

# A Randomized Trial Comparing Autologous Chondrocyte Implantation with Microfracture

## Findings at Five Years

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**Background:** The optimal treatment for cartilage lesions has not yet been established. The objective of this randomized trial was to compare autologous chondrocyte implantation with microfracture. This paper represents an update, with presentation of the clinical results at five years.

**Methods:** Eighty patients who had a single chronic symptomatic cartilage defect on the femoral condyle in a stable knee without general osteoarthritis were included in the study. Forty patients were treated with autologous chondrocyte implantation, and forty were treated with microfracture. We used the International Cartilage Repair Society, Lys-holm, Short Form-36, and Tegner forms to collect clinical data, and radiographs were evaluated with use of the Kellgren and Lawrence grading system.

**Results:** At two and five years, both groups had significant clinical improvement compared with the preoperative status. At the five-year follow-up interval, there were nine failures (23%) in both groups compared with two failures of the autologous chondrocyte implantation and one failure of the microfracture treatment at two years. Younger patients did better in both groups. We did not find a correlation between histological quality and clinical outcome. However, none of the patients with the best-quality cartilage (predominantly hyaline) at the two-year mark had a later failure. One-third of the patients in both groups had radiographic evidence of early osteoarthritis at five years.

**Conclusions:** Both methods provided satisfactory results in 77% of the patients at five years. There was no significant difference in the clinical and radiographic results between the two treatment groups and no correlation between the histological findings and the clinical outcome. One-third of the patients had early radiographic signs of osteoarthritis five years after the surgery. Further long-term follow-up is needed to determine if one method is better than the other and to study the progression of osteoarthritis.

**Level of Evidence:** Therapeutic Level I. See Instructions to Authors for a complete description of levels of evidence.

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In the literature, the prevalence of cartilage lesions in the knee in patients treated with arthroscopic knee surgery has ranged from 11% to 63%<sup>1-3</sup>. Autologous chondrocyte implantation was first described by Brittberg et al. in 1994<sup>4</sup>. The microfracture procedure was introduced by Steadman et al. more than twenty years ago and is now the method most commonly used to treat these lesions<sup>5</sup>.

A recent Cochrane review published in July 2006 included four randomized controlled trials comparing autologous chondrocyte implantation with other techniques<sup>6</sup>. The review revealed no evidence of significant differences between autologous chondrocyte implantation and other interventions. In addition, Jakobsen et al. found that most studies on cartilage repair had a very low methodological quality<sup>7</sup>. They concluded that no firm recommendations regarding which surgical procedure to choose for cartilage repair could be given.

In 2004, our group presented the two-year results of a randomized study comparing microfracture with autologous chondrocyte implantation in the knee<sup>8</sup>. Both methods had acceptable short-term clinical results, and in general small differences were found between the two treatments. The microfracture group had significantly more improvement in the Short Form-36 (SF-36) physical component score in the first two years than did the group treated with autologous chondrocyte implantation ( $p = 0.004$ ). There was no significant difference in macroscopic or histological results between the two treatment groups, and no association between the histological findings and the clinical outcome could be identified at the two-year time-point.

### Materials and Methods

As described in detail in our first article<sup>8</sup>, eighty patients with a single symptomatic cartilage defect and no general osteoarthritis in the knee were enrolled in this controlled randomized multicenter study. Forty patients were treated with autologous chondrocyte implantation and forty, with microfracture. The inclusion and exclusion criteria and the baseline characteristics of the patients are listed in the Appendix. The International Cartilage Repair Society (ICRS) form<sup>9</sup> was used to collect demographic data and to record the history, symptoms, functional score, pain as indicated on a visual analog scale, characteristics of the cartilage defect, and findings of the baseline clinical examination. In addition, the Lysholm score<sup>10</sup>, the Tegner score<sup>11</sup>, and the SF-36<sup>12</sup> were used. Informed consent was obtained from all patients, and the study protocol was approved by the National Review Board. Financial support was granted by the Norwegian Ministry of Health.

The etiology of the cartilage defect was trauma in 65% of the patients and osteochondritis dissecans in 28%; it was unknown in the rest. Most of the defects (89%) were located on the medial femoral condyle, with the remainder located on the lateral femoral condyle. All of the patients had a chronic cartilage defect, with a median duration of symptoms of thirty-six months, and 93% had had knee surgery before inclusion in the study. These operations included anterior cruciate ligament reconstruction (fifteen patients), meniscal

surgery (fourteen), arthroscopic lavage and débridement (twenty-nine), Pridie drilling (three), and operations for osteochondritis dissecans such as drilling or fixation of a fragment (thirteen). Autologous chondrocyte implantation was performed according to the recommendations of the Gothenburg group<sup>4,13</sup>. The conventional technique of autologous chondrocyte implantation was also used for the osteochondral defects. No included defects were deeper than 10 mm. The technique described by Steadman et al. was used for the microfracture procedures<sup>5,14</sup>. Both treatment groups were managed with an identical rehabilitation protocol, which included partial weight-bearing with crutches for eight weeks. At two years, second-look arthroscopy with a biopsy to obtain specimens for histological evaluation was done. An independent observer performed a follow-up clinical examination at twelve and twenty-four months using the same forms as had been used preoperatively.

The five-year follow-up evaluation was carried out by the first author (G.K.), for practical and economical reasons. The operation was considered to have failed if the patient needed a reoperation because of symptoms due to a lack of

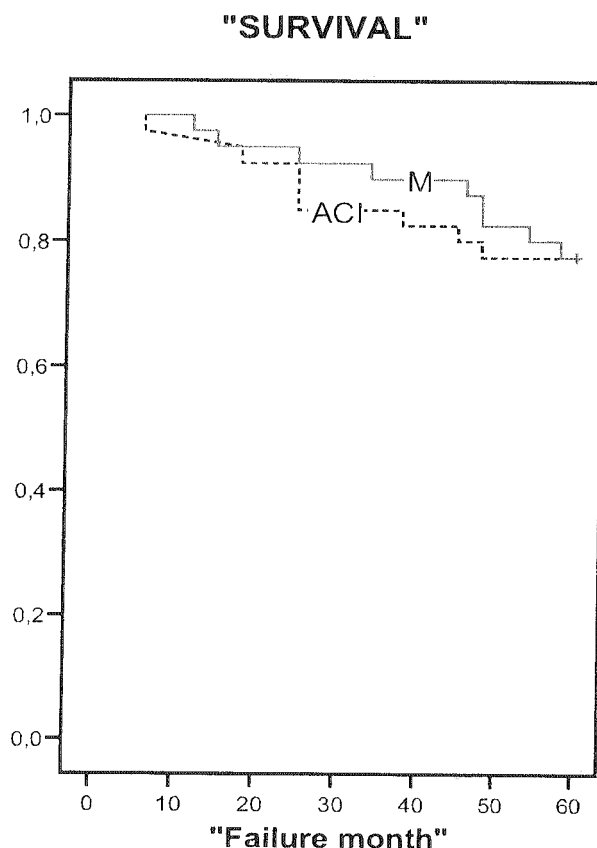


Fig. 1

At the time of the last follow-up (at sixty months), there were nine failures (23%) and thirty-one "survivors" (77%) in each group of forty patients. M = microfracture, and ACI = autologous chondrocyte implantation.

healing of the treated defect. The need for shaving or trimming of a lesion was not defined as a failure. As reported previously, shaving or trimming was performed prior to the second-look arthroscopy in ten patients (25%) treated with autologous chondrocyte implantation and four (10%) in the microfracture group<sup>8</sup>. The patients with a failure remained in the study, with their last recorded clinical follow-up scores before the failure considered to be their final clinical score. At five years, the radiographs were classified according to the system of Kellgren and Lawrence<sup>15</sup> (see Appendix). In addition, the distance between the tibia and femur on standing digital radiographs was measured in millimeters according to the ICRS form<sup>9</sup>. The distances were clustered into three groups: >4 mm, 2 to 4 mm, or <2 mm.

### Statistical Methods

An original sample-size estimation showed that forty patients in each group would be required to demonstrate a difference in the Lysholm and SF-36 scores between the groups of at least 0.75 standard deviation from the mean, with an alpha level of 0.05 and a power level of 90%.

T tests, the Pearson chi-square and Mann-Whitney U tests, and multiple linear regression models were used. The level of significance was  $p < 0.05$ .

### Results

At five years, no patient had been lost to follow-up. Seven patients had moved, were pregnant, or were not available for examination in the outpatient clinic. However, these patients (none of whom had a failure) were contacted by mail and/or telephone, and they returned their questionnaires. At the time of the five-year follow-up, there were nine failures (23%) in each group compared with two failures of the autologous chondrocyte implantation and one failure of the microfracture treatment at two years. The failures occurred at a mean of 26.2 months after the autologous chondrocyte implantation and 37.8 months after the microfracture treatment ( $p = 0.101$ ). The survival curve, up to sixty months, is shown in Figure 1.

In each group, one patient with a failure had a total knee replacement and the remaining patients with a failure were treated with a new cartilage-resurfacing operation. Seven pa-

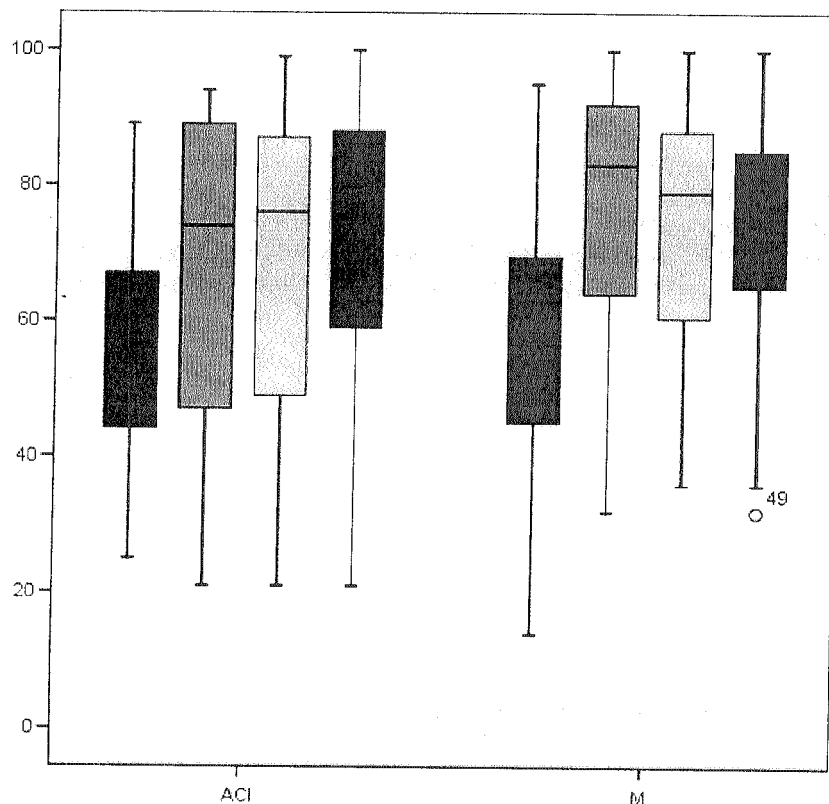


Fig. 2

Box plot showing the Lysholm scores preoperatively (blue) and at one (green), two (beige), and five (purple) years after the surgical procedure. The horizontal line across the interior of a box represents the median. Comparison of the Lysholm scores at five years after adjustment for pretreatment values (linear regression analysis) revealed no significant difference between the treatment groups ( $p = 0.227$ ). M = microfracture, and ACI = autologous chondrocyte implantation.

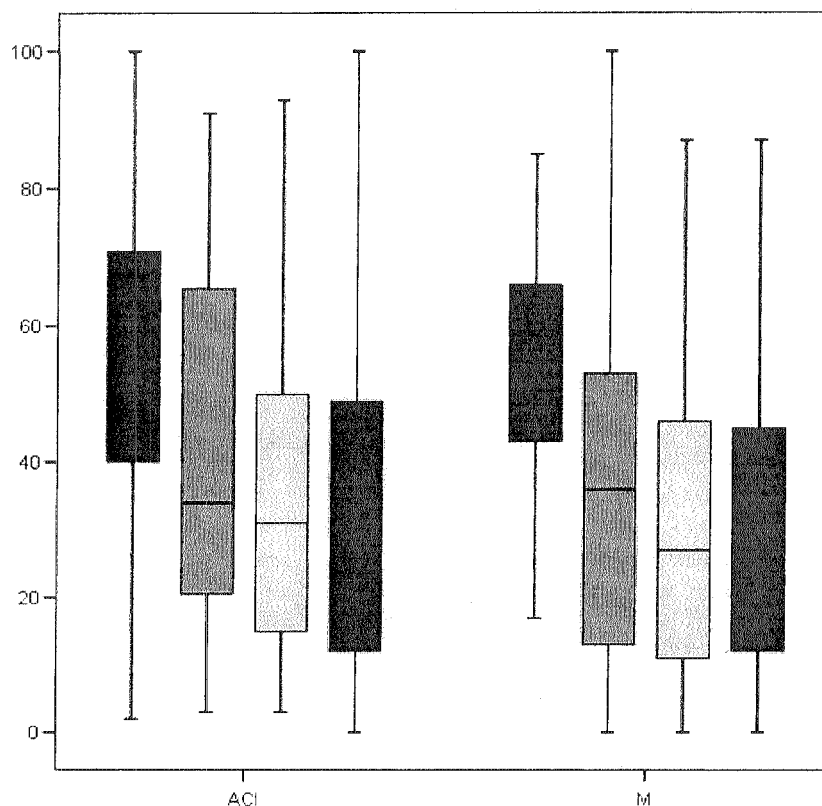


Fig. 3

Box plot showing the pain scores, according to a visual analog scale, preoperatively (blue) and at one (green), two (beige), and five (purple) years after the surgical procedure. The horizontal line across the interior of a box represents the median. Comparison of the pain scores at five years after adjustment for pretreatment values (linear regression analysis) revealed no significant difference between the treatment groups at five years ( $p = 0.278$ ). M = microfracture, and ACI = autologous chondrocyte implantation.

tients with a failure of autologous chondrocyte implantation were treated with microfracture alone, and one patient had, in addition to the microfracture, a high tibial osteotomy. Five patients who had a failure of the microfracture procedure were treated with a repeat microfracture procedure, two patients had mosaicplasty, and one patient had an autologous chondrocyte implantation procedure.

Clinical data on the patients who did not have a failure were collected at five years. The mean Lysholm scores and mean scores on the visual analog pain scale remained significantly improved ( $p < 0.05$ ) in both groups (Figs. 2 and 3). Compared with the baseline values, 72% of the patients had less pain, 80% had improvement in the Lysholm score, and 72% had improvement in the SF-36 physical component score. At two years, we reported that more active patients, as indicated by a Tegner score of  $>4$  points, had significantly better clinical results ( $p = 0.0005$ ). At five years, both groups had a significantly improved mean Tegner score compared with the baseline value: it improved from 3.28 to 4.05 points in the group treated with autologous chondrocyte implantation ( $p =$

0.007) and from 3.16 to 4.36 points in the microfracture group ( $p = 0.002$ ). However, with the numbers available, there was no difference between the two types of treatment ( $p = 0.323$ ).

No significant difference between the treatment groups was found in the Lysholm score ( $p = 0.227$ ) or the visual analog score ( $p = 0.278$ ) at five years after treatment, after adjustment for pretreatment measurements (with use of linear regression analysis). At the time of the two-year follow-up, the microfracture group had significantly more improvement in the SF-36 physical component score compared with the patients treated with autologous chondrocyte implantation ( $p = 0.004$ ). This difference was not found at five years ( $p = 0.054$ ) (Fig. 4). However, whereas there was no significant improvement in the SF-36 physical component score, from baseline to five years, in the group treated with autologous chondrocyte implantation ( $p = 0.309$ ), the microfracture group had a significant improvement in the score ( $p < 0.001$ ). Also, at five years younger patients (less than thirty years old) had a better clinical outcome than did older patients ( $p = 0.013$ ), regardless of their treatment group.

