Sex differences in knee cartilage volume in adults: role of body and bone size, age and physical activity

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Objective. To test the hypothesis that sex differences in knee cartilage volume may be mediated through body and bone size, age and/or physical activity.

Methods. A cross-sectional convenience sample of 372 subjects (males 43%; mean age 45 yr, range 26–61) was studied. Articular cartilage volumes and bone size were determined at the patella, medial and lateral tibia by processing images acquired in the sagittal plane using T1-weighted fat saturation magnetic resonance imaging. Height, weight, physical activity (lower limb muscle strength, endurance fitness and questionnaire items) and radiographic osteoarthritis (ROA) were measured.

Results. Gender explained 33–42% of the variation in knee cartilage volumes (all \( P < 0.001 \)). Males had 33–42% higher cartilage volume than females at all sites. In the whole group, the magnitude of sex differences decreased to 8–18% after adjustment for body height, weight and bone size, but remained significant (all \( P < 0.05 \)). Further adjustment for physical activity had no effect on the sex differences. The sex differences in cartilage volume were greater in those aged over 50 compared with those aged under 50 (\( P < 0.05 \) for age–sex interaction at all sites) and were independent of ROA.

Conclusions. Men have substantially higher knee cartilage volumes than women. These sex differences appear to be mediated in part by body and bone size but a significant amount remains unexplained. Furthermore, the differences become more marked over the age of 50 yr suggesting that both cartilage development and cartilage loss in later life contribute to sex differences in cartilage volume. Further longitudinal studies in large samples will be required to confirm these findings.

Key words: Knee, Cartilage, Volume, Sex, Age.

Osteoarthritis (OA) is a slowly progressive degenerative disease characterized by gradual loss of articular cartilage. It has a higher prevalence and is more often generalized in women than in men. Before the age of 50 yr, the incidence of this disease is low and men have a slightly higher prevalence than women, but after age 50, the disease becomes more frequent and women have a much higher prevalence [1, 2]. The reason for this variation is currently unknown, but sex differences in cartilage volume are a potential explanation.

We previously reported that males had significantly more knee cartilage than females in healthy children even after adjustment for other confounders and concluded that sex-related differences in cartilage development might be one explanation for sex variation in knee OA observed in later life [3]. In adults we reported that men had significantly larger patellar and femoral cartilage volume than women, independently of body and bone size. Tibial cartilage volume was larger in men but became non-significant after adjustment for body and bone size [4]. Faber et al. [5] reported sex differences of similar magnitude in tibial and femoral but not patellar cartilage volume in young healthy subjects. These differences became non-significant after adjustment for
Subjects and methods

The study was carried out in Southern Tasmania (latitude 42° south) primarily in the capital city of Hobart from June 2000 until December 2001. It was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee and all subjects provided informed written consent.

A convenience sample was utilized for this study. Subjects were selected from two sources. Half of the subjects were the adult children of subjects who had a knee replacement performed for primary knee osteoarthritis at any Hobart hospital in the years 1996–2000. This diagnosis was confirmed by reference to the medical records of the orthopaedic surgeon and the original radiograph where possible. The other half were randomly selected controls. These were selected by computer-generated random numbers from the most recent version of the electoral roll (2000). Subjects from either group were excluded on the basis of contraindication to magnetic resonance imaging (MRI) (including metal sutures, presence of shrapnel, iron filing in eye and claustrophobia). No women were on hormone replacement therapy at the time of the study. Knee pain was allowed in both groups.

Weight was measured to the nearest 0.1 kg (with shoes, socks and bulky clothing removed) using a single pair of electronic scales (Seca Delta Model 707) which were calibrated using a known weight at the beginning of each clinic. Height was measured to the nearest 0.1 cm (with shoes and socks removed) using a stadiometer. Body mass index (BMI) (kg/m²) was calculated.

Physical activity measures included lower limb muscle strength, endurance fitness and questionnaire items. Lower limb muscle strength (to the nearest 1.0 kg) was measured by dynamometry (TTM Muscle Meter, Tokyo, Japan). The muscles measured with this technique are mainly the quadriceps and hip flexors. Subjects were instructed in the technique before testing. The reproducibility of muscle strength testing results in our laboratory is excellent (intraclass correlation coefficient, ICC, 0.91) [3]. Endurance fitness was measured by use of bicycle ergometric testing [6]. Subjects were asked to cycle at a constant 60 rpm for 3 min each at three successively increasing but submaximal workloads. Work capacity at 170 beats/min was assessed by linear regression with extrapolation of the line of best fit to a heart rate of 170 beats/min. Physical activity was retrospectively assessed in the year prior to study entry using a questionnaire [7] which was modified after piloting to include popular Australian sports. The test–retest Spearman correlation of overall leisure physical activity in hours/week over the last year was found to be 0.66. This questionnaire has demonstrated predictive validity in our hands [3]. Subjects were unaware of their MRI results at the time of questionnaire completion. This questionnaire has items on days of either strenuous activity or light activity for greater than 20 min in the last two weeks [(1) none, (2) 1–2 days, (3) 3–5 days, (4) 6–8 days, (5) 9 or more days]; daily television watching in last week [(1) none, (2) 1 or less hours, (3) 2–3 h, (4) 4–5 h, (5) 6 or more hours]; number of competitive sports in the last 12 months [(1) none, (2) one, (3) two, (4) three, (5) four or more] and activities done at least 10 times in the last 12 months.

A standing anteroposterior semi-flexed view of the right knee was performed in all subjects. Radiographs were then assessed utilizing the Altman atlas [8]. Each of the following was assessed: medial joint space narrowing (0–3), lateral joint space narrowing (0–3), medial osteophytes (femoral and tibial combined) (0–3) and lateral osteophytes (femoral and tibial combined) (0–3). Each score was arrived at by consensus with two readers (GJ, FS) simultaneously assessing the radiograph with immediate reference to the atlas. Reproducibility was assessed in 50 radiographs, 2 weeks apart and yielded an ICC of 0.99 for osteophytes and 0.98 for joint space narrowing. This may represent an overestimate of the actual agreement owing to the high proportion of normal radiographs. However, this method also has very high reproducibility in our hands for radiographic osteoarthritis (ROA) of the hands with ICCs of 0.94–0.98 [9].

An MRI scan of the right knee was also performed. Knee cartilage volume was determined by means of image processing on an independent workstation using the software program Osiris as previously described [3, 4, 10, 11]. Knees were imaged in the sagittal plane on a 1.5–T whole-body magnetic resonance unit (Picker) with use of a commercial transmit–receive extremity coil. The following image sequence was used: a TI-weighted fat saturation 3D gradient recall acquisition in the steady state; flip angle 55°; repetition time 58 ms; echo time 12 ms; field of view 16 cm; 60 partitions; 512 × 512 matrix; acquisition time 11 min 56 s; one acquisition. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31 × 0.31 (512 × 512 pixels). The image data were transferred to the workstation. The volumes of individual cartilage plates (medial tibial, lateral tibial and patella) were isolated from the total volume by manually drawing disarticulation contours around the cartilage boundaries on a section by section basis. These data were then resampled by means of bilinear and cubic interpolation (area of 312 and 312 × 312 × 312) for the final 3D rendering. The volume of the particular cartilage plate was then determined by summing all the pertinent voxels within the resultant binary volume. Femoral cartilage volume was not assessed as we have previously published that two tibial sites and the patella site correlate strongly (0.75–0.77) with this site [10]. Using this method we had high intra- and interobserver reproducibility. The coefficient of variation (CV) at our institution for total cartilage volume measures in children was 2.1% for medial tibial, 2.2% for lateral tibial and 2.6% for patella [3], which is very similar to that reported by our group in adults [10, 11].

Knee tibial plateau bone area and patellar bone volume were also determined by means of image processing on an independent workstation using the software program Osiris (University of Geneva) as previously described [3, 4]. To transform the images to the axial plane, the Analyse Software package developed by the Mayo Clinic was employed. Medial and lateral tibial plateau bone area was determined by creating an isotropic volume from the three input images closest to the knee joint. The bone area of the medial and lateral tibial plateau was then directly measured from the reformatted axial images. The patellar bone area was determined individually by manually drawing contours around the target patella.
boundaries on a slice-by-slice basis on sagittal views. The volume of the patella bone was then determined by summing all the pertinent voxels within the resultant binary volume. Total volume was calculated for the patellar bone because of its irregular shape, which made it difficult to identify a simpler, representative measure of patellar size. The CVs for these measures in our hands are 2.2–2.6% [3].

Statistics

Unpaired t-tests or \( \chi^2 \)-tests were utilized for comparison of means or frequencies. Univariate regression analysis was used to examine the associations between sex and knee cartilage volume. The associations were further evaluated with multivariate regression analysis to look at change in parameter estimates after adjustment for potential mediators of the sex effect.

Multivariate regression analysis was also used to examine the age-sex interaction with knee cartilage volume. This was examined in two ways. Age was either considered as a continuous variable or dichotomized at 50 yr of age. A model was then constructed containing the age variable, sex and their interaction term (age \( \times \) sex). Statistical significance was determined based on the \( P \) value for the interaction term. All results were adjusted for case–control status and ROA score.

Results

A total of 372 subjects (female 214, male 158) aged between 26 and 61 (mean age 45 yr) took part in the present study. Demographic and study factors are presented in Table 1. Males and females were similar in terms of age, BMI, strenuous and light exercise in previous weeks, but males had greater height, weight, daily hours of television watching, number of competitive sports, lower limb muscle strength and endurance fitness (work capacity at 170 beats/min) than females (all \( P < 0.001 \)). ROA, while greater in women, was uncommon and was not significantly different between the two groups.

As documented in Table 2, males had significantly greater patellar, lateral tibial and medial tibial cartilage volume than females (all \( P < 0.001 \)). Sex explained

### Table 1. Characteristics of participants

<table>
<thead>
<tr>
<th></th>
<th>Male ((n = 158))</th>
<th>Female ((n = 214))</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>44.7 (7.0)</td>
<td>45.4 (6.8)</td>
<td>0.323</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>176.0 (6.6)</td>
<td>169.9 (5.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84.9 (13.1)</td>
<td>72.5 (16.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>27.4 (3.7)</td>
<td>27.0 (5.9)</td>
<td>0.456</td>
</tr>
<tr>
<td>Radiographic osteoarthritis (%)</td>
<td>15</td>
<td>19</td>
<td>0.203(^a)</td>
</tr>
<tr>
<td>Strenuous exercise in previous 2 weeks (1–5)</td>
<td>1.9 (1.2)</td>
<td>1.9 (1.3)</td>
<td>0.650</td>
</tr>
<tr>
<td>Light exercise in previous 2 weeks (1–5)</td>
<td>4.3 (1.2)</td>
<td>4.5 (1.0)</td>
<td>0.050</td>
</tr>
<tr>
<td>Daily hours of television watching</td>
<td>2.9 (0.8)</td>
<td>2.6 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of competitive sports</td>
<td>1.3 (0.6)</td>
<td>1.1 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lower limb muscle strength (kg)</td>
<td>171 (35)</td>
<td>93 (23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Work capacity at 170 beats/min</td>
<td>3.6 (1.1)</td>
<td>2.5 (0.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(^a\)\( \chi^2 \)-test, all others are unpaired t-test as mean (standard deviation).

### Table 2. Sex differences in knee cartilage volume: multivariate analysis in whole group

<table>
<thead>
<tr>
<th>Cartilage site</th>
<th>Male</th>
<th>Female</th>
<th>Adjusted step 1(^a)</th>
<th>Adjusted step 2(^b)</th>
<th>Adjusted step 3(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patella volume ((\mu l))</td>
<td>( R^2 ) 41%</td>
<td>Partial ( R^2 ) 39%</td>
<td>+1224 (+1067, +1381)</td>
<td>( R^2 ) 49%</td>
<td>Partial ( R^2 ) 6%</td>
</tr>
<tr>
<td>Medial tibial volume ((\mu l))</td>
<td>( R^2 ) 33%</td>
<td>Partial ( R^2 ) 32%</td>
<td>+656 (+557, +755)</td>
<td>( R^2 ) 46%</td>
<td>Partial ( R^2 ) 1%</td>
</tr>
<tr>
<td>Lateral tibial volume ((\mu l))</td>
<td>( R^2 ) 41%</td>
<td>Partial ( R^2 ) 40%</td>
<td>+858 (+750, +966)</td>
<td>( R^2 ) 55%</td>
<td>Partial ( R^2 ) 4%</td>
</tr>
</tbody>
</table>

\(^a\)Adjusted for case–control status and radiographic OA score.

\(^b\)Adjusted as for step 1, as well as for body height, weight and bone size at that site.

\(^c\)Adjusted as for step 2, as well as for physical activity (strenuous exercise, light exercise, daily hours of television watching, number of competitive sports, lower limb muscle strength and work capacity at 170 beats/min).

Bold denotes a statistically significant result.
between 33 and 42% of the variation in cartilage volume, which was statistically significant at all sites. Compared with females, males had 33–42% higher cartilage volume at the medial tibia, lateral tibia and patella sites after adjustment for case–control status and ROA. These differences decreased to 8–18% after further adjustment for body height, weight and bone size, but remained statistically significant (all $P < 0.05$) and remained largely unchanged (11–19%) after further adjustment for physical activity (strenuous and light exercise in previous weeks, daily hours of television, number of competitive sports, low limb muscle strength and endurance fitness).

Males had significantly greater patellar, lateral tibial and medial tibial cartilage volumes than females (all $P < 0.001$) both in the older (50–61 yr) and younger (26–50 yr) groups (Tables 3 and 4). Males had 45–58% higher cartilage volume at the medial tibia, lateral tibia and patella sites in the older group while, in the younger group, males had 30–37% higher cartilage volume at all sites. The age–sex interaction terms were significant at all sites for the age 50 cut-off point (Fig. 1).
and remained significant after adjustment for ROA score (all \( P < 0.05 \)). However, the interactions were only significant at the patella site if age was considered as a continuous variable (patella: \( P = 0.003 \); medial tibia: \( P = 0.134 \); lateral tibia: \( P = 0.225 \)). After further adjustment for body height, weight and bone size, males had 24% higher cartilage volume at the patella but not lateral tibia and medial tibia sites in the older group, and had 9–17% higher cartilage volume at the medial tibia, lateral tibia and patella sites in the younger group (all \( P < 0.05 \), Table 4).

There was no significant difference in the magnitude of the gender effect when the offspring group and the control group were examined separately (data not shown) so both groups were combined for all analyses. Knee pain and/or knee injury also had no impact on the sex differences in knee cartilage volumes (data not shown). The goodness of fit of the multivariate models was best if bone area/volume and height were included simultaneously (data not shown).

**Discussion**

This large cross-sectional study of 372 adults documents substantially higher knee cartilage volume at patella and tibial sites in males compared with females. The sex differences appeared, in part, to be mediated by body and bone size, but not physical activity. Furthermore, these differences became larger after the age of 50 suggesting that the sex differences are due to both cartilage development and cartilage loss in later life.

The current study indicates that the sex differences in knee cartilage volume are substantial in adults aged between 26 and 61. Men had 33–42% greater cartilage volume than women after adjustment for case-control status and ROA. The magnitude of these differences decreased to 8–18% but still remained statistically significant after further adjustment for body weight, height, bone size and physical activity. These are broadly consistent with our previous findings in both children [3] and a smaller group of adults [4]. In contrast, in a sample of 18 young subjects, Faber et al. [5] reported that men had 20–47% higher knee cartilage volume, and that the sex differences became non-significant at all sites after adjustment for body weight and height. These variations may reflect sample size considerations in that the previous studies were much smaller or that they studied younger subjects than the current study.

Currently, it is unclear why there are sex differences in cartilage volume. The current study indicates that a significant proportion of this difference can be explained by body and bone size, which is consistent with the literature that body or bone size is related to cartilage volume [3, 4, 12, 13] and implies that cartilage thickness is greater in males. However, comprehensive measures of physical activity and fitness did not contribute to the observed differences. The sex differences decreased but remained significant at all sites in the whole sample after adjustment for body weight and height. These variations may reflect sample size considerations in that the previous studies were much smaller or that they studied younger subjects than the current study.

FIG. 1. Age–sex interaction and knee cartilage volume. Sex differences in cartilage volume are present in both age groups and the sex differences in cartilage volume were significantly greater in those aged over 50 yr compared with those aged less than 50 yr at all sites. (A) Patellar cartilage, (B) lateral tibial cartilage and (C) medial tibial cartilage.
whatever measure was utilized. Therefore, the most likely candidates are sex hormones and growth factors. Oestrogen, progesterone and testosterone receptors are present in human fetal cartilaginous tissue [14], and androgens can stimulate human chondrocyte proliferation as well as collagen and proteoglycan synthesis [15]. Hormone replacement therapy has been associated with higher cartilage volume in post-menopausal women [16]. In addition, recent evidence suggested that there was a positive association between knee cartilage volume and serum testosterone at tibial cartilage sites, which only reached statistical significance for medial tibial cartilage where serum testosterone explained up to 8% of the variation in cartilage volume [17]. Similarly, growth factors such as transforming growth factor-β and insulin-like growth factor-1 play important roles in articular cartilage formation and proteoglycan synthesis [18]. The variations in sex hormones, growth factors and other factors that may underlie the unexplained component of the sex differences in knee cartilage volumes need to be further explored.

To our knowledge, no previous data are available on a possible modifying role of age on sex differences in knee cartilage volumes. We found that males had 45–58% greater knee cartilage volume than females in those aged over 50, while, in those aged under 50, males had 30–37% greater knee cartilage volume than females. These results were only consistent if an age cut-off point of 50 was utilized, but not if age was considered as a continuous variable. This suggests that women (but not men) have rapid cartilage loss around the time of the menopause. This may be part of a disease process but was independent of ROA and thus may reflect cartilage senescence. Initial longitudinal data do not confirm higher rates of loss in women with symptomatic knee osteoarthritis, but do suggest higher rates of loss in those with higher baseline cartilage volume [11]. A higher rate of loss in those with higher cartilage volume may reflect cartilage swelling in early osteoarthritis followed by greater loss or may reflect the statistical phenomenon of regression to the mean whereby outlying measurements are more likely to regress. Both of these factors are unlikely to apply to the current study. In addition, the sample reported by Wluka et al. [16] all had disease unlike the current sample and our results are consistent with the reported effect of hormone replacement therapy. They are also consistent with a recent report describing more substantial patella cartilage thinning with age in women than men [19]. The combination of lower cartilage development and higher cartilage loss after age 50 is a testable hypothesis as to why women have a higher prevalence of OA than men after age 50 yr [1, 2]. Intriguingly, adjustment for body and particularly bone size (but not ROA) led to minimal residual sex differences in cartilage volume at the medial and lateral tibial sites in those aged over 50 yr (but not those aged less than 50 yr). This is most likely to be the result of sample size considerations as approximately 25% were aged over 50 yr or may indicate possible mechanisms for the difference in the older age group.

This study has a number of potential limitations. First, the study was primarily designed to look at genetic mechanisms of knee osteoarthritis and utilized a matched design. The matching was broken for the current study but adjustment for case-control status did not alter the results. Indeed, while there was a reduction in power, the results otherwise did not differ if examined in offspring and controls separately. While the sample is a convenience sample, Miettinen [20] states that for these associations to be generalizable to other populations three key criteria need to be met regarding selection, sample size and adequate distribution of study factors, all of which are met by this study. They were also ideally placed to examine the associations between cartilage measures and age owing to the wide age range of the sample. Second, measurement error in the assessment of MRI may have weakened the sex associations. However, the assessment technique has high reproducibility in our hands suggesting this is not of major concern and is further offset by the blinded reading. The consistency of results also suggests that these observations are valid. The use of a single composite measure of lower limb muscle strength may miss changes between the sexes that exist in only one compartment or the relationship between the two compartments. Further studies will be required with isokinetic measurement of muscle function. Lastly, the study was cross-sectional in design and cannot comment on causal directions. While these observations make biological sense, longitudinal data in large samples of subjects both with and without knee osteoarthritis will be required to confirm these results.

In conclusion, men have substantially higher knee cartilage volumes than women. These differences appear to be mediated in part by body and bone size but a significant amount remains unexplained. Furthermore, the sex differences become more marked over the age of 50 yr suggesting that both cartilage development and cartilage loss in later life contribute to sex differences in cartilage volume.

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References

Sex differences in knee cartilage volume


