Gluteal atrophy and fatty infiltration in end-stage osteoarthritis of the hip
A CASE-CONTROL STUDY

K. Kivle,
E. S. Lindland,
K. E. Mjaaland,
S. Svenningsen,
L. Nordsletten

From Department of Orthopaedics, Sorlandet Hospital, Arendal, Norway

Aims
The gluteus minimus (GMin) and gluteus medius (GMed) have unique structural and functional segments that may be affected to varying degrees, by end-stage osteoarthritis (OA) and normal ageing. We used data from patients with end-stage OA and matched healthy controls to 1) quantify the atrophy of the GMin and GMed in the two groups and 2) describe the distinct patterns of the fatty infiltration in the different segments of the GMin and GMed in the two groups.

Methods
A total of 39 patients with end-stage OA and 12 age- and sex frequency-matched healthy controls were prospectively enrolled in the study. Fatty infiltration within the different segments of the GMin and the GMed was assessed on MRI according to the semiquantitative classification system of Goutallier and normalized cross-sectional areas were measured.

Results
The GMin was smaller in the OA-group (p < 0.001) compared to the control group, but there was no group difference in the size of the GMed (p = 0.101). Higher levels of fatty infiltration were identified in the anterior segment of the GMin (p = 0.006) and the anterior (p = 0.006) and middle (p = 0.047) segments of the GMed in the OA group. All subjects in the control group had fatty infiltration of the anterior segment of the GMin, but all except one had no fatty infiltration in the entire GMed.

Conclusion
End-stage OA was associated with significant atrophy of the GMin and higher levels of fatty infiltration, particularly in the anterior segments of the GMin and GMed. Minor fatty infiltration of the anterior segment of GMin appears to be a normal part of ageing. Our study has demonstrated different patterns of atrophy and fatty infiltration between patients with end-stage OA and healthy matched peers.

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Introduction
In the past, osteoarthritis (OA) was solely conceptualized as a degenerative joint disease caused by mechanical stress which affected the hyaline cartilage of the joint. However, today OA is understood as a multifactorial disease which affects the whole synovial joint and its adjacent musculature, but any causal relationship between muscular dysfunction and the pathogenesis of OA is unclear. Besides OA, senescence and other diseases affecting the joint or the adjacent muscles directly are likely to cause muscular weakness and atrophy. Reduced size of the muscle is the most noticeable part of atrophy, but atrophy also implies fatty infiltration and changes in the muscle structure.

The hip joint is surrounded by the gluteus minimus (GMin) and the gluteus medius (GMed). They are complex, active stabilizers of the hip joint during gait, with unique structural and functional segments acting as “muscles within muscles”. The relative...
contributions of the different segments of the GMin and GMed vary according to the position of the femur.\textsuperscript{4,5} The GMin consists of at least two functionally independent segments: the anterior part with vertically orientated fibres, which contracts most noticeably during the late stance phase of a gait cycle, and the posterior part with more horizontally orientated fibres, which is most active in early stance phase.\textsuperscript{4} Previous cadaveric and electromyography (EMG) studies suggest that the GMed consists of three independent segments; the anterior, middle and posterior segments.\textsuperscript{4,6} The anterior part of the GMed assists stabilization of the pelvis and contributes to its contralateral forward rotation.\textsuperscript{5} The vertically orientated fibres of the middle part of the GMed convey a great abductor force on the hip, and hence provide pelvic stability. The fibres of the posterior part of the GMed run close to parallel to the neck of the femur and, together with the GMin, stabilize the head of the femur during gait.\textsuperscript{5}

MRI offers detailed soft-tissue depiction, making it an excellent tool to investigate soft-tissue structures such as musculature and their corresponding pathologies in vivo. A large retrospective MRI study demonstrated increasing fatty infiltration of both the GMin and GMed with advancing age.\textsuperscript{2} Three systematic reviews concluded that data on muscle size in patients with OA were limited or presented moderate evidence for atrophy in OA,\textsuperscript{7-9} but recent studies with data adjusted to body weight suggest that atrophy of the GMin and GMed is associated with advancing severity of both clinical and radiological OA compared to a control group.\textsuperscript{10,11} In most cases, muscular atrophy is assessed by the cross-sectional area (Csa) or volume of the muscle, and these methods are almost equivalent in this context.\textsuperscript{12,17}

The purpose of this study was to investigate atrophy and fatty infiltration of the GMin and GMed and their segments in the setting of end-stage OA compared to a healthy matched control group. To our knowledge, no previous studies have investigated fatty infiltration of the different segments of the GMin and GMed in OA.

Methods
A total of 41 consecutive patients with end-stage OA of the hip were prospectively included in this study, together with twelve age- and sex-matched healthy controls. The trial was conducted in compliance with the Declaration of Helsinki\textsuperscript{14} and was approved by The Regional Committee for Medical and Health Research Ethics (2011/2581) and registered in the Clinical Trial Register (NCT01578746). All participants signed a written consent form.

All the patients in the OA group were scheduled for total hip arthroplasty, and were enrolled in a randomized controlled trial (RCT) comparing approaches in hip arthroplasty surgery.\textsuperscript{15} According to the Kellgren-Lawrence scale,\textsuperscript{16} the OA was verified by plain radiographs which corresponded to at least grade 2. The exclusion criteria were as follows: 1) body mass index (BMI) above 35 kg/m\textsuperscript{2}; 2) previous surgery or fracture of the hip; 3) infection or neoplasm; 4) dementia/psychiatric disease preventing cooperation; and 5) contraindications to MRI including pacemaker or other non-MRI compatible devices or foreign bodies, pregnancy, and claustrophobia. From the initially enrolled 41 patients, two were excluded because of severe pain or discomfort resulting in an inability to undergo an MRI scan. Therefore, 39 patients were available for further analyses.

Participants in the control group were age and sex frequency-matched to the patients in the OA group. The control group was included to assess the effect of OA in a secondary data analysis acquired in the RCT. The control group was recruited from hospital workers and from flyers placed at the hospital. We excluded all subjects with 1) OA in the lower limb; 2) previous hip surgery; 3) any pain in the hip or groin during physical activity or at rest; 4) present or previous rheumatic disorder, cancer, or neurological disease involving the lower limbs; 5) previous trauma in the hip area resulting in immobilization; 6) BMI above 35 kg/m\textsuperscript{2}; 7) any gait disorder; and 8) contraindications to MRI. They all had a clinical examination of the hip at study inclusion to ensure normal range of motion and normal muscle strength, defined as muscle activation against the examiner’s full resistance, and a negative Trendelenburg test after walking.\textsuperscript{17} There were no dropouts in the control group.

Patient characteristics. Baseline demographic and clinical characteristics of the participants in both groups, including age, sex, and BMI (n = 51), were collected prior to the MRI examination. All the participants in the OA group (n = 39) completed a patient-reported outcome measure, Oxford hip score,\textsuperscript{18} Harris Hip Score,\textsuperscript{19} and Trendelenburg test\textsuperscript{17} after their walking was assessed by a physiotherapist.

MRI. MRI was performed using a 1.5 T scanner (Siemens Aera, Erlangen, Germany). The MRI scan included the affected hip with its surrounding soft tissue in both groups, covering the area from the iliac crest to the lesser trochanter. The subjects were supine with the hip in a neutral position. The MRI protocol was standardized\textsuperscript{20} and body-surface coils were used.

Image analysis. All the MR images were evaluated by two independent experienced consultants (KK and ESL). Interobserver discrepancies were resolved in a consensus meeting. We have already demonstrated substantial reliability and agreement for MRI assessments of atrophy (intraclass correlation coefficient (ICC) 0.93 to 0.98) and fatty infiltration (average proportion of agreement 0.71, mean Cohen’s kappa 0.23 and mean prevalence-adjusted kappa 0.53) of the GMin and GMed in a previous study.\textsuperscript{20}

The CSA of GMin and GMed was evaluated separately on transversal T1-weighted images (Figure 1). A line was...
drawn vertically from the tip of the greater trochanter intersecting with a horizontal line at the level of the anterior superior iliac spine. The halfway cross-section was then selected, almost analogue to the inferior point of the sacroiliac joint recommended in a recent study.\textsuperscript{13} The tracings of GMin and GMed were done manually, using PACS Sectra software version 16 (Sectra, Sectra Workstation, Lindköping, Sweden), to calculate the CSA of both muscles. The total muscle mass is associated with body weight,\textsuperscript{21} therefore all the values of CSA were normalized to body weight (mm\textsuperscript{2}/kg) (N-CSA).

Fatty infiltration of the gluteals (GMin and GMed) were assessed on the transverse T1-weighted images. The slices analyzed were at the lower third and upper third of the distance between the tip of the greater trochanter and the anterior superior iliac spine. Both muscles were divided into three segments of similar size, a posterior, middle, and anterior segment (Figure 2).\textsuperscript{22} The mean value of the scores across the two cross-sections for both observers indicated the level of fatty infiltration for each segment. The fatty infiltration was assessed using a semiquantitative grading system originally described by Goutallier et al\textsuperscript{23} for the rotator cuff muscles in the shoulder based on CT. The grading system is, however, also suitable and reliable for the evaluation of the gluteal muscles on MRI.\textsuperscript{20,22} Grade 0 indicates no intramuscular fat; grade 1 implies some fatty streak; grade 2 that fat is present, but less fat than muscle tissue; grade 3 indicates equal amount of fat and muscle tissue; and grade 4 implies definitively more fat than muscle tissue.

**Statistical analysis.** Results were expressed as mean ± SD unless otherwise stated. For continuous variables, the groups were compared by an two-sided independent-samples t-test. The mean difference between the groups with 95% confidence intervals (CIs) was calculated. The categorical (ordinal) data were tested using the extension of the Fisher’s exact test by Freeman and Halton\textsuperscript{24} (Fisher-Freeman-Halton test) with two-tailed probabilities. Goutallier grades 2 to 4 were merged for further analyses to clearly discriminate moderate/severe fatty infiltration from minor fatty infiltration (grade 1).

The sample size of the control group was small (n = 12), but the Shapiro-Wilk test\textsuperscript{25} indicated no significant departure from normality, p = 0.197 (GMin) and p = 0.889 (GMed). A Q-Q plot of the expected and observed values was constructed that did not show a considerable departure from normality. The effect size was calculated for the difference in means between the groups according to Cohen.\textsuperscript{26} The interpretations were as reported by Cohen\textsuperscript{26} and Sawilowsky:\textsuperscript{27} d (0.01) = very small, d (0.2) = small, d (0.5) = medium, d (0.8) = large, d (1.2) = very large, and d (2.0) = huge.

Probability values of less than 0.05 were considered to indicate a significant difference for all statistical analyses.
Table I. Demographic and clinical characteristics of the participant groups.

| Characteristic                  | OA group     | Control group | p-value |
|---------------------------------|--------------|---------------|---------|
| Number of patients              | 39           | 12            | N/A     |
| Sex (M/F)                       | 13/26        | 4/8           | 1.000‡  |
| Included hip, % (Right/Left)    | 62/38        | 58/42         | 1.000‡  |
| Mean Age, yrs (SD)              | 65.8 (7.3)   | 68.1 (4.0)    | 0.173§  |
| Mean Height, cm (SD)            | 171 (10.2)   | 172 (9.3)     | 0.641§  |
| Mean Weight, Kg (SD)            | 79.5 (14.6)  | 78.3 (10.2)   | 0.767§  |
| Mean BMI, Kg/m² (SD)            | 27.2 (3.6)   | 26.3 (2.0)    | 0.320§  |
| Trendelenburg test, % (Pos/ Neg)| 54/46        | 0/100         | < 0.001‡|
| Mean Harris Hip Score (SD)*     | 54.7 (14.0)  | N/A           | N/A     |
| Mean Oxford Hip Score (SD)†     | 23.8 (7.5)   | N/A           | N/A     |

*Score ranges from 0 to 100 (worst to best); < 70 is considered a poor result.
†Score ranges from 0 to 48 (worst to best); < 27 is considered a poor result.
‡Fisher’s exact test
§Two-sided independent-samples t-test
BMI, body mass index; N/A, not applicable; OA, osteoarthritis.

Table II. Normalized cross-sectional areas for control and osteoarthritis group.

| Mean N-CSA, mm²/kg (SD) | OA group | Control group | Mean difference (95% CI) | p value* |
|-------------------------|----------|---------------|--------------------------|---------|
| Gluteus minimus         | 13.3 (4.1)| 18.8 (3.0)    | 5.5 (3.0 to 8.1)         | < 0.001 |
| Gluteus medius          | 43.5 (6.7)| 41.1 (3.4)    | -2.4 (-5.4 to 0.5)       | 0.101   |

*Two-sided independent-samples t-test
CI, confidence interval; N-CSA, normalized cross-sectional area; OA, osteoarthritis.

All the statistical analyses were conducted with SPSS v. 25 statistical software package (IBM, Armonk, New York, USA).

Results

There were no statistical differences between groups in terms of participant demographics (Table I). There were 21 in the OA group with a positive Trendelenburg test (54%, 21 of 39) versus none in the control group (p < 0.001, Fisher’s exact test).

Normalized cross-sectional areas in the osteoarthritis and control group. The N-CSA of the GMin was significantly lower in the OA group compared to the control group, 13.3 versus 18.8 mm²/kg (p < 0.001, two-sided independent-samples t-test) (Table II and Figure 3), and the mean difference was 5.5 mm²/kg (95% confidence interval (CI) 3.0 to 8.1). The effect size was very large (d = 1.54).

The mean difference in N-CSA of the GMed between the two groups was not significant (-2.4 mm²/kg (95% CI -5.4 to 0.5); p = 0.101 two-sided independent-samples t-test) (Figure 4), and the effect size was small (d = 0.46). The OA group had a notably wider range of values than the control group (30.4 to 11.7 mm²/kg).

Fatty infiltration in osteoarthritis and control group. The anterior segment of the GMin had higher levels of fatty infiltration in the OA group compared to the control group (p = 0.006, Fisher-Freeman-Halton test). However, no one in either group had normal musculature without intramuscular fat (grade 0) in the anterior segment (Figure 5). No differences were identified in the middle and posterior segments of the GMin (p = 1.000 and p = 0.417, Fisher-Freeman-Halton test).

Higher levels of fatty infiltration were identified in both the anterior and middle segments of the GMed in the OA group than in the control group (p = 0.006 and p = 0.047 respectively, Fisher-Freeman-Halton test) (Figure 6). There were no differences in fatty infiltration in the posterior segment between groups (p = 1.000, Fisher-Freeman-Halton test). In the control group, with one exception, no participant had fatty infiltration in the entire GMed. Figures 2 and 7 show representative cases of fatty infiltration of the GMin and GMed in a healthy control subject and a patient with end-stage OA.
Fig. 5
Bar graph of fatty infiltration of the gluteus minimus in the control and osteoarthritis (OA) group. Results of grading the fatty infiltration in the anterior, middle, and posterior part for both groups are shown. Green bars represent normal muscle (grade 0), yellow bars represent minor fatty infiltration (grade 1), and red bars represent moderate/severe fatty infiltration (grade ≥ 2).

Fig. 6
Bar graph of fatty infiltration of the gluteus medius in the control and osteoarthritis (OA) group. Results of grading the fatty infiltration in the anterior, middle, and posterior part for both groups are shown. Green bars represent normal muscle (grade 0), yellow bars represent minor fatty infiltration (grade 1), and red bars represent moderate/severe fatty infiltration (grade ≥ 2).

Discussion
This study demonstrates a distinct pattern of atrophy and fatty infiltration of the GMin and GMed in patients with end-stage OA compared to healthy matched peers. Atrophy of the GMin and higher levels of fatty infiltration, particularly in the anterior segments of the GMin and GMed, were found in end-stage OA. However, minor fatty infiltration in the anterior part of the GMin was present in all healthy matched controls in this study.

Skeletal muscle weakness and atrophy is an invariable part of normal ageing. Fatty infiltration of the skeletal muscles is a marker of senescence, even in subjects undergoing weight loss. A previous study reported fatty infiltration in the GMin and GMed in about one in five
hips in people aged between 50 to 59 years, and four in five above the age of 70 years. However, in a younger middle-aged population (aged 20 to 62 years) no age-dependency was found in a cross-sectional study. In the present study, all the healthy controls had fatty infiltration in the GMin, with the anterior segment most noticeably involved. The fatty infiltration in the anterior segment could be due to disuse caused by reduced stride length and concomitantly reduced peak hip extension in healthy elderly participants. A previous study identified minor (but no severe) changes in the GMed in healthy controls, which is almost consistent with our results. The results from the present study indicate a distinct pattern of fatty infiltration in normal ageing.

As in the controls, the fatty infiltration was most pronounced in the anterior segment of the GMin in the OA group. The changes from OA come in addition to the ageing changes demonstrated in the control group, and there was a significantly higher portion of moderate-severe fatty infiltration in the OA group (p = 0.006, Fisher-Freeman-Halton test). The anterior part is attached directly into the capsule, and it is possible that this part could be affected indirectly by the intra-articular inflammation in OA, or there may be a tear in the attachment. End-stage OA results in reduced range of motion in both the coronal and sagittal plane, and considerable decreased extension of the hip during the late stance phase, which may lead to disuse, especially of the anterior part of the GMin in OA with accompanying fatty infiltration. A recent EMG study demonstrated that altered GMin activity is associated with ageing but, to an even greater extent, OA of the hip. In this present study, fatty infiltration in the anterior and middle segment of the GMed was present in 59% and 31% respectively in the OA group, and almost nonexistent in the control group. The clinical importance of the minor fatty infiltration in the GMed seems to be a consistent finding, characteristic of OA.

The OA group demonstrated a significantly smaller size of the GMin (p < 0.001, two-sided independent-samples t-test), with a very large effect size (d = 1.54) compared to the control group. There was no difference in the size of the GMed between the groups, and the absence of atrophy in the GMed is consistent with the minor fatty infiltration in all parts of the GMed in the OA group. Although there is clear evidence for reduced muscle strength in OA of the hip, evidence is lacking for concomitant atrophy. This discrepancy could be explained by neuromuscular adaptations in OA, which reduces the muscular strength to a greater extent than the muscle size. However, the studies included in two of these meta-analyses were heterogeneous with different measurement methods and partially contradictory results. The most recent meta-analysis was based on unadjusted data from two cohorts, with no significant difference in muscle size in OA when compared to controls, and very low to low evidence of a smaller GMin and GMed when comparing affected and unaffected limbs in OA. Nevertheless, both the GMin and GMed were significantly smaller in the OA group when compared to healthy controls in the only study presenting data normalized to body weight. A recent study comparing mild and moderate-severe OA to healthy controls demonstrated a significantly reduced size of the GMin in both mild and moderate-severe OA, but asymmetry of the GMed was only present in moderate-severe OA.

Some previous studies have compared the affected limb against the unaffected limb instead of a control group. This could eliminate the between-person confounding, but the supposedly unaffected limb is probably affected by the OA, considering that end-stage OA modifies the load and gait pattern which could affect the muscles surrounding the contralateral hip.

There are limitations to this study that affect both the internal and external validity. The effects of age and sex, which were expected to be the main confounders, were taken into account in the study design. However, there could be other important confounders, such as physical activity level and genetic differences between the groups, influencing both the OA status and the atrophy of the gluteal muscles. Pathologies of the tendons or adjacent musculature has not been taken into account, which could be a potential bias. The sample size was relatively small, in particular the control group, but the limitations...
of the small sample size are to some extent offset by the large effect size and significant results. Finally, the matched case-control study design could not demonstrate a clear causation between OA and atrophy and fatty infiltration of the gluteal muscles.

In conclusion, the results of the current study indicated that end-stage OA of the hip was associated with significant atrophy of the GMin compared to the healthy controls. Fatty infiltration of the GMed seems to be a consistent finding characteristic of OA, not present in the healthy controls. Our results also indicate that minor fatty infiltration of the anterior part of the GMin may be a part of normal ageing. The changes demonstrated in end-stage OA are present before hip arthroplasty surgery and may influence the final result after surgery.

Take home message
- There are distinct patterns of atrophy and fatty infiltration of the gluteus minimus and medius in end-stage osteoarthritis and normal ageing.
- End-stage osteoarthritis is associated with high levels of fatty infiltration in the anterior part of the gluteus minimus and medius and atrophy of the gluteus minimus.

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