EXTENDED REPORT

Weight loss in obese people has structure-modifying effects on medial but not on lateral knee articular cartilage

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ABSTRACT

Background Obesity is an important risk factor for knee osteoarthritis (OA). Weight loss can reduce the symptoms of knee OA. No prospective studies assessing the impact of weight loss on knee cartilage structure and composition have been performed.

Objectives To assess the impact of weight loss on knee cartilage thickness and composition.

Methods 111 obese adults were recruited from either laparoscopic adjustable gastric banding or exercise and diet weight loss programmes from two tertiary centres. MRI was performed at baseline and 12-month follow-up to assess cartilage thickness. 78 eligible subjects also underwent delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), an estimate of proteoglycan content. The associations between cartilage outcomes (cartilage thickness and dGEMRIC index) and weight loss were adjusted for age, gender, body mass index (BMI) and presence of clinical knee OA.

Results Mean age was 51.7±11.8 years and mean BMI was 36.6±5.8 kg/m²; 32% had clinical knee OA. Mean weight loss was 9.3±11.9%. Percentage weight loss was negatively associated with cartilage thickness in the medial femoral compartment in multiple regression analysis (β=0.006, r²=0.19, p=0.029). This association was not detected in the lateral compartment (r²=0.12, p=0.745). Percentage weight loss was associated with an increase in medial dGEMRIC in multiple regression analysis (β=3.9, r²=0.26; p=0.008) but not the lateral compartment (r²=0.14, p=0.34). For every 10% weight loss there was a gain in the medial dGEMRIC index of 39 ms (r²=0.28; p=0.014). The lowest weight loss cut-off associated with reduced medial femoral cartilage thickness loss and improved medial dGEMRIC index was 7%.

Conclusions Weight loss is associated with improvements in the quality (increased proteoglycan content) and quantity (reduced cartilage thickness losses) of medial articular cartilage. This was not observed in the lateral compartment. This could ultimately lead to a reduced need for total joint replacements and is thus a finding with important public health implications.

INTRODUCTION

Obesity represents a major public health problem. The WHO estimates that more than one billion people are overweight and, of these, 300 million are obese.1 In addition, the levels of extreme obesity (obesity grade 3, body mass index (BMI) ≥40 kg/m²) are also escalating.2 Osteoarthritis (OA) is the most common form of arthritis and the leading cause of chronic disability among older people. Obesity is a significant risk factor for the incidence of knee OA, but the effects on disease progression are less consistent.3–5 In an analysis of the direct costs of obesity it was estimated that the cost of OA in the USA (US$5.3 billion) was second only to the cost of diabetes in obesity-associated conditions.6 OA has a significant negative impact on most economies—for example, in the UK economy, OA has a total cost estimated to be equivalent to 1% of Gross National Product per year.7 Obesity-related OA is estimated to be responsible for at least 10% of this cost.8OA affects articular cartilage and other structures such as subchondral bone and meniscus. Loss of articular cartilage is a marker of OA severity.9 The main function of articular cartilage is to permit frictionless and pain-free movement of the joint.10 Articular cartilage consists of a large extracellular matrix composed of water and proteoglycans entrapped within a collagenous framework. Proteoglycans are made up of glycosaminoglycans (GAGs) attached to a backbone of hyaluronic acid.11 Proteoglycans provide the cartilage with compressive stiffness.

Quantitative cartilage assessment using MRI allows the measurement of important cartilage structural features such as thickness and volume.12 In comparison with radiography, MRI detects morphological changes in cartilage at a much earlier stage of the disease—that is, it allows the detection of pre-radiographic OA.12 Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), a cartilage compositional measure, is used to assess the relative distribution of GAG in cartilage non-invasively.13 GAGs are negatively charged due to abundant carboxyl and sulfate groups that are ionised at physiological pH. The technique uses a negatively charged contrast agent, gadopentate dimeglumine (Gd-DTPA²−; Magnevist; Berlex Laboratories, Wayne, New Jersey, USA) which, when given time to penetrate the cartilage matrix in an inverse relationship to the concentration of negatively charged GAG,11 14 15 The concentration of Gd-DTPA will therefore be relatively low in normal (GAG-abundant) cartilage and relatively high in degraded cartilage (GAG loss). This allows calculation of the dGEMRIC index, with a low GAG content resulting in a low dGEMRIC index and a high GAG content yielding a high dGEMRIC
based on previously described and validated methods. The segmentations were used to analyse cartilage thickness and GAG content in a cohort of obese people participating in weight loss programmes.

METHODS

Study population
In this observational prospective cohort study, patients were recruited from two weight loss (non-surgical or surgical) programmes in which patients had voluntarily enrolled themselves. All subjects were obese (BMI >30 kg/m²), with most being obesity grade 2 or higher (ie, BMI >35 kg/m²). The non-surgical programme (dietary modification and exercise) was conducted at the Metabolism and Obesity Services Clinic of the Royal Prince Alfred Hospital, Sydney. The surgical group underwent laparoscopic adjustable gastric banding by one of two experienced surgeons at Royal North Shore Hospital, Sydney. All patients were screened during their initial visit to the respective centres and offered the opportunity to participate in this longitudinal observational study.

Apart from the usual MRI exclusion criteria, clinical exclusion criteria included inflammatory arthritis or psychiatric illness. dGEMRIC exclusion criteria include glomerular filtration rate <60 mmol/l, pregnancy or breast feeding. The American College of Rheumatology clinical classification criteria were used to define knee OA. This requires the presence of knee pain on most days of the last month and at least three of the following: age >50 years, morning stiffness <30 min, crepitus, bony tenderness, bony enlargement and no palpable warmth.

Assessments
One hundred and eleven subjects were recruited. Subjects were assessed at recruitment (baseline, prior to commencement of the weight loss programme) and again 12 months later.

Clinical assessment
The weight loss percentage was calculated as: (weight loss/baseline weight) × 100%. Weight loss is defined as any loss in weight and weight gain is defined as any gain in weight. Knee range of motion and alignment were assessed in all subjects. Measurement methods have been described in detail elsewhere.

MRI assessment
Cartilage thickness
Eligible subjects underwent baseline MRI of the symptomatic or dominant asymptomatic knee. Sagittal MRI images were obtained on a 3T scanner (Magnetom Trio; Siemens, Erlangen, Germany) as previously described. Cartilage segmentation was performed by a single trained reader (AA) blinded to all clinical data including age, presence of knee symptoms and degree of weight loss. The segmentations were used to analyse cartilage thickness (weight-bearing femoral cartilage and all of the tibial cartilage) using proprietary software (Chondrometrics, Aining, Germany), based on previously described and validated methods.

Knee dGEMRIC assessment
A standard dGEMRIC protocol was applied. dGEMRIC images were obtained in the sagittal planes as previously described. Double dose (0.2 mM/kg) GdDTPA was administered 90 min prior to imaging at baseline and 12 months. Subjects were required to walk for 15 min after injection. T1Gd maps were generated to calculate the dGEMRIC index with a pixel-by-pixel three-parameter T1 fit using Matlab software (The MathWorks, Natick, Massachusetts, USA). The mean medial and lateral dGEMRIC indices were obtained. The dGEMRIC indices were calculated after manual segmentation for four regions of interest (ROIs), two each from the medial and lateral sagittal sections, to yield the mean dGEMRIC index for an individual ROI, as well as averaged across sagittal views to obtain the medial and lateral dGEMRIC index. Full-thickness ROIs in the sagittal plane consisted of weight-bearing femoral cartilage and all of the tibial cartilage. All images were read by a single trained observer (AA) blinded to all clinical data. The BMI correction equation was also applied for completion. However, this may not be applicable for 3T MRI imaging.

Intraobserver reliability was measured using intraclass correlation coefficients (ICCs) after repeat mapping 1 week apart for 20 subjects for both cartilage thickness and dGEMRIC (ICC >0.91 for each ROI).

Statistical analysis
The mean change over 12 months and standardised response means (mean change/SD of change) were calculated. Spearman correlation analysis was used to analyse the association between change in dGEMRIC indices, cartilage thickness and percentage weight loss. The Mann–Whitney test was used for categorical variables. Linear regression was used to examine univariate associations between percentage weight loss (covariate) and MRI cartilage outcomes (dependent variable). Multiple regression analysis was adjusted for age, gender, baseline BMI and presence of clinical knee OA. All statistical analyses were carried out using SPSS standard version 16.0 (SPSS, Chicago, Illinois, USA). A p value <0.05 was regarded as statistically significant.

RESULTS

Cartilage thickness
One hundred and eleven subjects underwent baseline MRI assessment of cartilage thickness. Seventy-eight patients (70%) completed MRI follow-up for cartilage assessment at 12 months. The reasons for loss to follow-up are given in the online supplement (see figure S1). There were no significant demographic differences at baseline between the group that underwent MRI follow-up (n=78) at 12 months and the group that did not. The baseline characteristics of the cohort are shown in table 1. The group that underwent surgery for weight loss achieved greater weight loss than the non-surgical group (17.5% and 2.3%, respectively). There were no significant differences in mean cartilage thickness or dGEMRIC values or other demographic values at baseline between the two groups.

Change in cartilage thickness over 12 months
The mean change in compartment-specific cartilage thickness over 12 months is shown in table 2. Mean change in cartilage thickness was lower in subjects who lost weight, which was significant at the medial tibia (MT) and central medial femur (cMF). This was not observed in the lateral compartment. There was no difference in loss of cartilage thickness between subjects with and without clinical knee OA.

Change in cartilage thickness and weight loss
A higher percentage weight loss was associated with reduced loss of cartilage thickness in the medial femoral compartment in univariate (table 3) and multiple regression analysis adjusted.
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was still significantly associated with reduced cartilage thickness loss while adjusting for age, gender, baseline BMI and the presence of clinical OA.

Improved knee range of motion was associated with reduced loss of cartilage thickness in the medial compartment at 12 months (MT: r=0.20; p=0.079; cMF: r=0.37; p=0.001).

Of the 111 subjects who underwent baseline MRI, 78 subjects underwent baseline dGEMRIC assessment. The reasons for not undergoing dGEMRIC assessment are shown in the online supplement. Fifty-five patients (71%) completed follow-up dGEMRIC assessment at 12 months. The reasons for loss to follow-up are shown in the flow chart in the online supplement. There were no significant baseline differences between the group that underwent dGEMRIC assessment at 12 months and the group that did not. The baseline characteristics of the cohort are shown in table 1.

Change in dGEMRIC over 12 months

One subject with severe cartilage thinning was excluded from dGEMRIC assessment as previously described.11 The overall change in dGEMRIC indices is shown in table 4. Subjects who lost weight had a higher mean gain in medial and lateral dGEMRIC indices. However, these differences did not reach statistical significance.

Change in dGEMRIC index and weight loss

An improved medial dGEMRIC index correlated positively with percentage weight loss in univariate analysis for age, baseline BMI, gender and clinical knee OA (β=0.006, r²=0.19, p=0.029). A similar association did not reach statistical significance in the MT compartment. The degree of cartilage loss in the MT (p=0.181) and medial femoral (p=0.06) compartment was less with increasing quartiles of weight loss percentage but this model did not reach statistical significance. Lateral cartilage thickness loss was not associated with percentage weight loss in univariate or multivariable analysis.

The mean percentage weight loss for the cohort of 9% was used as a cut-off point for weight loss. Weight loss, any loss in weight; no change, no change in weight; weight gain, any gain in weight.

Table 1 Baseline characteristics of the obese cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Underwent cartilage thickness assessment</th>
<th>Underwent dGEMRIC assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>78</td>
<td>55</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.7±11.8</td>
<td>50.9±12.4</td>
</tr>
<tr>
<td>Female (%)</td>
<td>75%</td>
<td>67%</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>39.9±5.8</td>
<td>39.6±5.2</td>
</tr>
<tr>
<td>Knee osteoarthritis (ACR) (%)</td>
<td>32%</td>
<td>26%</td>
</tr>
<tr>
<td>Surgery for weight loss (%)</td>
<td>36%</td>
<td>44%</td>
</tr>
<tr>
<td>Weight loss (12 months) (%)</td>
<td>9.3±11.9</td>
<td>9.1±10.0</td>
</tr>
<tr>
<td>Medial tibial cartilage thickness (mm)</td>
<td>1.40±0.21</td>
<td>NA</td>
</tr>
<tr>
<td>Medial femoral cartilage thickness (mm)</td>
<td>1.75±0.34</td>
<td>NA</td>
</tr>
<tr>
<td>Lateral tibial cartilage thickness (mm)</td>
<td>1.93±0.32</td>
<td>NA</td>
</tr>
<tr>
<td>Lateral femoral cartilage thickness (mm)</td>
<td>1.95±0.36</td>
<td>NA</td>
</tr>
<tr>
<td>Medial dGEMRIC index (ms)</td>
<td>NA</td>
<td>545±84</td>
</tr>
<tr>
<td>Lateral dGEMRIC index (ms)</td>
<td>NA</td>
<td>539±91</td>
</tr>
</tbody>
</table>

Data shown are mean±SD or percentage.

ACR, American College of Rheumatology; BMI, body mass index; dGEMRIC, delayed gadolinium-enhanced MRI of cartilage.

Table 2 Mean±SD change in cartilage thickness (mm)

<table>
<thead>
<tr>
<th>Region</th>
<th>Univariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
</tr>
<tr>
<td>MT</td>
<td>−0.22</td>
</tr>
<tr>
<td>cMF</td>
<td>−0.39</td>
</tr>
<tr>
<td>LT</td>
<td>0.11</td>
</tr>
<tr>
<td>cLF</td>
<td>0.05</td>
</tr>
</tbody>
</table>

cLF, central lateral femur; cMF, central medial femur; LT, lateral tibia; MT, medial tibia.

Table 3 Change in cartilage thickness (mm) and weight loss: univariate analysis

<table>
<thead>
<tr>
<th>Region</th>
<th>Univariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>LT</td>
<td>0.11</td>
</tr>
<tr>
<td>cLF</td>
<td>0.05</td>
</tr>
</tbody>
</table>

cLF, central lateral femur; cMF, central medial femur; LT, lateral tibia; MT, medial tibia.
Lateral dGEMRIC index 23±107 27±114 −8±83
Lateral femoral 23±107 29±114 −2±89
Lateral tibial 23±135 24±138 19±128 (BMI corrected)

Medial dGEMRIC index 13±106 17±113 −3±78
Medial femoral 2±123.0 3±138 −5±60
Medial tibial 23±125.7 25±128 −4±123

Table 4 Mean±SD dGEMRIC index (ms)

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>Change</th>
<th>Cohort (n=54)</th>
<th>Weight loss (n=61)</th>
<th>Weight gain/no change (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial tibial</td>
<td>23±125.7</td>
<td>25±128</td>
<td>−4±123</td>
<td></td>
</tr>
<tr>
<td>Medial femoral</td>
<td>2±123.0</td>
<td>3±138</td>
<td>−5±60</td>
<td></td>
</tr>
<tr>
<td>Medial dGEMRIC index (BMI corrected)</td>
<td>13±106</td>
<td>17±113</td>
<td>−3±78</td>
<td></td>
</tr>
<tr>
<td>Lateral tibial</td>
<td>23±135</td>
<td>24±138</td>
<td>19±128</td>
<td></td>
</tr>
<tr>
<td>Lateral femoral</td>
<td>23±107</td>
<td>29±114</td>
<td>−2±89</td>
<td></td>
</tr>
<tr>
<td>Lateral dGEMRIC index (BMI corrected)</td>
<td>23±107</td>
<td>27±114</td>
<td>8±83</td>
<td></td>
</tr>
<tr>
<td>Lateral tibial</td>
<td>11±106</td>
<td>12±113</td>
<td>2±82</td>
<td></td>
</tr>
</tbody>
</table>

Medial dGEMRIC 45±116 −16±88
Medial dGEMRIC (BMI corrected) 22±114 −18±90

Table 5 Mean±SD change in medial dGEMRIC index (ms) according to 9% weight loss cut-off point

<table>
<thead>
<tr>
<th>Region</th>
<th>Group 1 (n=25) (weight loss ≥9%)</th>
<th>Group 2 (n=28) (gained weight, no change or weight loss &lt;9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial dGEMRIC</td>
<td>45±116</td>
<td>−16±88</td>
</tr>
<tr>
<td>Medial dGEMRIC (BMI corrected)</td>
<td>22±114</td>
<td>−18±90</td>
</tr>
</tbody>
</table>

BMI, body mass index; dGEMRIC, delayed gadolinium-enhanced MRI of cartilage.

Correlation between change in medial delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) and weight loss percentage.

(r=0.35; p=0.011; figure 1). In multiple regression analysis adjusting for age, gender, baseline BMI and presence of clinical knee OA, an improved medial dGEMRIC index correlated positively with percentage weight loss (β=3.9, r²=0.26; p=0.008). The degree of improvement in the mean medial dGEMRIC index improved incrementally with increasing quartiles of weight loss percentage, but this model did not reach statistical significance (p=0.07). The change in the lateral dGEMRIC index was not associated with percentage weight loss in univariate analysis or in multivariable analysis (adjusting for age, gender, baseline BMI and presence of clinical knee OA).

The mean percentage weight loss for the cohort of 9% was used as a cut-off point for weight loss to generate two groups (table 5). The mean difference in medial dGEMRIC index change between the two groups was 61 ms (95% CI −118 to −5; p=0.034; effect size 0.6). Overall, 7% weight loss was the lowest cut-off associated with a significant difference in medial dGEMRIC index in this cohort. Figure 2 shows the changes seen in the medial dGEMRIC index in a study participant with weight loss.

Improved knee range of motion correlated with improved medial dGEMRIC index in univariate analysis (r=0.28; p=0.046). The multivariable model that included age, gender, baseline BMI, knee OA and change in knee range of motion accounted for 28% of the variance in medial dGEMRIC with percentage weight loss (r²=0.28; p=0.014). In this model, for every 10% weight loss there was a gain in the medial dGEMRIC index of 39 ms.

Change in dGEMRIC index and cartilage thickness

Reduced loss of MT cartilage thickness was positively associated with improved MT dGEMRIC index (r=0.35, p=0.011). These associations were not significant in multivariable regression analysis.

DISCUSSION

This is the first prospective study to evaluate the impact of weight loss on knee articular cartilage structure and quality. To the best of our knowledge, there are no other published studies assessing the impact of weight loss intervention on knee articular cartilage. We demonstrated that weight loss is associated with reduced cartilage thickness losses in the medial femoral compartment as well as improved medial dGEMRIC index (ie, proteoglycan content). No association was identified between weight loss and change in cartilage thickness or dGEMRIC index in the lateral compartment. Improved knee range of motion was independently associated with reduced loss of cartilage thickness. The degree of weight loss observed in the surgical and non-surgical groups is similar to published reports.26–28

There have been several published reports of the annual rate of change of cartilage thickness.29–31 Recent early data from the osteoarthritis initiative (OAI), a multicentre observational study evaluating risk factors for the incidence and progression of symptomatic knee OA, demonstrated a modest but significant loss of tibio-femoral cartilage thickness over 1 year in people with frequent knee symptoms and radiographic knee OA. The effect sizes (standardised response mean) of cartilage thickness loss in the OAI cohort varied within knee joint compartments (MT −0.16; cMF −0.30; lateral tibia −0.23; cLF −0.02). These cartilage thickness losses are larger than those of our weight loss subgroup in the medial compartment (MT −0.06; cMF 0.12). In addition, the OAI subcohort had severe knee OA whereas our cohort consisted largely of subjects without clinical knee OA, albeit at higher risk of knee OA due to morbid obesity. Notably, our study involved effective weight loss interventions, and we hypothesised lower effect sizes, indicating reduced cartilage loss. Interestingly, however, the patients who gained weight demonstrated effect sizes similar to the OAI cohort with knee OA (MT −0.35; cMF −0.33). The difference in mean cartilage thickness findings in the cLF between recent studies and this cohort could partly be related to the large range of weight loss shown in this relatively small cohort compared with the OAI cohorts. Increasing levels of obesity can impair the quality of the MRI images obtained and hence alter measurements. However, a surface coil is required in the research setting and, in our study,32 very obese patients with a thigh too large for the coil were excluded. This acquisition methodology limits variability in the obtained images.
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Importantly, weight loss was associated with lower cartilage thickness losses in the medial compartment and after adjustment for potential confounders. Similarly, the effect of weight loss on the dGEMRIC index remained significant after adjustment for potential confounders. We did not observe similar associations between lateral cartilage thickness loss or the dGEMRIC index with weight loss. The differential change in the medial compared with the lateral compartment is not unexpected as previous studies have found that the medial compartment generally exhibits higher rates of cartilage loss in people with knee OA. This finding is likely to be attributable to the greater proportion of ground reaction forces borne by the medial tibiofemoral compartment, even in normally aligned knees.

A previous study also demonstrated a lower medial dGEMRIC index in varus-aligned knees and a lower lateral dGEMRIC index in valgus-aligned knees. While this remains speculative, the potential for improvement for most obese people with knee OA undergoing weight loss is possibly greater in the medial compartment. The lack of association in the lateral compartment is due to a large extent to matrix improvement and not dose-related. Recent body composition analysis in obese subjects after bariatric surgery showed that extracellular water does not change with weight loss. As GdDTPA$^{2-}$ is distributed solely in extracellular water, this should not affect the dGEMRIC results. Future research incorporating body composition analysis (adipose tissue vs lean tissue) would be informative to interpret weight loss-mediated changes in cartilage.

In this cohort there was no association between baseline or change in alignment and subsequent cartilage loss. Varus–valgus alignment has been associated with subsequent progression of knee OA. However, most subjects in this cohort had varus alignment with little absolute change over 12 months, potentially reducing the likelihood of detecting any associations.

Improved knee range of motion was associated with reduced loss of cartilage thickness after adjustment for confounders. An association with reduced knee circumference was also detected. We had previously demonstrated an association between reduced range of knee movement and cartilage defect scores. Cartilage integrity is dependent on cyclical loading. Biomechanical and metabolic factors such as leptin and other adipocytokines are postulated to play a role in obesity-mediated OA. The mechanism behind weight loss-mediated improvements in the dGEMRIC index and reduced cartilage loss is probably due to a combination of these factors.

In this non-randomised study, the group that underwent surgery had less cartilage thickness loss and larger improved dGEMRIC measures than the non-surgical group (data not shown). These differences are probably secondary to the higher weight loss observed in the surgical cohort. Potential biochemical and
metabolic differences between the surgical and non-surgical groups (such as differences in absorption and cytokine levels) may in part also explain the differences, independent of weight loss. Randomised controlled trials comparing surgery and non-surgical interventions will be necessary to assess the influence of these biochemical and metabolic differences on knee structural outcomes, but this will be difficult to achieve in practice as marked mean differences in weight loss between these two interventions are likely to remain.

In summary, this is the first prospective study to assess the impact of weight loss on important cartilage morphometric measures such as cartilage thickness and dGEMRIC index. This has important ramifications as our findings indicate that weight loss can lead to improved cartilage structural outcomes and may reduce the need for total joint replacements. This is pertinent as, to date, there are no drug therapies that can slow down cartilage loss. This has significant public health and economic implications, given the rising burden of both obesity and knee OA.57

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