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The association of cartilage volume with knee pain

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Summary

Objective: Whilst the characteristic pathologic feature of OA is the loss of hyaline cartilage, prior studies have demonstrated a poor relationship between severity of reported knee pain and degree of radiographic change. The aim of this study was to examine the association between knee symptoms and MRI cartilage volume.

Design: A cross-sectional study was performed to assess the association between knee symptoms and MRI cartilage volume in an unselected, community based population. The subjects were 133 postmenopausal females. The subjects had a T2-weighted fat saturated sagittal gradient-echo MRI performed of their right knee. Femoral, tibial and patella cartilage volumes were measured using three-dimensional (3D) Slicer, a software that facilitates semi-automatic segmentation, generation of 3D surface models and quantitative analysis. Qualitative data relating to symptoms, stiffness, pain, physical dysfunction and the quality of life using the WOMAC were recorded. The statistical analyses conducted to determine measures of association between knee pain/symptoms and cartilage volume were correlation, multiple regression and inter-quartile regression.

Results: Assessment of the association between patella cartilage volume and the WOMAC domains showed an inverse relationship between patella cartilage volume and pain, function and global score in a model including body mass index, physical activity and leg extensor power (all $P=0.01$). Inter-quartile regression comparing the lowest 25% with highest 25% patella cartilage volume demonstrated a stronger inverse relationship ($P=0.005$).

Conclusion: This study suggests that alterations in patella volume are associated with pain, function and global scores of the WOMAC. In participants with more knee pain, there was an association with severity of patella cartilage reduction. Other MRI cartilage volume features were not strongly associated with WOMAC sub-scores.

Key words: Cartilage volume, Knee, Pain, Patella.

Introduction

The knee joint is a frequent site of pain in osteoarthritis (OA)[1], but the mechanisms that lead to knee pain in OA remain unclear[2]. Traditionally, radiographic appearance has been the cornerstone of diagnosis because the effects of the pathological processes can be identified as features on the X-ray: joint space narrowing, subchondral sclerosis and osteophyte formation. However, less than 50% of people with evidence of OA on plain radiographs have symptoms related to these findings[3,4], with substantive evidence demonstrating a poor relationship between severity of reported knee pain and degree of radiographic change[5–7].

The syndrome of OA is a multifactorial process characterized by changes in structure and function of the joint with the central component being degradation and subsequent loss of articular cartilage[8]. Whilst the characteristic pathologic feature of OA is the loss of hyaline cartilage this tissue does not contain pain fibers. Pain fibers are present in several other structures, however, that are often affected by pathologic processes in knee OA, including the joint capsule, ligaments in and around the knee joint, the outer third of the meniscus, possibly the synovium, the bone in the periosteum and the bone marrow[9]. However, cartilage loss on arthroscopy appears to show substantial correlation with pain and disability[10]. Because cartilage in OA holds such a central position in the etiopathogenesis, pathological investigations and drug development for OA it is critical to understand whether it is clinically meaningful; that is, whether it relates to pain and/or function.

In OA of the knee, cartilage is lost slowly. It can take decades for cartilage to thin from its typical thickness of a few millimeters to complete loss, and this rate of loss is highly variable between individuals[11]. Techniques for measuring joint space width (JSW) in the medial tibiofemoral compartment, taken from carefully acquired radiographs, have become accepted for quantifying changes in articular cartilage thickness in the medial compartment of OA knee[12]. JSW reliably measures cartilage thickness from tibial plateau and distal portion of the femoral condyle in one combined measurement, especially when image-processing techniques are applied to digitized radiographs[13]. Such techniques only examine one anatomical

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site, and cartilage loss occurs throughout the joint. Most frequently, femoral cartilage lesions occur at, or posterior to, the most distal point on the femoral condyles[14], and the more posteriorly sited lesions would be missed on a single semi-flexed radiographic view. Moreover, it only provides an indirect assessment of cartilage thickness.

Until recently, development in our understanding of OA was limited by the lack of sufficiently sensitive endpoints to detect early OA and small changes in progression. Understanding of this disease and our ability to establish efficacious treatment strategies have been confounded by the inability to easily visualize the state of cartilage. Magnetic resonance imaging (MRI) has many advantages in providing such visualization, and recent efforts are yielding a variety of approaches that offer the potential for monitoring cartilage degradation non-destructively. MRI of the knee has the advantage of covering the whole joint in one examination. Various researchers have used cartilage volume and thickness measured from MRI of the knee to examine both normal and arthritic cartilage in patients[15,16]. Recent research using MRI suggests an association between bone marrow lesions and the presence of pain in knee OA[17].

The aim of this study was to examine the association between knee symptoms and MRI cartilage volume in an unselected, community based population.

Materials and methods

DESIGN

A cross-sectional single center study of postmenopausal female twin pairs recruited from the general population via a media campaign was carried out.

STUDY POPULATION

The subjects were 133 postmenopausal females (age range 49–80 years) from the Australian National Health and Medical Research Council (NHMRC) twin registry, a volunteer sample recruited through a local media campaign. Research was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association and was approved by the hospital's Human Research Ethics Committee. Consent was obtained from each subject after full explanation of the purpose, nature and risk of all procedures used.

DATA ASCERTAINMENT

Demographic information was obtained by a standardized investigator-administered questionnaire. The following data were collected: personal details and lifestyle factors, physical activity (Framingham Physical Activity Index[8]), usual and past use of tobacco, menstrual cycle patterns and use of oral contraceptives and reproductive history, occupational history and past knee injury/trauma. In addition, qualitative data relating to symptoms, stiffness, pain, physical dysfunction and the quality of life using the WOMAC[19] were recorded. Lower limb strength was measured on the Nottingham dynamic leg extensor power rig[20]. Finally, clinical assessment was performed. This included a medical history concentrating on joint, bone, major organ disease, the use of medications, height, weight and clinical examination of the knees, hips and hands. OA was classified using the ACR Clinical Criteria[21].

MAGNETIC RESONANCE IMAGING

Knees were imaged on a 1.5-T whole body magnetic resonance unit (Signa Advantage GE Medical Systems Milwaukee, WI) using a commercial transmit–receive extremity coil. The following image sequence was performed: three-dimensional (3D) spoiled gradient-echo (SPGR) images; flip angle 40°; repetition time 30 ms; echo time 7 ms; field of view 13 cm; bandwidth 16 kHz; 256×256 matrix; slice thickness 1.2 mm; acquisition time 5 min 42 s; one acquisition. This method of acquisition has been previously validated for cartilage volume measurements[22,23].

VOLUME MEASUREMENT

Cartilage volumes were measured using 3D Slicer, a software that facilitates semi-automatic segmentation, generation of 3D surface models and quantitative analysis[24]. The measurement time to assess cartilage volume for each subject was approximately 20 min. The process incorporated automated intensity based segmentation, with manual separation of femoral, tibial and patella cartilages and correction of errors.

REPRODUCIBILITY

Reproducibility of this method was previously examined on a sample of 10 subjects[25]. Three observers trained in interpretation of musculoskeletal MRI held three standardization sessions to minimize inconsistencies and independently measured cartilage volumes on all of the subjects blinded to patient details. One observer repeated these measures a fortnight later. The intraclass correlation (ICC) was computed from the analysis of variance on the variation in cartilage volume explainable by different observers. The intra-observer ICCs were 0.99 (95% CI 0.98–1.00) for tibial, patella and femoral cartilage volumes, whereas the ICCs were 0.96 (95% CI 0.92–1.00) for femoral cartilage volume and 0.97 (95% CI 0.94–1.00) for tibial and patella cartilage volumes. The mean (range) cartilage volumes for the 10 subjects were patella, 2.1 ml (1.0–3.4); tibia, 3.5 ml (1.7–6.4) and femoral, 8.9 ml (5.4–14.2). The precision of this method after subject re-positioning in the MRI machine has not been assessed.

STATISTICAL ANALYSIS

The aim of the analysis was to examine the association of knee pain/symptoms with cartilage volume.

Firstly, association was assessed by constructing a correlation matrix of the variables of interest, namely the various domains of the WOMAC and the cartilage volume measures were obtained. Where an association was detected, the influence of confounders was assessed by adjusting for age, body mass index (BMI), physical activity, leg extensor strength and relatedness using a generalized estimating equation. The strength of association between symptom score and cartilage volume was further assessed in a stepwise regression model with backward elimination, after adjustment using forced entry for the following independent variables: age, BMI, physical activity and leg extensor strength. Subsequent regression of the difference in quantiles for significant variables was estimated from the variance–covariance matrix of the estimators. Data

Table I
Characteristics of population studied (mean (SD))

	Total (*n*=133)	Knee pain (*n*=97) (WOMAC pain domain>0)	No knee pain (*n*=36) (WOMAC pain domain=0)
Age (years)	60.1 (7.7)	61.1 (7.4)	58.4 (8.9)
Height (cm)	159.9 (6.3)	160.1 (6.2)	158.3 (6.7)
Weight (kg)	65.5 (11.6)	66.4 (12.1)	61.1 (10.4)*
BMI (kg/m^2)	25.6 (4.4)	25.9 (4.7)	24.3 (3.4)
Physical activity†	34.5 (5.9)	34.8 (6.1)	33.9 (5.3)
Previous knee injury (%)	34.4	38.1	19.4
Leg extensor power (W)‡	62.6 (25.1)	61.3 (25.3)	65.3 (24.7)
Knee OA by ACR Clinical Criteria¶	19 Right, 12 left, 9 bilateral	19 Right, 12 left, 9 bilateral	
Femoral cartilage volume (ml)	10.0 (2.1)	10.2 (2.0)	9.4 (1.9)
Tibial cartilage volume (ml)	4.5 (1.2)	4.5 (1.3)	4.3 (0.9)
Patella cartilage volume (ml)	2.9 (0.8)	2.9 (0.8)	2.8 (0.7)
Total cartilage volume (ml)	17.3 (3.5)	17.6 (3.7)	16.5 (3.1)

*Significant difference between two groups (P=0.02).
†Framingham Physical Activity Index[18].
‡Nottingham University leg extension power rig[20].
¶OA was classified using the ACR Clinical Criteria[21].

analysis was performed and intraclass correlations were estimated using STATA[26].

Results

The basic characteristics of the subjects studied are demonstrated in Table I. One hundred and thirty-three postmenopausal females, mean age 60.1 years (range=49–80 years), mean BMI 25.6 (SD=4.4), were recruited. Subjects with knee pain (WOMAC pain domain>0) were on average 3 years older, 1.8 cm taller, 5.3 kg heavier, had weaker leg extensor power of 4 W and were more likely to have had a previous knee injury than those without knee pain.

Qualitative data relating to the domains of the WOMAC are presented in Table II. These represent those subjects who had a pain score>0. This shows a wide range for all three domains and the global score although the majority would be considered mild.

The correlation between the WOMAC domains and the cartilage volume measures is presented in Table III. There was an inverse correlation between patella cartilage volume and WOMAC sub-scores for pain, function and global score. GEE adjustment for relatedness did not alter the results.

Further assessment of the association between patella cartilage volume and the WOMAC domains is presented in Table IV. This shows an inverse relationship between patella cartilage volume and pain, function and global score (all P=0.01) with an R^2 of 40% or greater with a model including age, BMI, physical activity and leg extensor power. BMI was the only other independently significant predictor for the outcome measures of pain and function.

Table II
WOMAC characteristics of pain population (mean (SD) of 97 postmenopausal females)

WOMAC domain	
Pain (/50)	5.5 (4.6) (Range=0.1–29.6) (Median=3.2)
Stiffness (/20)	4.4 (4.5) (Range=0–18.1) (Median=3)
Function (/170)	21.3 (23.3) (Range=1–109.7) (Median=12.6)
Global (/240)	31.2 (31.8) (Range=1.9–154.1) (Median=17.1)

The strength of this association was stronger if the delineation of the pain groups compared was set at higher cut-points for pain (e.g., pain>2 (P=0.008) and pain>5 (P=0.008)).

Assessments of the inter-quartile regression are presented in Table V. Comparing the lowest 25% patella cartilage volume with highest 25% cartilage volume showed an inverse relationship (P=0.005). This suggests

Table III
Correlation coefficients for relationship between WOMAC and MRI findings

	Pain	Stiff-ness	Function	Global
Femoral cartilage volume	0.01	–0.08	–0.05	–0.04
Tibial cartilage volume	–0.00	–0.07	–0.05	–0.05
Patella cartilage volume	–0.21	–0.11	–0.23	–0.22
Total cartilage volume	–0.04	–0.10	–0.10	–0.09

Table IV
Association between pain and patella volume in a stepwise multiple regression model (after adjustment using forced entry for the following independent variables: age, BMI, physical activity and leg extensor power)

	R^2	Measure	Coefficient (95% CI)	*P* value
Pain	0.40	BMI	0.3 (0.2 to 0.4)	0.000
		Patella	–1.2 (–2.1 to –0.2)	0.01
Function	0.42	BMI	1.2 (0.7 to 1.6)	0.000
		Patella	–4.8 (–8.5 to –1.0)	0.01
Global	0.45	BMI	1.7 (1.1 to 2.2)	0.000
		Patella	–6.5 (–11.6 to –1.4)	0.01

Table V
Difference in quartiles (25–75%) for WOMAC domains and patella cartilage volume (unadjusted variables)

WOMAC domain	Coefficient (95% CI)	*P* value
Pain	–2.2 (–3.7 to –0.7)	0.005
Function	–8.4 (–15.2 to –1.6)	0.02
Global	–11.9 (–16.5 to –7.3)	0.000

that more extreme the populations compared, the stronger the inverse relationship.

Discussion

This study suggests that alterations in patella volume are associated with pain, function and global scores of the WOMAC. In participants with less patella cartilage volume, there was an association with severity of pain. Other MRI cartilage volume features were not strongly associated with WOMAC sub-scores.

Epidemiological research has previously relied upon a global definition of OA incorporating X-ray features of both osteophytes and joint space narrowing. Whilst this may be more sensitive in radiographic surveys[27], seeking links between radiographic change and symptoms may be more successful if individual features are incorporated[17,28,29]. Previous research has demonstrated that bone marrow edema, knee effusions, popliteal cysts and synovial thickening are associated with pain in OA[17,28]. The results of this study suggest another individual feature that should be included in knee OA MRI assessment is patella cartilage volume.

This supports previous research that has shown that symptomatic knee OA may often be related to patellofemoral disease that is not revealed by conventional antero-posterior radiographs[30,31]. Our study confirms the suggestion that joint space narrowing, previously detectable on skyline views, is a major cause of disability in OA (independent of age, BMI, physical activity and leg extensor power). This study also confirmed BMI as a predictor of both pain and loss of function.

Data from the Framingham OA study[4] and from the Boston OA of the Knee study[32] suggest that including lateral radiographs (assessing patellofemoral disease) produces a greater concordance between clinical symptoms and radiographic OA. McAlindon *et al.* showed that patellofemoral joint OA was significantly associated with disability (64 vs 25% in controls)[31].

There are a number of limitations to these findings that need to be considered. The results are cross-sectional and any relationship between patella cartilage volume and pain should be corroborated in a longitudinal study.

Cartilage contains no nociceptive nerve fibers, hence the source of this pain is currently unexplained. One likely possibility is that the reduction in cartilage alters the biomechanical load through the retropatellar surface, placing greater deforming stress upon the underlying subchondral bone.

The qualitative assessment of symptoms did not consider the distribution of pain around the knee and further assessment should elucidate whether this pain is more anterior than either lateral or medial for example.

The number of subjects who had OA defined by ACR Clinical Criteria is small ($n=22$). It would be interesting to repeat this research in a larger sample with a broader representation of disease severity.

One limitation of conventional weight-bearing antero-posterior knee radiograph, in which the joint is imaged in extension, is that changes in knee pain may affect extension, thereby altering the apparent thickness of the articular cartilage[33]. Unlike plain radiography, MRI provides a direct assessment of cartilage volume so this is unlikely to affect the results.

In this population-based sample there is a suggestion that knee symptoms relate more to patella volume than other cartilage volumes. Further research on OA should include an assessment of patella cartilage volume. This finding has important implications for future epidemiological research and clinical trials evaluating interventions purported to have symptom modifying benefit through structural modification.

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