Cartilage repair

A critical review

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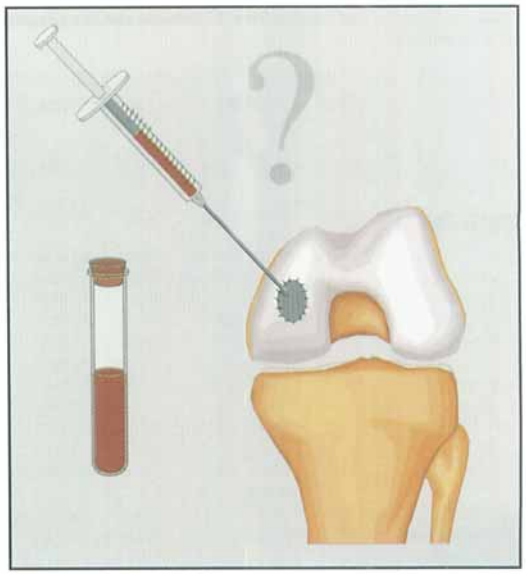

In 1994, news media all over the world presented a new cure for knee cartilage lesions that was suggested to eliminate the need for 500,000 artificial joint replacements per year in the USA. This was based on an article published in the *New England Medical Journal* entitled "Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation" by Brittberg et al. (1994a). The proposed technique was later made commercially available by Genzyme Tissue Repair (Boston, Mass., USA). In this review we examine information about experimental and clinical cartilage repair and conclude that there is so far no scientific evidence for a breakthrough in this area.

Arthrosis, the commonest cause of disability in old age, has a large impact on hospital costs (Praemer et al. 1992, Jacobson and Lindgren 1996). Primary arthrosis, by definition of unknown etiology, is commonest and results in widespread degeneration of the joint cartilage. Secondary arthrosis is caused by joint trauma or a preexisting malalignment (Dieppe 1995, Radin 1995) and may be arrested by normalizing the mechanical dysfunction (Radin and Burr 1984).

Arthrosis research mainly followed two lines. One line examines possible causes of the primary disease with epidemiologic or chemical methods, in order to find ways to stop its initiation or progression or to reverse the condition (Kuettner et al. 1992). The other line concentrates on repair of localized cartilage injuries.

Unlike studies of arthrosis, experimental studies of cartilage repair regularly use a model with a hole drilled into an otherwise normal cartilage. This model is similar to the rare clinical condition of a chondral fracture or osteochondritis. In spite of their rare occurrence, the healing of such defects in otherwise normal joints has been a major research area for many years, with the underlying assumption that healing techniques, if effective, could also be used in primary arthrosis in man.

Animal studies

A partial thickness cartilage injury provokes proliferation and matrix synthesis in the chondrocytes, but no healing response that fills the defect (Buckwalter 1992). Injuries through cartilage and subchondral bone cause an inflammatory reaction and are repaired by fibrous cartilage which differs from normal hyaline cartilage both mechanically and chemically. Most researchers have tried to improve the healing by drilling into the subchondral bone marrow in order to use the marrow cells for repair. With this technique the defect is filled in a couple of months with fibrocartilage fixed to the bottom of the defect (Wei and Messner 1996), but the repair tissue does not usually bond to the adjacent cartilage (Ritsilä et al. 1980, 1981, O'Driscoll et al. 1988, 1986, Messner et al. 1993, Shapiro et al. 1993, Messner 1994). Degeneration follows and the repair tissue may disintegrate and leave a bare bony surface (Buckwalter 1992). The capacity to heal full-thickness defects is slightly better in very young than in fully grown animals (Wei and Messner 1996). There have been numerous attempts to stimulate the healing by filling the defect with periosteum, perichondrium, demineralized bone, alginate sponges with precultivated autologous cells and also with synthetic materials (Engkvist and Johansson 1980, Rubak 1982a,b, Aston and Bentley 1986, Widenfalk et al. 1986, Grande et al. 1989, Billings et al. 1990, Dahlberg and Kreicbergs 1991, Shapses et al. 1991, Caplan et al. 1992, Anastasiou et al. 1993, Bulstra et al. 1993, Barone et al. 1995, Chu et al. 1995, Shiba et al. 1995). To improve the quality of healing, continu-

Table 1. Summary of results from 12 clinical studies of cartilage regeneration with different methods, all producing "hyaline-like" cartilage

Study	Year	Method	Joint	Design	n	Age	Months FU	Defect size cm^2	Symptom score	E	G	(E+G)/N
Muckle and Minns	1989	Carbon plugs	Knee	Cohort	47	18–72	30–66	?	?		36	0.8
Brittberg et al.	1994b	Carbon plugs	Knee	Cohort	37	25–53	33–63	1.2–16	Larson,VAS Tegner	9	21	0.8
Brittberg et al.	1994a	Periost.+ cells	Knee	Cohort	23	14–48	16–66	1.6–6.5	Own score	7	9	0.7
Homminga et al.	1990	Perichondrium	Knee	Cohort	25	18–45	12–32	1–5	Ranawat et al.	18	6	0.9
Lorentzon et al.	1996	Periosteum	Knee	Cohort	18	19–52	15–59	0.75–16	Brittberg 1994a	14	4	1
Hoikka et al.	1990	Periosteum	Knee	Cohort	13	16–55	8–108	?	Freeman et al.	0	8	0.6
Niederman et al.	1985	Periosteum	Knee	Case review	5	16–34	12	3-12	None	4	1	–
Jensen and Bach	1992	Periosteum	Knee	Case review	3	14–16	6–12	?	None	0	3	–
Engkvist and Johansson	1980	Perichondrium	Finger/ toe	Cohort	26	10–65	3–41	Total joint	Own	13	3	0.6
Tippett	1996	Osteotomy + drilling	Knee	Cohort	133	?	62	?(A)	Maquet et al.	?	?	0.9
Johnson	1996	Abrasion	Knee	Cohort	399	?	24–60	?(A)	Own	?	?	0.3
Messner and Maletius	1996	None	Knee	Cohort	28	14-38	144–180	>1	Lysholm/ Tegner	10	12	0.8

A arthrosis, E excellent, G good, (E+G)/N the sum of excellent and good cases as a fraction of the total number of cases, FU follow-up time

ous passive motion (O'Driscoll et al. 1986), pretreatment of the defect with chondroitinase ABC or addition of growth factors (Hunziker and Rosenberg 1992, 1994, Jingushi et al. 1994, Hunziker and Schaenk 1995, Hsieh et al. 1996) have been tried. Penetration of the subchondral bone plate, combined with transplantation of periosteum or perichondrium into the defect increases the regeneration and results in a highly cellular tissue (Messner 1993, Grande et al. 1989), the structural, chemical and mechanical properties of which are, however, far from normal (Shapses et al. 1991, von Shroeder et al. 1991, Messner et al. 1993, Wakitani et al. 1994). Implantation of artificial or biological scaffolds loaded with autologous (Kawamura et al. 1996) or allogeneic cartilage cells, growth factors, or polylactic acid matrix with periosteal cells (von Schroeder et al. 1991) as well as dacron, teflon or carbon fiber pads have been tried (Muckle and Minns 1989, Messner 1993, 1994, Messner and Gillquist 1993, Messner et al. 1993) and recently an artificial osteochondral composite graft was introduced (Oka et al. 1995).

Most cells in the healing tissue seem to come from the synovium (Hunziker and Rosenberg 1994) or bone marrow, if the subchondral bone plate is penetrated (Shapiro et al. 1993). Grande et al. (1989), using periosteal grafts and precultivated autologous cartilage cells in rabbits, found that only 7.8% of the cells in the repair came from the transplanted cells. Brittberg et al. (1996) demonstrated that precultivated autologous cartilage cells transplanted into a defect with an intact subchondral bone plate increased the amount of repair tissue both with periosteum and carbon fiber pads. However, they found much less repair tendency in untreated or periosteum-only treated defects than other authors (Messner 1993, Messner and Gillquist 1993, Messner et al. 1993, O'Driscoll 1986, Wei and Messner 1996) possibly because they did not penetrate the subchondral bone plate. The good results of the chondrocyte/periosteum transplantation technique into defects with an intact subchondral bone plate were verified in a 6-month study on dogs by a group from Genzyme Tissue Repair (Barone et al. 1995). Generally, all experimental methods result in tissue that is softer than normal cartilage, with a higher creep under constant loading, abnormal morphology, and chemical composition (O'Driscoll et al. 1988, Shapses et al. 1991, Wei and Messner 1996). Furthermore, it undergoes the same degenerative changes after 1 year as the healing tissue in untreated defects (Messner and Gillquist 1993, Messner et al. 1993). The cartilage adjacent to the repair area also shows progressive degeneration (O'Driscoll et al. 1988, Wei and Messner 1996) that may be caused by the operative procedure, edge stress in the defect or disturbed joint mechanics. Thus, most repair enhancement methods have failed to improve cartilage mechanics more than that found after the natural repair of an untreated osteochondral defect.

Clinical studies

There are only a few studies of repair enhancement of isolated chondral defects in patients (Engkvist and Johansson 1980, Sully et al. 1980, Niederman et al. 1985, Muckle and Minns 1989, Hoikka et al. 1990, Homminga et al. 1990, Jensen and Bach 1992, Bulstra et al. 1993, Brittberg et al. 1994a, 1994b, Lorentzon et al. 1996) and usually the number of patients is small.

Tippett (1996) and Johnson (1996) have reported the clinical outcome with use of Pridie drilling or abrasion chondroplasty with or without osteotomy for knee chondral defects. Important information, like defect size and patient's age, is missing; therefore it is difficult to draw any conclusions. Bulstra et al. (1993) briefly presented a successful outcome after 1.5–4 years' follow-up in two thirds of 60 patients after perichondral transplantation in knees, 60% of which had arthrosis grades I–II. The procedure failed with arthrosis grade II.

A survey of the 12 best-reported clinical studies is presented in Table 1. The 4 studies with most data and patients are summarized below.

Messner and Maletius (1996) studied the prognosis of untreated knee cartilage defects. Only 28 such cases could be found in 4,000 consecutive arthroscopies during the 4-year period 1978–1981 (Messner and Maletius 1996). 21/28 patients were able to return to the preinjury team sport and and at the follow-up after 14 years, 22 had excellent or good knee function. 12 cases had radiographic joint space narrowing, in all cases less than 50%. Notably, there was no difference in radiographic changes between the involved and the non-involved knee.

In 1990, Homminga et al. published a 1–2 year follow-up of perichondral grafting to isolated knee cartilage defects (1–5 cm^2) in 25 patients between 18 and 45 years old. The symptoms were evaluated in detail before and after operation, using a previously published score (Ranawat et al. 1976). Follow-up arthroscopies were done in all cases and biopsies were obtained from the repair tissue in 3 cases. The biopsies showed hyaline-like material. Arthroscopic probing showed increasing resistance of the tissue with time. At a 1-year follow-up, 18/ 25 patients were free of symptoms and had returned to previous sport and work activities. The improvement was maintained in 14 patients followed for 2 years.

Brittberg et al. (1994b) presented results of carbon fiber implants in 37 patients with a follow-up between 3 and 5 years. The age range was 25–53 years, but the defects were larger (2–16 cm^2) and the follow-up longer than in Homminga's study. All patients had undergone various operations before, without success. For the evaluation of the clinical findings, previously documented scores were used. The authors found 30/36 excellent/good results. No follow-up arthroscopies were done.

In the same year, Brittberg et al. published a new treatment for chondral defects in the *New England Journal of Medicine* (1994a) that aroused world-wide media attention and attracted both public and commercial interest (Dickman and Strobel 1995). In 23 patients (age 14–48) with 16 isolated chondral defects in the femur and 7 in the patella, healthy chondrocytes were obtained from an uninvolved area of the knee during arthroscopy, isolated and cultured for 2–3 weeks. In a second operation, the chondrocytes were transplanted into the defect under a cover of periosteum that was sutured to the surrounding cartilage. The defects were 2–7 cm^2, like those in Hommingas et al.'s study (1990), but smaller than the defects in the author's own previous study (Brittberg 1994b). Symptoms were evaluated at a follow-up between 1.5 and 5.5 years (in one-third of the patients less than 3 years) by a new, simple score devised by the authors. "Excellent" included no pain, swelling or locking during strenuous activity. Arthroscopy 3 months after the operation showed filled defects. At a new arthroscopy after 1 year, the resistance of the repair tissue to probing had increased and biopsies showed hyaline-like cartilage in 12 patients and fibrous cartilage in 10. Complete relief of symptoms (excellent) occurred in 7/23 patients and diminished symptoms (good) in 9. Since 5 of 7 patients with patellar transplants had a fair or poor result, the authors concluded that cultured autologous chondrocytes could be used to repair deep cartilage defects in the femorotibial articular surface of the knee. They suggested that the technique might eliminate the need for 500,000 arthroplasties per year in the USA.

Comments to the studies (Table 1)

Patient selection

Most studies concern isolated traumatic or osteochondritic chondral defects and a few include patients with chondromalacia patellae. The study by Engqvist and Johansson (1980) includes joint destruction of varying etiology and it can be assumed that Tippett (1996) and Johnson (1996) also included patients with frank arthrosis, even if no details are given. Patient selection is similar in the three best-reported studies with the largest number of patients (n 23–37; Homminga et al. 1990, Brittberg et al. 1994a,b, Messner and Maletius 1996). However, Brittberg et al. (1994b) used carbon plugs in patients with worse problems and larger

defects than in the other studies. Therefore one may expect worse results in the study of carbon fiber plugs. The wide age range (14–48) in the four studies (Homminga et al. 1990, Brittberg et al. 1994a,b, Messner and Maletius 1996) may be a confounding factor. Regarding the variability in age and the reported effect of periosteum alone, one would need a very large number of well defined patients (> 100) to prove that a new technique leads to improved results. Such a large group of patients with isolated chondral defects could, in a reasonably short time, be obtained only by a multicenter study.

Study design

It is surprising that there is no randomized clinical trial. Nor has there been any attempt to compare the outcome to untreated patients. The absence of a control group makes it impossible to determine whether there is a real effect and if so, the cause of it. With a control group, it would have been possible to evaluate if the cultured chondrocytes had brought an improvement over what could be expected with periosteum alone or no treatment.

Tissue quality

Since Homminga et al. (1990) had only 3 biopsies in 25 patients, the findings by Brittberg et al. (1994a) alone can be analyzed. Only 12 of 22 patients (fraction 0.5 confidence interval: 0.3–0.8) had a hyaline-like cartilage in the defect. However, arthroscopic biopsies may be difficult to evaluate because of their limited size and uncertain location. No mechanical analysis can be done. The subjective testing of of the healing tissue with a probe (Homminga et al. 1990 , Brittberg et al. 1994a) is not acceptable as evidence of improvement.

Evaluation of outcome

The main effect of cartilage repair in patients is based on the subjective and functional outcome. It is important to use a well documented and validated score for the subjective results. Several suitable scores have been used by other authors under similar conditions, which should make a comparison of effects easier. Both the pre- and postoperative symptoms must be documented in detail, because patients with isolated cartilage defects and otherwise normal articular cartilage are not always symptomatic. In the study of carbon fiber plugs, Brittberg et al. (1994b) reported the pre- and postoperative findings in detail as did Homminga et al. (1990), but in the study of autologous chondrocyte transplantation, Brittberg et al. (1994a) failed to document both the symptoms and the patient's work and sport activities. A change from high to low activities could explain the clinical improvement. Therefore the evidence for real improvement is weak.

The wide range of follow-up times in the studies (1.5–6.5 years) confounds the results. From experimental studies it is obvious that the time factor is important; there may be an early improvement that disappears later.

When the outcome evaluation is mainly based on subjective evidence, the clinical and arthroscopic reexaminations may easily be biased, if done by the responsible surgeon. Observer bias is especially common in the evaluation of subjective phenomena like symptoms and signs (Silverman 1985).

Comparison between studies (Table 1)

One should note that no treatment (Messner and Maletius 1996) or Pridie drilling with osteotomy (Tippett 1996) has the same rate of excellent/good results as the studies using various implants (Engkvist and Johansson 1980, Muckle and Minns 1989, Homminga et al. 1990, Brittberg et al. 1994a,b, Lorentzon et al. 1996). Abrasion chondroplasty, described by Johnson (1986) as a means to induce healing of defects, has a much lower success rate (Johnson 1996). Presumably the patients treated with abrasion chondroplasty had worse problems than the patients in the other studies, but no details are available.

After chondrocyte transplantation (Brittberg et al. 1994a) 7 patients became symptom-free and 9 reported pain only during strenuous activity or a fraction of 0.7 good/excellent cases (95% CI 0.5–0.9). The confidence interval shows that the expected result, if the study were repeated, could be anything from 50% to almost 90% good/excellent. The results were marginally improved by subdividing the material into smaller subgroups: 14/16 defects in the femoral condyles were good/excellent, while the patellar defects generally failed. In contrast to Brittberg et al. (1994a), Lorentzon et al. (1996) had success in all 18 patients with a patellar defect treated with periosteum and drilling of the subchondral boneplate.

Using carbon plugs Brittberg et al. (1994b) found 30/36 excellent/good results (fraction 0.8), not differing from the later study of autologous chondrocyte transplantation. In comparison, Homminga et al. (1990) had 18/25 (0.7) patients completely free of symptoms (return to previous sport and work activities, excellent result) versus only 7/23 (0.3) in Brittberg's study ($p < 0.001$). If Brittberg's patients who felt pain during sports are included, the comparison is 18/25 versus 14/23 ($p < 0.02$). In both cases, Homminga's results are statistically superior to Brittberg's. In conclusion, there is no evidence that the results of

chondrocyte transplantation (Brittberg et al. 1994a) are better than those that have been reported before. Surprisingly, none of the previously published clinical studies using periosteal or perichondral transplants are discussed by Brittberg et al. in the *New England Journal of Medicine*. Not even their own publication from the same year (1994b) describing the results of carbon plugs is mentioned. It would have been normal scientific policy to discuss the group's own results with carbon fiber plugs as well as Homminga et al.'s (1990) results with periosteum. The effect of chondrocyte transplantation would certainly have looked different, had the discussion included these two studies.

Careful scientific design is important for a valid evaluation of a new technique. The lack of a control group and exclusion of critical references can lead to false interpretation of data. If the technique has implications for medical practice, it is necessary that the basis for conclusions is not biased and that the results are compared to previous studies. The clinical success of cartilage repair is difficult to define. The symptoms of isolated cartilage defects may resolve in the long term, even without treatment, despite initial symptoms of catching, locking and swelling. There is no evidence that cartilage repair procedures diminish the risk of future arthrosis. In order to evaluate whether arthrosis can be avoided by the procedure, long-term follow-up with weight bearing radiograms is needed.

It is the responsibility of the surgeon to decide whether the doubtful benefit of a cartilage repair procedure justifies the operation and long rehabilitation. He also must take into account that long-term knee function can be good after untreated limited cartilage defects, and if arthrosis develops it is rather limited and often asymptomatic after 12 to 15 years. Certainly, the step from animal experiments on cartilage repair to a clinical application is a step too far, too soon.

Publication of orthopedic studies

The presentation of data in the article by Brittberg et al. (1994a) is very easy to misunderstand; laymen and doctors without orthopedic knowledge may easily believe that the problem of knee arthrosis has been solved, as it was also reported by the media. This is especially serious since the article was published in a widely circulating, prestigious journal. The fact that the material was published in this journal aroused enormous media interest. In contrast, Homminga's study (1990) aroused no media interest at all, in spite of the significantly better results!

It is surprising that reviewers in a highly recognized journal fail to notice serious scientific flaws and overestimation of clinical results. Perhaps this is due to lack of orthopedic expertise? Interestingly, an editorial in the *New Engl J Med* with regard to Brittberg's publication (Mankin 1994) also fails to mention the previous studies by Homminga (1990) and Brittberg et al. (1994a).

In this case, the ignorance about previous studies seems to be the most serious shortcoming, but the confounding of isolated defects with arthrosis also leads to erroneous conclusions.

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