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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, Lysholm, 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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A commentary is available with the electronic versions of this article, on our web site (www.jbjs.org) and on our quarterly CD-ROM (call our subscription department, at 781-449-9780, to order the CD-ROM).

In the literature, the prevalence of cartilage lesions in the knee in patients treated with arthroscopic knee surgery has ranged from 11% to 63%¹⁻³. Autologous chondrocyte implantation was first described by Brittberg et al. in 1994⁴. 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 lesions⁵.

A recent Cochrane review published in July 2006 included four randomized controlled trials comparing autologous chondrocyte implantation with other techniques⁶. 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 quality⁷. 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 knee⁸. 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 article⁸, 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) form⁹ 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 score¹⁰, the Tegner score¹¹, and the SF-36¹² 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

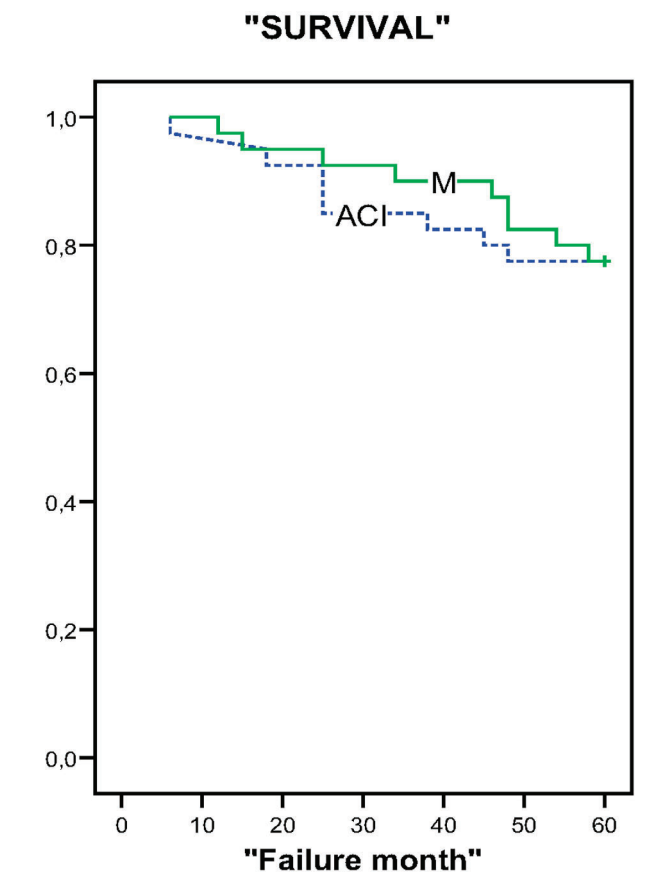


Fig. 1

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.

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^{4,13}. 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^{5,14}. 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

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 group⁸. 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 Lawrence¹⁵ (see Appendix). In addition, the distance between the tibia and femur on standing digital radiographs was measured in millimeters according to the ICRS form⁹. 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-

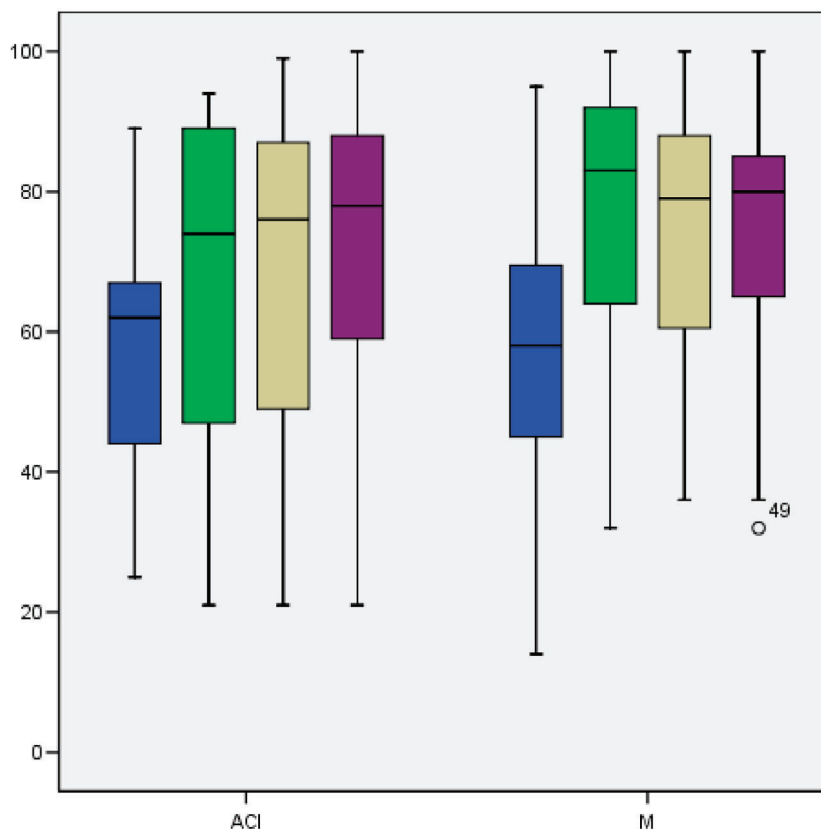


Fig. 2

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.

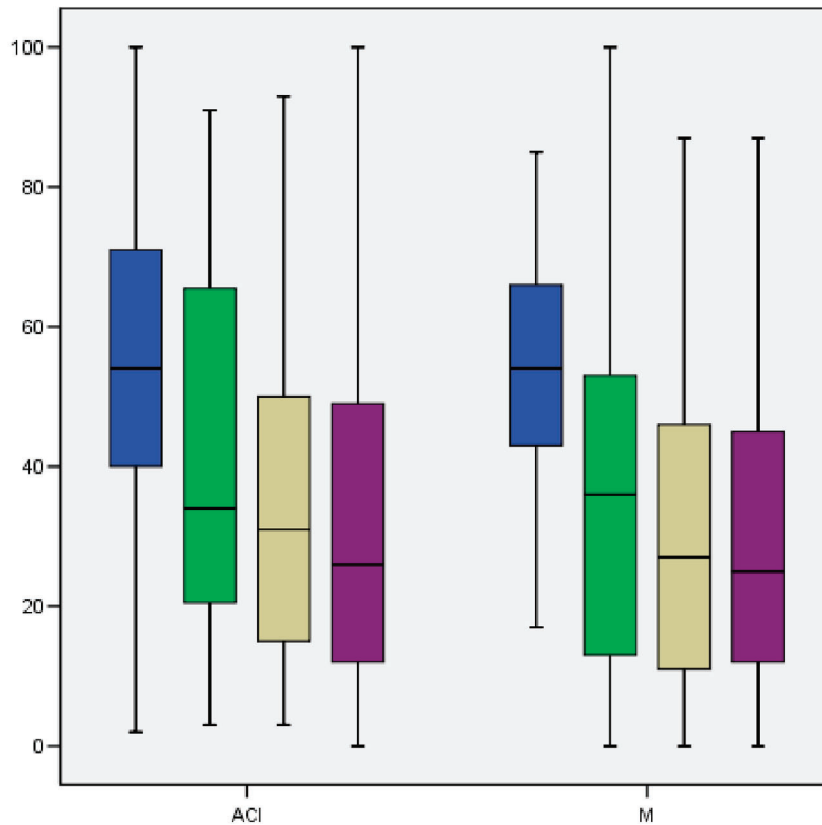


Fig. 3

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.

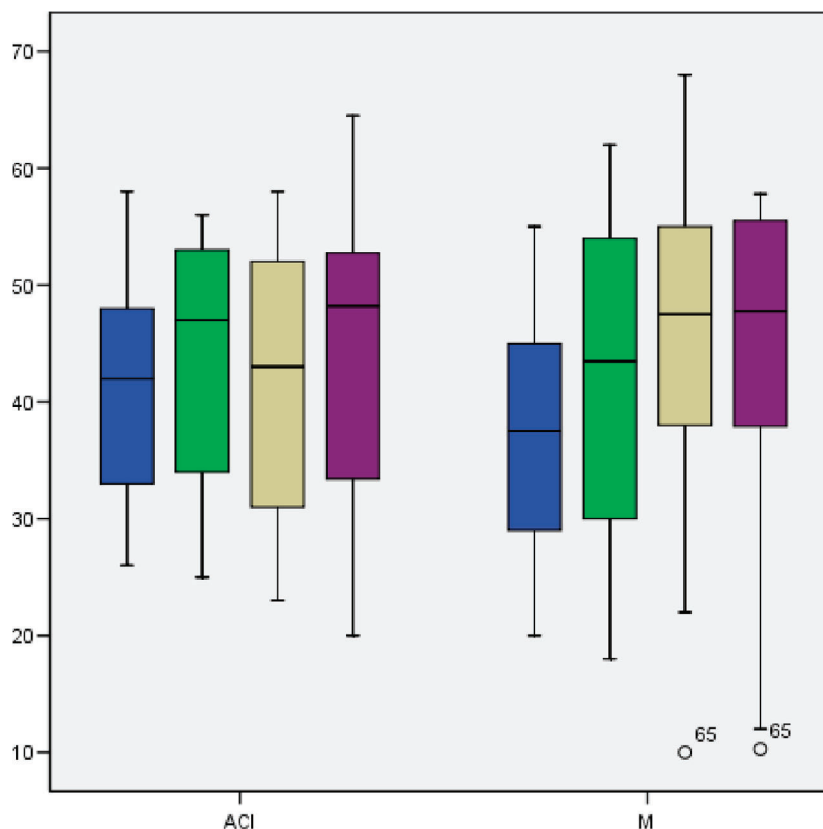


Fig. 4

Box plot showing the SF-36 physical component 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 SF-36 scores at five years after adjustment for pretreatment values (linear regression analysis) revealed no significant difference between the treatment groups at five years ($p = 0.054$). M = microfracture, and ACI = autologous chondrocyte implantation.

At the time of the two-year follow-up, histological evaluation was performed on biopsy specimens from sixty-seven patients (84%). There was no significant difference between the treatment groups with regard to the frequency with which hyaline and fibrocartilage repair tissues were found ($p = 0.08$). There was also no association between the clinical outcomes (according to the Lysholm score [$p = 0.160$], the visual analog scale [$p = 0.175$], and the SF-36 physical component score [$p = 0.850$]) at five years and the histological quality of the specimens (as assessed with a semiquantitative grading system ranging from 1 [best] to 4 [worst]) at two years. A comparison of the histological quality of biopsy specimens from twelve patients with a failure with that of fifty-five patients without a failure revealed that none of the failures were in knees with the best cartilage-quality score ($p = 0.001$). However, comparison of the histological quality scores of patients with and without failure with use of cross-tabulation showed no general significant difference ($p = 0.118$) (Table I). We found an association between the quality of the repair seen macroscopically (recorded at the arthroscopy done at two years) and the risk of

treatment failure ($p = 0.020$). A good repair according to the macroscopic appearance reduced the risk of treatment failure, and a bad repair increased the risk of failure.

TABLE I Cross-Tabulation Comparing Histological Qualities of Survivors and Failures

Histological Grade*	Total No. of Knees	No. of Failures by 5 Yr
1	10	0
2	16	3
3	29	6
4	12	3

*Grade 1 = predominantly hyaline tissue, grade 2 = fibrocartilage-hyaline mixture, grade 3 = fibrocartilage, and grade 4 = inadequate biopsy or no repair tissue (predominantly bone). None of the patients with a failure had the best-quality cartilage ($p = 0.001$).

Twenty-four percent (fifteen) of the sixty-two patients in the study in whom the procedure did not fail demonstrated a reduced joint space (<4 mm) on standing knee radiographs and 34% (twenty-one) of the patients had at least grade-2 changes according to the system of Kellgren and Lawrence at five years. However, with the numbers studied, no significant difference was found between the group treated with autologous chondrocyte implantation and the microfracture group regarding the frequency of radiographic changes at five years.

We did find an association between osteoarthritis, as measured on the Kellgren and Lawrence scale, and pain, as measured on the visual analog scale, at five years ($p = 0.035$). For this regression analysis calculation, the five-year visual analog score was used as the dependent variable and the radiographic grade was used as a constant predictor. This association suggests that patients with pain in the knee were more likely to have radiographic signs of early osteoarthritis. The same association was found between the SF-36 physical component score and radiographic evidence of osteoarthritis when the distance between the femur and tibia was measured ($p = 0.026$). With the numbers available, we did not find a significant association between the Lysholm score and radiographic evidence of osteoarthritis, as demonstrated by the distance between the femur and tibia ($p = 0.208$) or according to the scale of Kellgren and Lawrence ($p = 0.294$).

Discussion

In this prospective randomized study of relatively large chronic cartilage defects, both autologous chondrocyte implantation and microfracture resulted in significant clinical improvement at five years after treatment. Seventy-two percent of the patients had less pain and 80% of the patients had a better Lysholm score five years after treatment compared with preoperatively. However, there was a 23% rate of treatment failure in each group.

Autologous chondrocyte implantation and microfracture yielded similar results at two and five years. There was no significant difference between the groups regarding the clinical scores or failure rate at five years. A major strength of the study is that no patients were lost to follow-up, although some were only contacted by telephone and/or mail. This is also one of the largest, most comprehensive studies of these two procedures, which included evaluation of clinical results, histological examination of biopsy specimens from cartilage repair sites at two years, macroscopic results, and radiographs of patients randomized to treatment with autologous chondrocyte implantation or microfracture. A relative weakness of the study is that, unlike the two-year follow-up evaluation, which was performed by an independent observer, the five-year follow-up evaluation was carried out by an author of the study. However, the risk of bias was reduced by using patient-based scoring forms.

Autologous chondrocyte implantation is a more technically demanding procedure than microfracture; it also requires two separate operations, including an arthrotomy for the implantation of the cells. However, all surgeons were exper-

rienced knee surgeons trained in both procedures. Our rehabilitation protocol was in line with recommendations^{4,5}. As was the case in other published reports^{4,5,7}, we have no data on patient compliance with the rehabilitation protocol. The location of the defect may also be an important factor. Recently, microfracture was found to have less favorable results when it was used to treat patellofemoral lesions, and autologous chondrocyte implantation may be a better option for trochlear defects¹⁶. Most (89%) of the defects in this study were located on the medial femoral condyle, with the remaining ones on the lateral femoral condyle. Finally, our cohort of patients had chronic and relatively large lesions. No patient with an acute injury was included.

Another limitation of our study is the lack of a control group that was not treated with surgery or was treated simply with arthroscopic lavage. Our patients had experienced pain for a long period of time, and the majority had undergone previous surgery and conservative treatment. Consequently, it would have been difficult to assign patients to such control groups.

The natural history of cartilage injuries is still not well understood, and we do not know which patients will benefit from surgical interventions. Linden performed a long-term follow-up study of patients with osteochondritis dissecans of the femoral condyles¹⁷. He concluded that patients with adult-onset osteochondritis dissecans had osteoarthritis ten years earlier than might be expected for the onset of primary osteoarthritis. In contrast, when the osteochondritis dissecans was diagnosed in childhood, the patient had no increased risk of osteoarthritis later in life when compared with the normal population. Shelbourne et al. found that chondral injuries noted at the time of anterior cruciate ligament reconstruction did not influence the clinical outcome of the operation at a mean of 8.7 years¹⁸. However, the defects were small, and the population was young. In contrast to the observations in that study, two of us (J.O.D. and T.G.) found a significant relationship between cartilage injury detected prior to anterior cruciate ligament reconstruction and osteoarthritis found eight years postoperatively ($p < 0.005$)¹⁹.

In our study, we included only chronic symptomatic lesions (median duration of symptoms, thirty-six months). Acute chondral and subchondral injuries may heal completely or partially with repair tissue and become asymptomatic regardless of treatment, and this makes it difficult to include these injuries in a controlled study. Some studies have included patients with acute lesions. For example, 21% of the lesions were acute in the evaluation of microfracture by Steadman et al.⁵. It is difficult to understand the mechanism of chronic pain and disability. Even though cartilage defects are found, they can be asymptomatic and the pain may be caused by other conditions in the knee or the surrounding structures. Referred pain and a psychosomatic influence also have to be considered, but these aspects are not easily evaluated in a study such as the present one. Bodily pain lasting for more than six months is often classified as chronic²⁰.

In our trial, there was a 23% failure rate in each treatment group by the five-year follow-up time-point. Peterson et

al. reported a failure rate of 11% after autologous chondrocyte implantation on the femoral condyles, with most of the failures occurring less than two years postoperatively¹³. Their clinical success rate has been quoted to be from 80% to 90%, and they concluded that a graft surviving for two years is likely to remain viable three to eight years later. In a recent study of the clinical outcomes of autologous chondrocyte implantation in the United States (data derived from the Carticel prospective cartilage repair registry), a five-year follow-up was completed for eighty-seven of 100 patients²¹. The treatment failed in thirteen patients (15%), and overall sixty-two patients had improved scores at the time of follow-up. However, the results for the thirteen missing patients are unknown. The mean defect size in that study was 4.9 cm², which is comparable with the defect size in our study.

Success rates similar to those reported for autologous chondrocyte implantation have been reported after microfracture procedures. Steadman et al. found that, at seven years after microfracture surgery, 80% of their patients rated their condition as improved⁵. All of these patients were less than forty-five years of age when they were enrolled in the study, and the mean size of the defects (2.77 cm²) was smaller than it was in our study. That study also included some acute defects. Recently, Kreuz et al. reported good short-term results following microfracture, although they observed deterioration of some of those results starting at eighteen months after the surgery¹⁶.

Horas et al. presented the results of a prospective, comparative trial of the two-year outcomes of forty patients randomized to be treated with either autologous chondrocyte implantation or osteochondral cylinder transplantation²². Each group consisted of twenty patients. No significant difference in the Tegner and Meyers scores was found between groups, although the Lysholm scores at six, twelve, and twenty-four months were significantly higher in the group treated with osteochondral cylinder transplantation ($p < 0.05$).

Bentley et al. reported that autologous chondrocyte implantation yielded better results than did mosaicplasty, although the difference was not significant in the overall series, and they found hyaline cartilage in seven of nineteen biopsy specimens obtained at one year after autologous chondrocyte implantation²³. In contrast to many rehabilitation protocols, the protocol in that study included immobilization in a cylinder cast for ten days after the surgery. Subgroup analysis showed that the Cincinnati score was significantly better for patients in whom the medial femoral condyle had been treated by autologous chondrocyte implantation than it was for those who had mosaicplasty at that location ($p < 0.032$).

The above studies^{22,23}, in addition to the one from our group⁸, were three of the four studies included in the recent Cochrane review⁶. The fourth study included in that review was a non-randomized study comparing twenty-seven matrix-guided autologous chondrocyte implantation procedures with seven microfracture operations²⁴. The authors reported significantly better Lysholm scores at twenty-four months in the group treated with matrix-guided autologous chondrocyte implantation ($p = 0.049$), but differences in the Tegner and

ICRS scores at twenty-four months were not significant.

The preliminary results of a clinical study comparing periosteal covering of femoral defects in the knee with and without implantation of cultured autologous chondrocytes was presented at the ICRS conference in San Diego in 2006²⁵. No clinically relevant difference between the two groups was found at twelve months. However, biopsies done at the same time-point showed significantly more hyaline cartilage in the group that received chondrocytes ($p = 0.003$).

In our study, 34% of the patients had radiographic evidence of early osteoarthritis at five years after treatment. This is remarkable considering that, at this time-point, our patients were in their late thirties and the fact that radiographic evidence of osteoarthritis was an exclusion criterion at the outset of the study. An unfortunate weakness of our original study design, however, was that the Kellgren and Lawrence methodology was not used. The standing knee radiographs were merely graded as normal by the radiologist if there was at least a 4-mm distance between the tibia and femur. Lohmander et al. found that 51% of female soccer players (mean age at assessment, thirty-one years) had radiographic changes (comparable with a Kellgren and Lawrence grade of 2) in the knee twelve years after injury to the anterior cruciate ligament²⁶. At baseline, 93% of our patients had had previous surgery. Thus, considering the relatively large and chronic defects that were included in our study, it may not be surprising that early radiographic signs of arthritis were present in about one-third of the patients at the time of the five-year follow-up. As described by Englund, several studies have shown only a limited correlation between radiographic signs of osteoarthritis and clinical outcome scores, and he reported that nearly half of patients who had radiographic evidence of osteoarthritis of the knee were asymptomatic²⁷. However, we found an association between pain and radiographic evidence of osteoarthritis as defined with the Kellgren and Lawrence scale, and this has also been reported by others^{28,29}.

A comparison of the histological quality of the repair tissue between patients with and without failure of treatment revealed no significant difference, but none of the patients with a failure in our study had the best-quality cartilage. This finding suggests that repair cartilage, which is predominantly hyaline, at two years may reduce the risk of later failure.

The results of our study led us to propose that microfracture, a low-cost and minimally invasive procedure, should be preferred as the first-line cartilage repair procedure for defects located on the medial or lateral femoral condyle of the knee. Autologous chondrocyte implantation may be preferred as a second-line treatment, particularly for large defects that are not contained.

Further research is needed to improve current surgical treatment of cartilage defects. There must be improvements in surgical techniques as well as in the field of cellular and molecular biology. Valid clinical answers in this field can be obtained only through the combination of additional randomized clinical trials and strictly controlled independent registry reviews.

Appendix

eA Tables showing the inclusion and exclusion criteria and the basic patient characteristics of the original study as well as the Kellgren and Lawrence grading system are available with the electronic versions of this article, on our web site at jbsj.org (go to the article citation and click on "Supplementary Material") and on our quarterly CD-ROM (call our subscription department, at 781-449-9780, to order the CD-ROM). ■

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