AN ANALYSIS OF THE QUALITY OF CARTILAGE REPAIR STUDIES — *An Update*

Rune B. Jakobsen - First Author
Oslo Sports Trauma Research Center,
Norwegian School of Sport Science
PB 4014 Ullevaal Stadion,
N-0806 Oslo,
Norway
Tel: 47 23262000
Fax: 47 23262307

Lars Engebretsen, MD, PhD - Second Author
Orthopaedic Center
Ulleval University Hospital
Oslo 0407
NORWAY
Tel: 47 9507 9529
Fax: 47 2211 7470
E-mail:
lars.engebretsen@medisin.uio.no

Note to the reader: This article is an update to a previously published article[1], containing previously published results as well as new results. The reader is referred to the previously published paper for the details on materials and methods and for detailed discussion of older results.

INTRODUCTION

Surgical treatment for cartilage injury is of major interest to orthopaedic surgeons because most lesions of articular cartilage do not heal spontaneously and may predispose the joint to the subsequent development of secondary osteoarthritis.[2, 3] In a series of 993 knee arthoscopies performed because of pain, substantial cartilage lesions considered suitable for surgical treatment were detected in 6% of the patients.[4] Treatment for articular cartilage injuries includes the microfracture technique[5], autologous periosteal transplantation[6], autologous osteochondral transplantation[7], autologous chondrocyte implantation with[8, 9] and without[10] the assistance of various three dimensional matrices. In addition techniques utilizing allografts exist, though not widely used and therefore not a subject in this review. Much controversy is related the best treatment option. Numerous published articles, in which the above treatment options were used, have described good or excellent results for a majority of patients, yet several authors have pointed out methodological weaknesses in the published studies. [11-13]

The purpose of this and the previously published article was to determine whether the optimistic reports in the literature are supported by sound methodological quality in the studies. Our main hypothesis was that the majority of the studies have methodological limitations that may limit the value of the reported results. We addressed the methodological limitations by calculation a modified Coleman Methodology Score (CMS)[14] and a level-of-evidence rating.[15] In the previously published article we correlated this to the reported results to test whether studies of lesser methodological quality reported higher rates of success. In this article we have solely looked at the methodological quality of new studies (published over the last 2 years?).

MATERIALS AND METHODS

We refer the reader to the previously published paper in The Journal of Bone and Joint Surgery American Volume, October, 2005 p. 2232[1] for a detailed materials and methods description. We used the exact same search strategy and selection criteria for this update and searched the Medline In-process and other Non-Indexed Citations, EMBASE and CINAHL using OVID. We also searched the Cochrane Central Register of Controlled Trials. All searches were performed and finished on April 4th, 2006.

We rewieved 158 abstracts of which eighteen filled the selection criteria.

SPSS software (version 13.0.0; SPSS, Chicago, Illinois) was used to analyze the data.

RESULTS

In our first article on this topic we included sixty-one studies reporting on 3987 operations of which 260 were from randomized controlled trials. The average CMS was 43.5 (95% C.I., 40.3 to 46.7) with especially low scores in five categories: [1] type of study, [2] description of postoperative rehabilitation, [3] outcome criteria,[4] outcome assessment, and[5] subject selection process. At that time we found thirty-five retrospective studies, twenty-two prospective studies and only four randomised controlled trials.

In this update eighteen studies[16-33] reported on 1003 operations (median 46) of which 195 were from randomised controlled trials and 116 from non-randomised controlled trials. The average CMS was 56.3 (95% C.I., 49.3 to 63.2), which was a statistical significant improvement ($p<0.0001$). However, methodological limitations were still frequently found in the above-mentioned categories. The average CMS for each criterion and the total CMS are given in Table I. The distribution of the studies with regard to type of treatment, type of study, and level-of-evidence rating is given in Table II.

In our first review we analyzed the outcome results with respect to type of therapy, but could not find any significant differences between the reported outcomes (forty-seven studies; $p = 0.11$).

AN ANALYSIS OF THE QUALITY OF CARTILAGE REPAIR STUDIES — *An Update (cont.)*

Indeed, large variations in reported outcome were demonstrated within each treatment modality (Fig. 1). We found that the CMS correlated positively with the level-of-evidence rating ($r = 0.668$, $p < 0.0001$), but the variations within each level were large. In this update we find the same trend (Fig. 2), but find an even larger variations in the level-IV evidence.

Also in the first article we identified several double publications[34-37], in addition to one article describing a group of patients(38) that may have been a subgroup of the patients included in a randomized trial.[34]. We found no double publications in the update.

Interestingly we noticed that in one article patients received identical surgical treatment but were divided into two groups with different rehabilitation protocols[33] and another article reported on a new retrograde technique for treating tibial cartilage defects[39] One article also reported on autologous chondrocyte implantation in combination with autologous osteochondral transplantation[29] and several papers on various types of matrix-assisted chondrocyte transplantation alone[8, 9] or compared to other treatments.[27]

DISCUSSION

We refer the reader to the original article[1] for a detailed discussion on methods and previous results. This discussion only takes into account findings from the newly included articles.

Research on the surgical treatment of cartilage injury has been extensive over the last two decades, and although numerous articles have been published reporting mostly good to excellent results, the methodology of the studies in general has been questioned.[11]

We previously showed that the majority of papers in this area had methodological deficiencies. This is still the main finding even though it is encouraging to find a significantly improved CMS.

A total of 6 randomized controlled trials have been performed in cartilage treatment comparing autologous chondrocyte implantation and autologous ostechondral transplantation (mosaicplasty) (three studies)[24, 34, 40], autologous chondrocyte implantation and microfracture[41], autologous osteochondral transplantation (mosaicplasty) and microfracture[17], and autologous chondrocyte implantation and matrix-assisted autologous chondrocyte implantation[27]. The CMS varied between 56 and 79. Four of these found no significant difference between treatments. One well performed study (CMS = 79) found arthroscopic autologous osteochondral transplantation to be superior to microfracture[17]. Another study found autologous chondrocyte implantation to be superior to autologous osteochondral transplantation (mosaicplasty), but were of lesser methodological quality (CMS = 56)[40].

As of today no treatment modality has emerged clearly superior to other modalities and it seems that several surgical methods provide a comparable good-to-excellent functional outcome at least in the one to five year postoperative period. More well-designed and well-performed randomized controlled trials are needed to determine whether this is truly the case.

The increased focus on methodology in major journals by marking original articles with a level-of-evidence is highly appreciated. However, we would like to emphasize the fact that randomized controlled trials can have serious design flaws (i.e. not using independent reviewers, no statistical power analysis, not using an adequate randomization procedure, not accounting for eligible subjects not included in study), and therefore be rated as level-of-evidence II. We would also like to draw the reader's attention to the fact that several well-performed case series (level-IV evidence) score very well on the CMS. These studies largely take into consideration multiple aspects of good methodological quality such as independent investigator, sufficient number of patients, well-described rehabilitation protocol, validated outcome measures and so forth, and are mainly lacking in not having a control group. We therefore recommend the reader to not entirely dismiss articles marked level-IV evidence, yet themselves assess the methodological quality of the paper when interpreting the results (for example using a grading system like the CMS).

On the basis of our findings in this update we maintain the recommendation to readers of cartilage studies to be cautious when interpreting result. In our first article we proposed the following guidelines for future studies, and although methodology has improved we find it worthwhile to repeat the guidelines here:

1. Studies should be prospective with a clearly defined hypothesis and one clearly defined primary end point. They should be randomized controlled trials with an adequate randomization procedure and power analysis for the primary end point. Secondary end point should only be used a supportive evidence to the primary hypothesis.
2. Patient inclusion and exclusion criteria should be clearly established and reported. The recruitment rate should be reported, and attempts should be made to account for eligible patients who are not included and those who are lost follow-up.
3. The outcome measure should be validated for use on patients with cartilage injuries.
4. Outcome assessment should be made by an independent investigator. The assessment should be in a written form and ideally be completed by the patient without investigator assistance.

AN ANALYSIS OF THE QUALITY OF CARTILAGE REPAIR STUDIES — *An Update (cont.)*

5. The timing of the outcome assessment should be clearly stated. Results from various time-points after surgery should not be reported as one outcome. Assessments should be both clinical and functional. The minimum duration of follow-up should be more than twenty-four months.
6. Detailed rehabilitation protocols should be established and reported. Attempts should be made to monitor compliance. The protocols should be applied in a standardized manner to both patient cohorts.

REFERENCES

1. Jakobsen RB, Engebretsen L, Slauterbeck JR. An analysis of the quality of cartilage repair studies. Journal of Bone & Joint Surgery - American Volume. 2005;87(10):2232-9.
2. Buckwalter JA, Lane NE. Athletics and osteoarthritis. Am J Sports Med. 1997 Nov-Dec;25(6):873-81.
3. Shapiro F, Koide S, Glimcher MJ. Cell origin and differentiation in the repair of full-thickness defects of articular cartilage. J Bone Joint Surg Am. 1993 Apr;75(4):532-53.
4. Aroen A, Loken S, Heir S, Alvik E, Ekeland A, Granlund OG, et al. Articular cartilage lesions in 993 consecutive knee arthroscopies. Am J Sports Med. 2004 Jan-Feb;32(1):211-5.
5. Blevins FT, Steadman JR, Rodrigo JJ, Silliman J. Treatment of articular cartilage defects in athletes: an analysis of functional outcome and lesion appearance. Orthopedics. 1998 Jul;21(7):761-7; discussion 7-8.
6. Hoikka VE, Jaroma HJ, Ritsila VA. Reconstruction of the patellar articulation with periosteal grafts. 4-year follow-up of 13 cases. Acta Orthop Scand. 1990 Feb;61(1):36-9.
7. Hangody L, Kish G, Karpati Z, Szerb I, Udvarhelyi I. Arthroscopic autogenous osteochondral mosaicplasty for the treatment of femoral condylar articular defects. A preliminary report. Knee Surg Sports Traumatol Arthrosc. 1997;5(4):262-7.
8. Ronga M, Grassi FA, Bulgheroni P. Arthroscopic autologous chondrocyte implantation for the treatment of a chondral defect in the tibial plateau of the knee. Arthroscopy. 2004 Jan;20(1):79-84.
9. Marcacci M, Berruto M, Brocchetta D, Delcogliano A, Ghinelli D, Gobbi A, et al. Articular cartilage engineering with Hyalograft C: 3-year clinical results. Clin Orthop Relat Res. 2005 Jun(435):96-105.
10. Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. N Engl J Med. 1994 Oct 6;331(14):889-95.
11. Messner K, Gillquist J. Cartilage repair. A critical review. Acta Orthop Scand. 1996 Oct;67(5):523-9.
12. Jobanputra P, Parry D, Fry-Smith A, Burls A. Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review. Health Technol Assess. 2001;5(11):1-57.
13. Wasiak J, Villanueva E. Autologous cartilage implantation for full thickness articular cartilage defects of the knee. Cochrane Database Syst Rev. 2002(4):CD003323.
14. Coleman BD, Khan KM, Maffulli N, Cook JL, Wark JD. Studies of surgical outcome after patellar tendinopathy: clinical significance of methodological deficiencies and guidelines for future studies. Victorian Institute of Sport Tendon Study Group. Scand J Med Sci Sports. 2000 Feb;10(1):2-11.
15. Wright JG, Swiontkowski MF, Heckman JD. Introducing levels of evidence to the journal. J Bone Joint Surg Am. 2003 Jan;85-A(1):1-3.
16. Mithofer K, Minas T, Peterson L, Yeon H, Micheli LJ. Functional outcome of knee articular cartilage repair in adolescent athletes. American Journal of Sports Medicine. 2005 Aug;33(8):1147-53.
17. Gudas R, Kalesinskas RJ, Kimtys V, Stankevicius E, Toliusis V, Bernotavicius G, et al. A prospective randomized clinical study of mosaic osteochondral autologous transplantation versus microfracture for the treatment of osteochondral defects in the knee joint in young athletes. Arthroscopy. 2005 Sep;21(9):1066-75.
18. Barber FA, Chow JCY. Arthroscopic chondral osseous autograft transplantation (COR procedure) for femoral defects. Arthroscopy. 2006 Jan;22(1):10-6.
19. Marcacci M, Kon E, Zaffagnini S, Iacono F, Neri MP, Vascellari A, et al. Multiple osteochondral arthroscopic grafting (mosaicplasty) for cartilage defects of the knee: prospective study results at 2-year follow-up. Arthroscopy. 2005 Apr;21(4):462-70.
20. Fu FH, Zurakowski D, Browne JE, Mandelbaum B, Erggelet C, Moseley JB, Jr., et al. Autologous chondrocyte implantation versus debridement for treatment of full-thickness chondral defects of the knee: an observational cohort study with 3-year follow-up. American Journal of Sports Medicine. 2005 Nov;33(11):1658-66.

AN ANALYSIS OF THE QUALITY OF CARTILAGE REPAIR STUDIES — *An Update (cont.)*

21. Mithofer K, Peterson L, Mandelbaum BR, Minas T. Articular cartilage repair in soccer players with autologous chondrocyte transplantation: functional outcome and return to competition. American Journal of Sports Medicine. 2005 Nov;33(11):1639-46.
22. Henderson I, Francisco R, Oakes B, Cameron J. Autologous chondrocyte implantation for treatment of focal chondral defects of the knee—a clinical, arthroscopic, MRI and histologic evaluation at 2 years. Knee. 2005 Jun;12(3):209-16.
23. Mithoefer K, Williams RJ, 3rd, Warren RF, Potter HG, Spock CR, Jones EC, et al. The microfracture technique for the treatment of articular cartilage lesions in the knee. A prospective cohort study. Journal of Bone & Joint Surgery - American Volume. 2005 Sep;87(9):1911-20.
24. Dozin B, Malpeli M, Cancedda R, Bruzzi P, Calcagno S, Molfetta L, et al. Comparative evaluation of autologous chondrocyte implantation and mosaicplasty: a multicentered randomized clinical trial. Clinical Journal of Sport Medicine. 2005 Jul;15(4):220-6.
25. Browne JE, Anderson AF, Arciero R, Mandelbaum B, Moseley JB, Jr., Micheli LJ, et al. Clinical outcome of autologous chondrocyte implantation at 5 years in US subjects. Clinical Orthopaedics & Related Research. 2005 Jul(436):237-45.
26. Minas T, Bryant T. The role of autologous chondrocyte implantation in the patellofemoral joint. Clinical Orthopaedics & Related Research. 2005 Jul(436):30-9.
27. Bartlett W, Skinner JA, Gooding CR, Carrington RWJ, Flanagan AM, Briggs TWR, et al. Autologous chondrocyte implantation versus matrix-induced autologous chondrocyte implantation for osteochondral defects of the knee: a prospective, randomised study. Journal of Bone & Joint Surgery - British Volume. 2005 May;87(5):640-5.
28. Marcacci M, Berruto M, Brocchetta D, Delcogliano A, Ghinelli D, Gobbi A, et al. Articular cartilage engineering with Hyalograft C: 3-year clinical results. Clinical Orthopaedics & Related Research. 2005 Jun(435):96-105.
29. Sharpe JR, Ahmed SU, Fleetcroft JP, Martin R. The treatment of osteochondral lesions using a combination of autologous chondrocyte implantation and autograft: three-year follow-up. Journal of Bone & Joint Surgery - British Volume. 2005 May;87(5):730-5.
30. Ma H-L, Hung S-C, Wang S-T, Chang M-C, Chen T-H. Osteochondral autografts transfer for post-traumatic osteochondral defect of the knee-2 to 5 years follow-up. Injury. 2004 Dec;35(12):1286-92.
31. Chow JCY, Hantes ME, Houle JB, Zalavras CG. Arthroscopic autogenous osteochondral transplantation for treating knee cartilage defects: a 2- to 5-year follow-up study. Arthroscopy. 2004 Sep;20(7):681-90.
32. Koulalis D, Schultz W, Heyden M, Konig F. Autologous osteochondral grafts in the treatment of cartilage defects of the knee joint. Knee Surgery, Sports Traumatology, Arthroscopy. 2004 Jul;12(4):329-34.
33. Marder RA, Hopkins G, Jr., Timmerman LA. Arthroscopic microfracture of chondral defects of the knee: a comparison of two postoperative treatments. Arthroscopy. 2005 Feb;21(2):152-8.
34. Horas U, Pelinkovic D, Herr G, Aigner T, Schnettler R. Autologous chondrocyte implantation and osteochondral cylinder transplantation in cartilage repair of the knee joint. A prospective, comparative trial. J Bone Joint Surg Am. 2003 Feb;85-A(2):185-92.
35. Horas U, Schnettler R, Pelinkovic D, Herr G, Aigner T. [Osteochondral transplantation versus autogenous chondrocyte transplantation. A prospective comparative clinical study]. Chirurg. 2000 Sep;71(9):1090-7.
36. Peterson L. Long-term clinical results of using autologous chondrocytes to treat full-thickness chondral defects. J Sports Traumatol Relat Res. 1998;20(2):103-8.
37. Peterson L, Minas T, Brittberg M, Nilsson A, Sjogren-Jansson E, Lindahl A. Two- to 9-year outcome after autologous chondrocyte transplantation of the knee. Clin Orthop Relat Res. 2000 May(374):212-34.
38. Horas U, Schnettler R. Chondral defects of the knee treated by transplantation of autogenous osteochondral plugs. Orthopedics & Traumatology. 2002;10(3):220-34.
39. Ueblacker P, Burkart A, Imhoff AB. Retrograde cartilage transplantation on the proximal and distal tibia. Arthroscopy. 2004 Jan;20(1):73-8.
40. Bentley G, Biant LC, Carrington RW, Akmal M, Goldberg A, Williams AM, et al. A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. J Bone Joint Surg Br. 2003 Mar;85(2):223-30.
41. Knutsen G, Engebretsen L, Ludvigsen TC, Drogset JO, Grontvedt T, Solheim E, et al. Autologous chondrocyte implantation compared with microfracture in the knee. A randomized trial. Journal of Bone & Joint Surgery - American Volume. 2004;86-A(3):455-64.