 15 min on a stationary bicycle following the contrast injection[10].

All dGEMRIC Indices were corrected for BMI dosing-bias according to the formula described by Tiderius *et al.*: T1 (corrected) = T1 (measured) + 3 (BMI-20)[24].

BODY MASS INDEX

BMI was calculated by obtaining height and weight by a wall-mounted ruler and a calibrated scale. The standardized formula for BMI (kg/m^2) was used.

ISOKINETIC MUSCLE TESTING

Isokinetic muscle strength was measured with a computerized dynamometer, Biodex® (Biodex System III Pro with Biodex Advantage Software), which is a commonly used and validated instrument for muscular testing[25]. Isokinetic strength of the knee extensors and flexors was tested at the angular velocity of 60°/s in the range of 15−95° of flexion. The subject was sitting with the thigh supported with 90° hip flexion and the arms folded over the chest. The body and thigh were secured to the chair with straps. Identical oral instructions were given to all patients. We measured concentric Peak Torque in Newton meter (Nm), which refers to the highest registered muscle contraction, evaluated as force times length of the moment arm over a certain joint. In order to allow comparisons between individuals, Peak Torque was calculated in percentage of body weight.

FUNCTIONAL PERFORMANCE (ONE-LEG HOP TEST)

For the functional performance, we used the one-leg hop test described by Tegner *et al.*, which has been shown reliable in both sedentary individuals and athletes[26]. The subject, standing on one foot, with his hands on the back, was asked to jump as far as possible and land steadily on the same foot. The subject had to be able to land and stand on one leg long enough for the examiner to measure the hop distance. The test was repeated at least three times, or as long as the subject made further progress. The best result was recorded.

SUMMARIZED TESTS PROCEDURE

After informed consent, height and weight were obtained. Magnevist® was given intravenously, followed by the bicycle warm-up and the one-leg hop test. Isokinetic strength of the lower extremities was then measured. The same examiner (YE) investigated all patients. Finally, the dGEMRIC analysis was performed approximately 2 h after the contrast injection.

STATISTICAL ANALYSIS

We used the Statistical Package for the Social Sciences (SPSS 14.0) for the statistical analyses. To compare dGEMRIC Index for medial and lateral compartments we used the paired samples *t*-test. The muscle strength values, BMI and functional parameters were correlated to dGEMRIC Index using Spearman's correlation. No corrections for multiple comparisons were made for the correlation analysis.

Results

Fifty-six patients met the study criteria and 45 of these (16 women) accepted MRI examination. There were no differences between men and women regarding age ($P = 0.21$), BMI-level ($P = 0.69$), strength ($P = 0.12-0.86$), one-leg hop test ($P = 0.28-0.98$) or self-reported knee pain ($P = 0.64$). The mean BMI value for the group was 26.5, range 20.0−34.3 (Table I). Thirty-one patients (69%) had a BMI > 25. Nine patients (20%) were considered obese with a BMI of 30 or above.

dGEMRIC INDEX

In the medial compartment, the mean dGEMRIC Index was 14.4% lower (374 ± 61 ms, mean ± SD) than in the lateral reference compartment (437 ± 59 ms, mean ± SD), consistent with a lower GAG content medially ($P < 0.001$).

There was no difference in the dGEMRIC Index between men and women ($P = 0.46$ medial, $P = 0.85$ lateral). Neither was there any correlation between the dGEMRIC Index and age ($r = -0.19$, $P = 0.21$ medial, $r = -0.21$, $P = 0.16$ lateral) nor between the time-span from meniscectomy to the dGEMRIC analysis ($r = 0.07$, $P = 0.66$ medial, $r = -0.02$, $P = 0.88$ lateral).

Table I
*Descriptive characteristics, strength and performance measures and dGEMRIC Index of the study group**

Characteristic	Value
Age, years	45.7 (3.2)
Men/women, *n*	29/16
Time since surgery in years	3.9 (1.3)
Higher/lower activity level, *n*	30/15
BMI, kg/m^2	26.5 (3.3)
Knee pain? Yes/No	33/12
Operated knee, Right/Left	26/19
Knee extensor strength† (%)	193 (48)
Knee flexor strength† (%)	103 (28)
One-leg hop (cm)	108 (33)
dGEMRIC Index medial (ms), corrected	374 (61)
dGEMRIC‡ Index, medial (ms), uncorrected**	355 (65)
dGEMRIC Index, lateral (ms), corrected	437 (59)
dGEMRIC‡ Index, lateral (ms), uncorrected**	417 (60)

Higher activity level = recreational sports as golf, hiking, biking, lower activity level = yard work, shopping, etc.

*Values are the mean ± SD unless otherwise indicated.

†Knee extensor/flexor strength = Peak Torque/body weight at 60°/s.

‡Medial = femoral cartilage of medial knee compartment, lateral = femoral cartilage of lateral knee compartment.

**dGEMRIC Indices corrected for BMI dosing-bias are presented. Uncorrected dGEMRIC Indices are presented in order to facilitate comparisons with previously published studies.

MUSCLE STRENGTH, FUNCTIONAL PERFORMANCE, BMI AND dGEMRIC INDEX

With respect to the medial femoral cartilage, the dGEMRIC Index correlated positively with both knee flexor and knee extensor strength relative to body weight, ($r = 0.50$, $P = 0.001$ and $r = 0.47$, $P = 0.001$, respectively) (Fig. 1a, Table II). After *controlling* for BMI, we found that the association between muscle strength and the dGEMRIC Index persisted ($r = 0.46$, $P = 0.002$ and $r = 0.37$, $P = 0.012$). Similarly, there was a positive correlation between the dGEMRIC Index and the one-leg hop test ($r = 0.42$, $P = 0.004$) (Table II). Regarding dGEMRIC Index and BMI, we found a negative correlation ($r = -0.35$, $P = 0.019$) (Fig. 2a, Table II).

With respect to the lateral compartment, there were only weak and non-significant correlations between the dGEMRIC Index and muscle strength (Fig. 1b) and one-leg hop test ($r = -0.01$–0.14, $P > 0.38$) (Table II). There was only a trend towards a negative association between the lateral dGEMRIC Index and BMI ($r = -0.15$, $P = 0.32$) [Fig. 2(b), Table II].

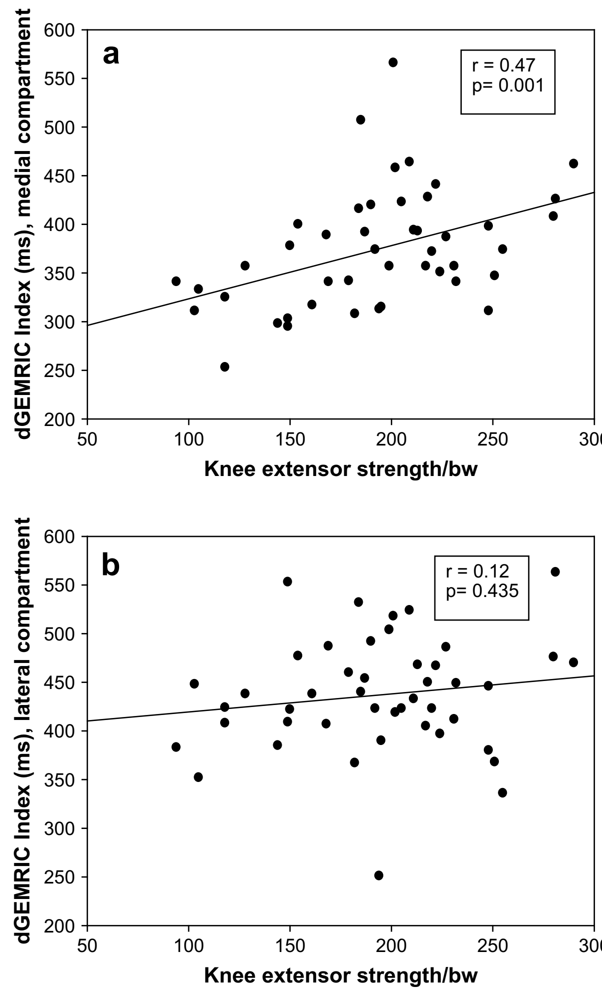

Fig. 1. (a) Scatter plot of medial compartment dGEMRIC Index vs knee extensor strength. The figure illustrates that increasing quadriceps strength relative to body weight is associated with increasing dGEMRIC Index medially ($r = 0.47$, $P = 0.001$). (b) Scatter plot of lateral compartment dGEMRIC Index vs knee extensor strength. The figure illustrates that there is only a weak association between quadriceps strength and lateral dGEMRIC Index ($r = 0.12$, $P = 0.435$).

Discussion

In the present study of patients having had a medial meniscectomy, we provide evidence that the molecular status of the femoral cartilage in the diseased compartment is related to both impaired muscle function and high BMI, two factors that according to the literature are of importance for knee OA development. To our best knowledge, this is the first study to demonstrate a relationship between dGEMRIC Index and tests of muscle function. Furthermore the inverse relationship between dGEMRIC Index and BMI has previously been shown only in patients with established OA[24].

The positive correlation between muscle strength and the dGEMRIC Index of the medial compartment, irrespective of BMI, indicates that better thigh muscle strength is associated with higher cartilage GAG content[9]. Muscles have a joint protective function as they stabilize the joints, have a shock absorbing capacity, control movements and generate sensory information[27,28]. If the muscles fail to absorb forces across the joint properly, more force will be transmitted to the cartilage and bone. According to the muscular dysfunction theory, this may cause microtrabecular damage and sclerosis in the subchondral bone which in turn may alter the stresses and strains across the articular cartilage eventually leading to cartilage degradation[29,30]. However, the opposite may also be true, the decreased cartilage GAG content suggested in the present study that impairs the biomechanics of the cartilage may alter the subchondral bone stress with subsequent sclerosis. Nonetheless, after meniscectomy, the altered joint biomechanics result in a higher pressure per unit cartilage area during gait[31,32], which implies that meniscectomized knee joints have less capacity for load distribution. Muscular stabilization of the knee joint may be of particular importance after

Table II

Correlations between variables. All muscular parameters were positively correlated to medial dGEMRIC Index, whereas BMI was negatively correlated to medial dGEMRIC Index*

	dGEMRIC Index, medial†	dGEMRIC Index, lateral‡	Knee extensor strength**	Knee flexor strength**	One-leg hop	BMI
dGEMRIC Index, medial†	–	–	–	–	–	–
dGEMRIC Index, lateral‡	**0.5 (<0.001)**	–	–	–	–	–
Knee extensor strength**	**0.47 (0.001)**	0.12 (0.435)	–	–	–	–
Knee flexor strength**	**0.50 (0.001)**	0.14 (0.376)	**0.79 (<0.001)**	–	–	–
One-leg hop	**0.42 (0.004)**	0.06 (0.716)	**0.86 (<0.001)**	**0.73 (<0.001)**	–	–
BMI	**−0.35 (0.019)**	−0.15 (0.316)	−0.26 (0.086)	−0.23 (0.123)	**−0.30 (0.047)**	–

dGEMRIC Index = relaxation time expressed as T1-value.

*Correlation analyses were performed according to Spearman, *r*-values are presented with *P*-values within brackets. Significant correlations are bolded.

†Medial = femoral cartilage of medial knee compartment.

‡Lateral = femoral cartilage of lateral knee compartment.

**Strength = Peak Torque/body weight at 60°/s.

meniscectomy, because that procedure has been suggested to increase joint laxity[33].

The positive correlation between the functional performance, assessed with one-leg hop, and medial dGEMRIC Index implies that patients who jump farther have a better cartilage quality. The one-leg hop test reflects strength but also challenges functional knee stability and balance. This result may therefore imply higher cartilage GAG content in physically more active individuals. In support, differences in the dGEMRIC Index have previously been shown in healthy subjects with different habits of physical activity[34].

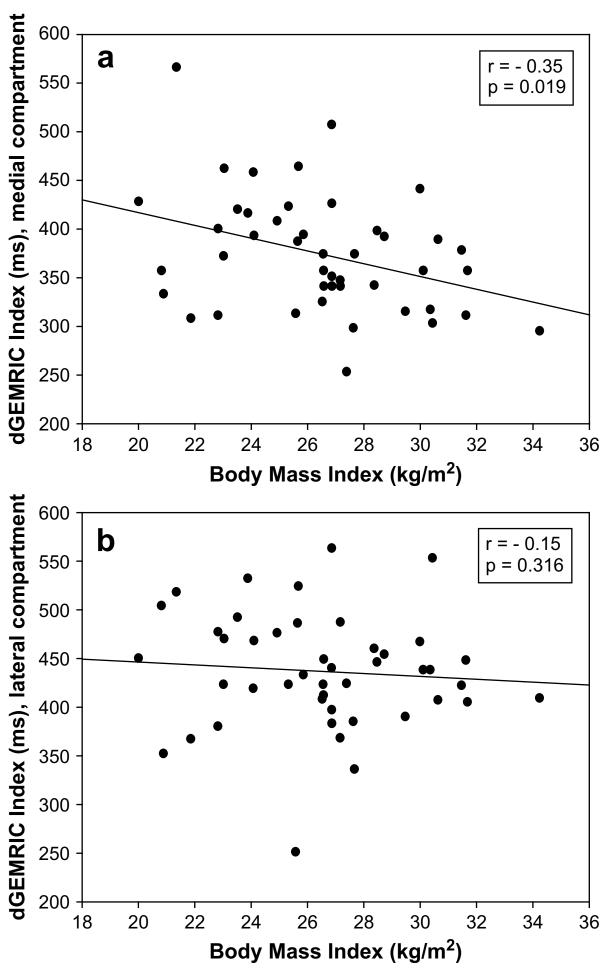

Fig. 2. (a) Scatter plot of medial compartment dGEMRIC Index vs BMI. The figure illustrates that increasing BMI value is associated with decreasing dGEMRIC Index medially ($r = -0.35$, $P = 0.019$). (b) Scatter plot of lateral compartment dGEMRIC Index vs BMI. The figure illustrates that there is only a weak association between lateral dGEMRIC Index and BMI ($r = -0.15$, $P = 0.316$).

Many authors have suggested a link between muscle function and knee joint disease[7,8,30,35], but still the mechanism behind this is not fully explored. The association between reduced muscle strength and knee OA is well documented, but it is not clear which comes first, the weakening or the osteoarthritic changes. It is often assumed that intra-articular damage precedes muscle weakness but Slemenda *et al.*[7] and Thorstensson *et al.*[8] have shown that reduced knee extensor strength is a predictor of radiographic knee OA in subjects with knee pain. There has been a similar discussion with regard to BMI and OA, however, the Framingham study finally showed that a high BMI was a cause for OA rather than a consequence[5]. Quadriceps strengthening has proven to give symptom relief and improved function in patients with knee OA[36], but evidence on the capability of muscle strengthening to prevent OA incidence or OA progression is still insufficient. In a recent randomized study of older adults who performed either muscle strength training or range of motion (ROM) exercises over a 30-month period, a lower prevalence of radiographic progression of knee OA was seen in the strength training group than in the ROM group[37]. If training of muscle strength and muscular control is given in early stage OA, one may speculate that in addition to improved neuromuscular function that can give symptom relief, the biomechanical properties of the cartilage could improve by increasing the GAG content. A high GAG content improves the mechanical stiffness and may decrease the stress to the cartilage fibernetwork. It has been suggested in animal models[38–40] that moderate exercise may protect against cartilage degradation. In a subset of patients in the present study it has previously been shown that exercise during 4 months seems to increase the cartilage GAG content in meniscectomized patients[18].

The negative correlation between BMI and the dGEMRIC Index indicates that a high BMI is related to a low GAG content which potentially increases the risk for OA in meniscectomized patients. Our results are consistent with a recent study of patients with unicompartmental radiographic knee

OA[24]. In the compartment without radiographic JSN, there was a negative correlation between the dGEMRIC Index and BMI. In the compartment with JSN, the dGEMRIC Index was generally very low but without correlation with BMI. The authors suggest that a high BMI is a risk factor for disease progression in OA, whereas in cases with established radiographic changes, a floor-effect in terms of GAG loss has already been reached[24]. That study also showed that there is a dose-bias inherent with the dGEMRIC technique in obese subjects. Because Gd-DTPA^{2-} distributes only in the extra-cellular water, obese individuals will receive a higher Gd-DTPA^{2-} concentration in the cartilage than lean individuals when dosing by weight. Consequently, the dGEMRIC Index in obese individuals will be falsely too low when dosing by weight[24]. In that study a formula for dose-correction was calculated, based on plasma experiments of Gd-DTPA^{2-} concentration in patients with different BMI. In the present study, all dGEMRIC values have been corrected accordingly[24].

The increased risk for knee OA in obese individuals has been attributed mainly to biomechanical factors[41]. In patients that are obese, joint reaction forces after meniscectomy may rise to harmful levels also during normal activities. Englund and Lohmander found in a follow-up 22 years after meniscectomy, that subjects with obesity had a greater likelihood of tibiofemoral radiographic OA than those with normal weight[42]. In addition, instability following meniscectomy may lead to changes in contact position, which means a shift of load to regions of the cartilage that cannot resist chronic ambulatory loading[43].

The association between meniscus injury/surgery and subsequent OA is well established[4,33,44]. Recently published studies suggest that a meniscus injury in the middle-aged patient can be considered as an early sign of OA, because the meniscal tear is part of a degenerative process affecting the whole joint[45]. The lack of association between the dGEMRIC Index and the time-span between the meniscus surgery and the dGEMRIC investigation in the present study (1–6 years) supports impaired cartilage quality already at the time for the meniscectomy. Accordingly, molecular OA-related cartilage changes are likely present in knees sustaining a degenerative meniscus injury. This is further supported by the fact that symptoms and function are similar in meniscectomized patients and patients with radiographic OA[19]. It is intriguing that the dGEMRIC Index in the medial compartment of these meniscectomized patients is 14% lower than that of previously investigated healthy volunteers and similar to what has previously been found in patients with arthroscopic fibrillations that subsequently developed radiographic OA changes[16,20].

We conclude that the lower dGEMRIC Index of the medial compartment suggests decreased cartilage GAG content after medial meniscectomy, indicating an early stage OA. Furthermore, results suggest that overweight is a factor that deteriorates cartilage, whereas strong and co-ordinated leg muscles may have a protective effect on the cartilage integrity.

Conflict of interest

The authors of the manuscript "Relationship between cartilage glycosaminoglycan content (dGEMRIC) and OA risk factors in meniscectomized patients" declare that they have no financial or personal relationships that could bias their work.

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