Knee Surg, Sports Traumatol, Arthrosc
(2001) 9 : 358–363

KNEE

DOI 10.1007/s001670100209

A. Lindahl
M. Brittberg
L. Peterson

Health economics benefits following autologous chondrocyte transplantation for patients with focal chondral lesions of the knee

Received: 30 September 1999
Accepted: 31 January 2001
Published online: 29 June 2001

A. Lindahl (✉)
Institute of Laboratory Medicine,
Department of Clinical Chemistry
and Transfusion Medicine,
SE 41345 Sahlgrens University Hospital,
Gothenburg, Sweden
e-mail: anders.lindahl@clinchem.gu.se,
Tel.: +46-31-3424089,
Fax: +46-31-828458

M. Brittberg · L. Peterson
Department of Orthopedic Surgery,
Gothenburg University,
Gothenburg, Sweden

Abstract Autologous chondrocyte transplantation (ACT) for the treatment of cartilage injuries has been in clinical use for several years. Since this new technique is potentially more costly and invasive than traditional conservative therapies, we evaluated the effect of ACT on clinical outcome, absenteeism, disability status, and total direct economic burden in 57 patients with full-thickness chondral lesions of the knee treated between 1987 and 1996. Patients graded good or excellent following ACT in the treatments groups were: femoral condyles (28/33), femoral condyles with anterior cruciate ligament (ACL) repair (5/5), osteochondritis dissecans (7/8), and patellar lesions (9/11). Pre-ACT, 57/57 patients were disabled and post-ACT (mean follow-up 7.3years) 44/57 had no sickness, 10/57 had minor disability, and 1/57 was disabled. Two of the 57 patients suffered re-injury during the follow-up time. In the 10-year period prior to ACT, the average cost of absenteeism and surgery was SEK 982,457 ($ 122,807) and SEK 47,000 ($ 5,875), respectively, compared to the post-ACT period where both absenteeism and medical costs were dramatically reduced: SEK 9,508 ($ 1,189) and SEK 7,050 ($ 881), respectively. In conclusion, 49 of the 57 patients improved clinically as a result of the ACT treatment. A dramatic cost-saving effect was demonstrated over a projected 10-year period due to reduced absenteeism and disability.

Keywords Articular cartilage · Chondrocytes · Economics · Sick leave · Knee injuries

Introduction

Large, full-thickness chondral lesions of the knee are a relatively common problem in orthopedics, affecting thousands of individuals annually. Various authors have independently documented the presence of these lesions associated with acute hemarthrosis of the knee, with an incidence of 5–10% in these patients [15]. A recent study by Curl and colleagues has underscored the prevalence of these lesions, with more than 63% of 31,516 knee arthroscopies demonstrating chondral lesions, with nearly 20% of these being grade IV (exposed bone) in nature [3].

Therapeutic alternatives for these injuries have traditionally been limited to a variety of techniques (e.g., abrasion, drilling, microfracture) designed to penetrate the subchondral bone plate, supplying pluripotent stem cells capable of forming a fibrocartilage tissue. The clinical course of these repairs may be unpredictable, most likely due to incomplete filling of the defect and the inferior nature of the repair tissue itself [1, 5, 18]. This appears particularly true for larger defects (>2 cm^2) and individuals participating in activities that place an increased impact load on the joint. Although these individuals may initially receive clinical benefit from these methods, most steadily deteriorate over a relatively short period of time.

In an attempt to improve the clinical course of patients with these defects, autologous chondrocyte implantation was introduced in Sweden in 1987, and the results of the first human trial was published in the *New England Jour-*

nal of Medicine in 1994 [2]. This procedure utilizes tissue culture techniques to replicate chondrocytes from a small sample of the patient's own normal articular cartilage. These cultured chondrocytes are implanted beneath a periosteal patch, forming a hyaline-type repair tissue that completely fills the defect. The hyaline nature of the repair tissue appears substantially more durable than fibrocartilage alternatives: arthroscopic probe measurement indicates a comparable stiffness to undamaged articular cartilage, and 96% of patients with excellent/good results at 2 years maintain this status for a further 10 years [16, 17].

Recently, a number of groups have independently replicated our initial results and documented improvement in approximately 85% of patients with femoral lesions [6, 7, 9, 10, 13]. While the majority of these studies have focused on clinical outcomes, one recently published study assessed the benefit of improved knee function on health-related quality of life (QOL), and compared the direct medical costs associated with ACT to those of other therapies [12]. The study concluded that ACT results in a statistically significant improvement in QOL at a cost comparable to or less than that of other commonly reimbursed orthopedic, biotechnology, and chronic disease therapies. The study did not, however, attempt to assess whether the total (medical and non-medical) economic burden is reduced following ACT.

Because this issue is essential in evaluating any new technology, particularly one that is potentially more costly and invasive than traditional conservative therapies, we evaluated the effect of ACT on clinical outcome, absenteeism, disability status, and total direct economic burden in patients with full-thickness chondral lesions of the knee.

Materials and methods

Patients

Fifty-seven Swedish patients underwent ACT between November 1987 and February 1996 and were assessed with regard to both clinical and economic status. Owing to the difficulty of obtaining data about patients' financial status, this cohort was chosen a priori, independent of clinical outcome, based on the patient's residence in Sweden (where economic data is collected) and sufficient time of follow-up. This cohort represents all Swedish patients with a minimum of a 5-year follow-up and all patients from the Gothenburg area with a minimum of a 2-year follow-up. No patients were lost to follow-up. In order to assess the net change in disability and corresponding costs, patients were evaluated with respect to both the period from initial disability determination until chondrocyte transplantation (the pre-ACT period) and the crossover into post-ACT period, and were followed up for a minimum of 2 years.

Operative technique

With the patient under general or spinal anesthesia, a medial or lateral parapatellar arthrotomy was performed in a tourniquet-controlled bloodless field. The chondral lesion was debrided back to the best available cartilage, while still maintaining a contained lesion. At all times, care was taken not to penetrate the subchondral bone plate or provoke bleeding from the wound bed. A periosteal flap was harvested from the proximal medial subcutaneous border of the tibia. The flap was fitted and sutured to the surrounding rim of the debrided cartilage with interrupted 5–0 or 6–0 Vicryl or Dexon sutures with the deep cambium layer facing the subchondral bone plate. The periosteal rim was sealed with a fibrin glue (Tisseel, Immuno AG, Vienna, Austria), except for one corner where the implanted chondrocytes were injected into the defect. Continuous passive motion was administered for 48 h after surgery. Rehabilitation on crutches began with gradual weight-bearing for 8 weeks, progressing to full weight-bearing by 10–12 weeks. Emphasis during rehabilitation was on functional use of the limb and active muscle recruitment [17].

Clinical evaluation

Pre-ACT and post-ACT clinical status was assessed by a retrospective review of medical records, a survey questionnaire, and by prospective clinical examination. This information included patient demographics, lesion characteristics, time of initial injury diagnosis, number of surgeries prior to ACT, date of ACT implantation, number of post-ACT surgeries, and post-implant clinical status. Overall clinician assessment following ACT was graded as poor, fair, good, and excellent, based on the modified Cincinnati rating scale [14].

Absenteeism and disability

Information on absenteeism and disability status was obtained from 23 regional Swedish social affairs offices ("Försäkringskassan"), which maintain diagnosis-specific information on all employed Swedish citizens. Reported sick-days include absenteeism solely due to the affected knee. Disability status was specified as 1 of 5 conditions ranging from "early retirement" to "no sickness". The pre-ACT period begins with the first disability diagnosis for the affected knee and ends on the day prior to implantation. The post-ACT period includes the time from the day of implant until the last follow-up date. Rehabilitation time is calculated separately for ACT and alternative surgical procedures.

Costs

Direct medical costs were based on the actual cost of service reported at the treating facility (Eastern Hospital at Sahlgrenska University Hospital and Gothenburg Medical Center, Gothenburg Sweden and Kungsbacka Hospital, Kungsbacka, Sweden). Costs for procedures included in the reference case are shown in Table 1; in order to account for variations in treatment costs across various countries, a wide range of treatment costs is assessed in the sensitivity analysis. Medical costs include actual surgical costs, cell processing costs, and rehabilitation costs. The cost of disability to Swedish society (SEK 231,510) was based on figures supplied by the Swedish Institute for Health Economics for an average male, age 25–34, on sick leave during 1996, and includes the cost (SEK 117,000) of reimbursement for lost wages. To account for the inclusion of holidays and weekends in the sick-days figure reported by the social affairs offices, the total number of sick-days was multiplied by 0.7 in calculating the total economic burden.

United States dollar equivalents are given based on a conversion rate of 8 Swedish Kroner per dollar. All figures are 1998 SEK/USD with prior costs adjusted at a 3% annual rate to account for inflation. Future expenditures are discounted at an annual rate of 3% in the reference case, to account for time preference. The impact of variations in the discount rate is assessed in the sensitivity analysis.

Table 1 Costs used in baseline and sensitivity analyses

	Baseline cost SEK (US $)	Range for sensitivity analysis
Arthroscopic surgery	SEK 10,000 ($ 1,250)	SEK 5,000 ($ 625) to SEK 100,000 ($ 12,500)
ACT (including cost of cells)	SEK 100,000 ($ 12,500)	SEK 60,000 ($ 7,500) to SEK 240,000 ($ 30,000)
Rehabilitation following arthroscopy	SEK 13,500 ($ 1,688)	SEK 7,000 ($ 875) to SEK 27,000 ($ 3,375)
Rehabilitation following ACT	SEK 81,377 ($ 10,172)	SEK 5,000 ($ 625) to SEK 150,000 ($ 18,750)
Cost of disability (per year)	SEK 231,520 ($ 28,939)	SEK 150,000 ($ 18,750) to SEK 600,000 ($ 75,000)

Model and statistical methods

In the base case analysis, we project 10-year costs based on the conservative assumption that the observed number of surgeries in the pre-ACT period were the actual number in 10 years, and that the annual rate of reoperation following ACT remained constant over the 10 years. The cost of illness was based on the annual incidence rate of absenteeism during both the pre-ACT and post-ACT periods, assuming the rate is constant over the entire 10-year period. In order to determine the impact of changes in this assumption, we altered the reoperation distribution in the sensitivity analysis, allowing projected surgeries to occur earlier or later in the 10-year period.

We used multivariate and univariate analyses of variance (ANOVAs) and covariance to assess differences in clinical outcome, disability status, number of operative procedures, and absenteeism. Exact statistical tests on proportions were used to compare the probability of absenteeism. Statistical significance was set at the 0.05 level.

Results

Demographic and clinical evaluations

Mean follow-up for the 57 patients evaluated is 5 years, range 2–10 years. Demographics and lesion characteristics are shown in Table 2. The majority of treatments (58%) were for isolated defects located on the femoral condyles. Five additional condylar defects (9%) were treated concomitantly with surgical repair of ligamentous instability, and eight defects (14%) on the distal femur were due to osteochondritis dissecans. The remaining 11 defects (19%) were located on the patella.

Clinical outcome based on the modified Cincinnati Knee Rating System is shown in Table 3.

Table 2 Patient demographics and lesion characteristics

Mean age (range)	31 (15–49)
Sex	61% male
Lesion Location	
Femoral chondyle	33
Femoral condyle with ACL repair	5
Osteochondritis dissecans	8
Patella	11

Table 3 Clinical outcome after ACT

Defect location	Number good/excellent clinical rating/total (%)
Femoral condyle	28/33 (85%)
Femoral condyle + ACL repair	5/5 (100%)
Osteochondritis dissecans	7/8 (88%)
Patella	9/11 (82%)

Table 4 Disability and absenteeism

	Pre-ACT	Post-ACT
Disability status		
No sickness	0	44 (77%)
Partial/minor disability	0	10 (17%)
Disabled	57 (100%)	1 (2%)
Re-injured	0	2 (4%)
Mean days absent/year (range)	155 (5–365)	1.5 (0–58)
Mean reoperation rate/year (range)	0.2 (0.0–0.6)	0.03 (0.0–0.6)

Disability and absenteeism

As shown in Table 4, intervention with ACT resulted in reductions for both the number of disabled individuals and the number of missed days of work. The probability of an individual reporting no disability increased from 0% prior to implantation to 87% in the period following ACT ($P<0.01$). Patients were also less likely to require one or more days of sick leave in the post-ACT period (78% vs 18%, $P<0.01$).

Costs

In the 10-year period prior to ACT, the average patient was projected to require a total of 2 surgical procedures at a nominal cost of SEK 47,000 ($ 5,875), including rehabilitation. An additional nominal cost of SEK 982,457 ($ 122,807) per patient was also incurred due to the cost of absenteeism from work (mean 155 days per year).

In the post-ACT period, both medical costs and absenteeism costs were dramatically reduced. The average patient required only 0.3 additional surgical interventions in the 10-year period following ACT, at a nominal cost of

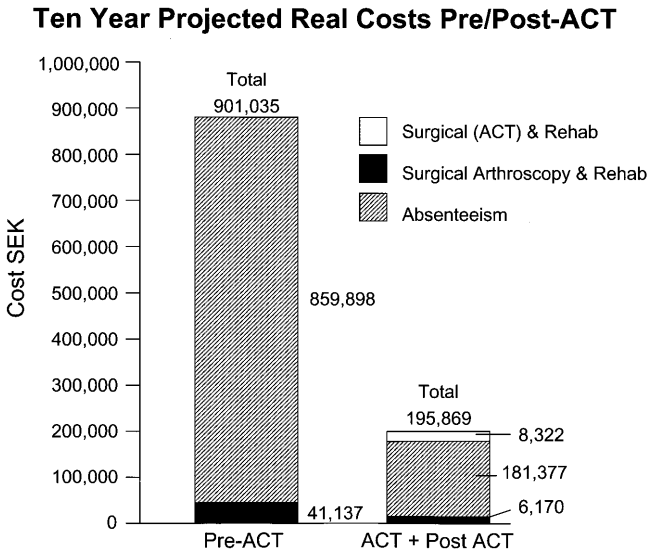

Fig. 1 Ten-year projected real costs pre/post-ACT

SEK 7,050 ($ 881), with additional nominal absenteeism costs of SEK 9,508 ($ 1,189).

As demonstrated in Fig. 1, intervention with ACT resulted in a significant real cost-savings: SEK 705,166 ($ 88,146). The value in Fig. 1 appropriately represent real costs (i.e. adjusted to 1998 SEK/$) and thus differ from the previously reported nominal costs where the timing of expenditures is not considered.

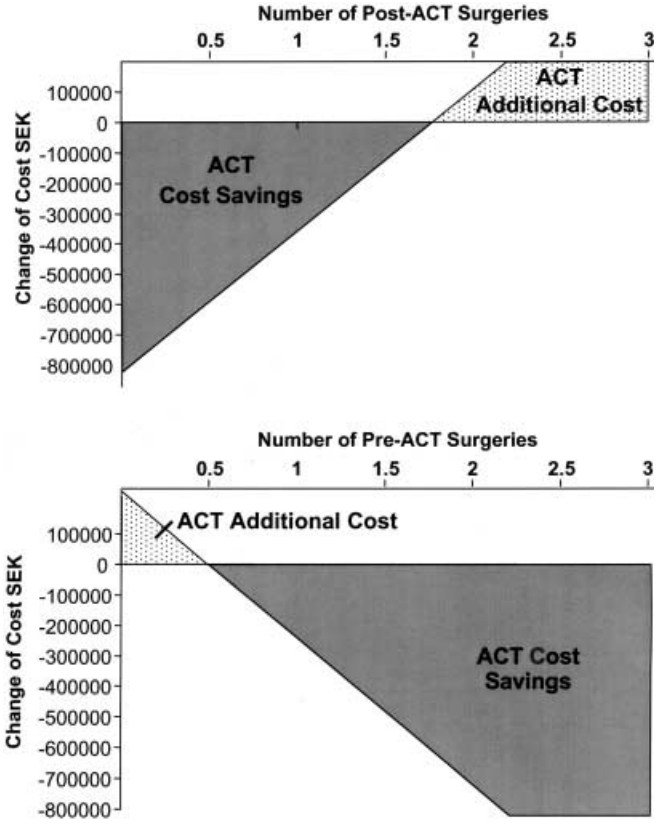

Fig. 2 Sensitivity analysis

Sensitivity analyses

Our sensitivity analyses indicate that estimates of the economic impact of treatment with ACT were not substantially influenced by increases in the number of post-ACT surgeries required. We recalculated the projected 10-year cost of ACT treatment, assuming the total number of post-ACT surgeries varied from 0.1 to 5, with accompanying rehabilitation and absenteeism costs included (Fig. 2, top panel). The threshold for equal costs during the pre-ACT and post-ACT periods was found to occur when the total number of post-ACT surgeries exceeded 1.8. If lost days of work were allowed to vary independent of the number of surgeries, the threshold occurred when absenteeism in the post-ACT period exceeded 128 days. The bottom panel of Fig. 2 is based on a range of total pre-ACT surgeries (0.1–5) and the reference case assumption of 0.3 post-ACT surgeries. The threshold for equal costs in this analysis was 0.5 total pre-ACT surgeries in a 10 year period, below which costs are lower in the pre-ACT period. Similarly, the results were also sensitive to the average number of workdays lost per year in the pre-ACT period, with the threshold for equal costs at 28 days per year.

If the average cost of surgeries in the pre-ACT or post-ACT periods is varied, the magnitude of the cost difference varies slightly; however, no reasonable increase in the cost of post-ACT surgeries (including reimplantation with ACT) results in a cost advantage for the pre-ACT period. If the post-ACT surgeries are always assumed to be reimplantation with ACT, a reoperation rate of 18.3% per year would be required for cost-equivalence. Reasonable reductions in pre-ACT surgery cost do not produce substantial changes in costs.

ACT surgery has a wide range of costs worldwide, primarily due to variations in cell processing fees. Sensitivity analyses indicate that ACT costs ranging from SEK 60,000 ($ 7,500) to SEK 240,000 ($ 30,000) reduce, but do not eliminate, the cost-savings afforded by ACT; range: SEK 745,166 ($ 93,146) to SEK 656,166 ($ 82,021).

Other variables had minimal or no impact on our estimate. Using a discount rate of 0% rather than 3%, increased the cost-savings SEK 831,522 ($ 103,940); a change in rate from 3% to 7% reduced the savings to SEK 565,300 ($ 70,663). Changes in the timing of subsequent surgeries, including timing all surgeries in sequential years at the beginning or end of the 10-year period, had only minimal effect on the overall cost-savings.

Discussion

Although many studies have examined the clinical effectiveness of various repair techniques for chondral lesions, we are aware of none that have correlated the clinical benefits of the treatment, with the effect on workplace disability, absenteeism, and the economic burden to society. In this study, disability status and absenteeism were dramatically improved following treatment with ACT.

Furthermore, our reference case analysis indicated that in patients with these relatively large lesions, treatment with ACT reduces both the number of patients on disability and absenteeism, resulting in a cost-savings of SEK 705,166 ($ 88,146). These savings stem both from a reduction in the number of required surgeries, and a decrease in absenteeism from work. Our study suggests that treatment with ACT is particularly successful in returning individuals currently on disability to the workforce.

In this young patient population, there is a concern that results may be rendered less valid by patients who are students, and therefore may not contribute sick leave costs. We therefore specifically examined the data for patients of potential student age (≤21 years). Only one patient was less than 18 years of age and clearly a student (age 15). This patient did not contribute disability days or costs to either the pre-ACT or post-ACT periods. Three additional students were of probable student age (18–21 years). Two of these individuals contributed disability days (and costs) in the pre-ACT period and therefore had their post-ACT values included as well. One patient had no disability days or costs in either the pre-ACT or post-ACT periods.

When evaluating any economic model, it is important to consider the sensitivity of the model to any underlying assumptions used. We systematically assessed these assumptions in our analyses and determined that ACT remains cost saving under a variety of scenarios. Of particular importance was the observation that the cost-savings remain robust even when ACT treatment costs increase – as may occur in markets such as the United States, where cell therapies are regulated by the federal government.

Our sensitivity analysis also specifically addressed variations in reoperation rate. Data from one center in the United States has indicated a higher reoperation rate than in our experience. The authors of this study do not comment on the potential underlying cause of this higher rate, although their early position on the learning curve and differences in patient selection may result in some of the difference. Because of the early nature of their results – with a mean follow-up of only 16 months – we are unable to directly compare reoperation rates to our series. The sensitivity analysis, however, indicates that *every* patient would need to undergo 1.8 post-ACT surgeries (or alternatively that 30% of patients would need to undergo a mean of 6 post-ACT surgeries) in order for post-ACT costs to exceed pre-ACT values [8]. We believe this scenario to be unlikely.

A large portion of the cost-savings achieved with ACT is as a result of reduced absenteeism in the workplace. This finding is particularly important in light of the young age and employment status of the majority of patients with chondral injury. The average age in our sample was 31, and many of the patients were involved in professions requiring physical labor. Even minor pain or functional impairment may thus result in substantial absenteeism or early retirement, with the costs being carried forward for the remaining decades of the individual's productive work life. Thus, the total lifetime economic benefit of intervention with ACT may exceed that demonstrated in the 10-year period modeled in this analysis.

When is the use of ACT cost-effective? Currently it is difficult to predict, a priori, in which patients the greatest economic benefit will be obtained. Our analysis suggests that ACT is cost-saving when more than 50% of patients initially treated with an alternative surgery will fail and require additional surgical intervention during a 10 year period. Alternatively, even when this figure is not exceeded, ACT is cost-effective when annual absenteeism due to the affected knee exceeds 28 days with alternative treatment.

Determining which patients fit this description at the time of initial diagnosis remains a clinical challenge. At present, the best support for making this decision comes from the few case series reporting subset analyses for patients undergoing debridement/lavage and marrow stimulation techniques. These series generally demonstrate that large lesion size and high patient demand are predictors of poor outcome for these alternative treatments. For example, Dzioba reports that 100% of patients with large, chronic, and/or full-thickness lesions failed to respond to treatment with debridement and drilling [4]. Similarly, Steadman and colleagues report that treatment with microfracture resulted in an improvement in only 65% of patients involved in strenuous sports and labor, versus 75% in others [19]. At present, the best available evidence would seem to indicate that it is patients with larger defects (>2 cm^2), and those who have failed alternative treatments, for whom ACT is most cost-effective [11]. Definitive results await completion of additional trials, particularly those that assess optimal treatments for patients with moderately sized defects (1–2 cm^2).

References

1. Bert JM (1993) Role of abrasion arthroplasty and debridement in the management of osteoarthritis of the knee. Rheum Dis Clin North Am 19: 725–739
2. Brittberg M, Lindahl A, Nilsson A et al (1994) Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. N Engl J Med 331:889–895
3. Curl WW, Krome J, Gordon ES et al (1997) Cartilage injuries: a review of 31,516 knee arthroscopies. Arthroscopy 13:456–460
4. Dzioba RB (1988) The classification and treatment of acute articular cartilage lesions. Arthroscopy 4:72–80
5. Friedman MJ, Berasi CC, Fox JM et al (1984) Preliminary results with abrasion arthroplasty in the osteoarthritic knee. Clin Orthop 182:200–205
6. Gillogly SD, Voight M, Blackburn T (1998) Treatment of articular cartilage defects of the knee with autologous chondrocyte implantation. J Orthop Sports Phys Ther 28:241–251
7. Haugegaard M, Lundsgaard C, Vibe-Hansen H (1998) Treatment of cartilage defects with autologous chondrocyte implantation – preliminary results. Acta Orthop Scand 2:11
8. Koh J, Potter H, Buly R et al (2000) Autologous chondroctye implantation (ACI) of the knee: early results. Paper presented at the 67th Annual Meeting of the American Academy of Orthopedic Surgeons, Orlando, FL
9. Lohnert J, Ruhnau K, Gossen A et al (1999) Autologous chondrocyte transplantation (ACT) in the knee joint – first clinical results. Arthroscopy 12: 34–42
10. Mandelbaum B, Browne J, Erggelet C et al (2000) 3-year multicenter outcome of autologous chondrocyte implantation of the knee. Paper presented at the 67th Annual Meeting of the American Academy of Orthopedic Surgeons, Orlando, FL, USA
11. Mandelbaum BR, Browne JE, Fu F et al (1998) Articular cartilage lesions of the knee. Am J Sports Med 26:853–861
12. Minas T (1998) Chondrocyte implantation in the repair of chondral lesions of the knee: economics and quality of life. Am J Orthop 27:739–744
13. Minas T, Chiu R (2000) Autologous chondrocyte implantation. Am J Knee Surg 13:41–50
14. Noyes FR, Barber SD, Mooar LA (1989) A rationale for assessing sports activity levels and limitations in knee disorders. Clin Orthop 246:238–249
15. Noyes FR, Bassett RW, Grood ES et al (1980) Arthroscopy in acute traumatic hemarthrosis of the knee. J Bone Joint Surg Am 62:687–695
16. Peterson L, Lindahl A, Brittberg M et al (2000) Durability of autologous chondrocyte transplantation of the knee. Paper presented at the 67th Annual Meeting of the American Academy of Orthopedic Surgeons, Orlando, FL, USA
17. Peterson L, Minas T, Brittberg M et al (2000) 2 to 9 year outcome after autologous chondrocyte transplantation of the knee. Clin Orthop 374:212–234
18. Rand JA (1991) Role of arthroscopy in osteoarthritis of the knee. Arthroscopy 7:358–360
19. Steadman JR, Rodkey WG, Singleton SB et al (1997) Microfracture technique for full-thickness chondral defects: technique and clinical results. Operative Tech Orthop 7:300–304