

# Clinical Results of Autologous Chondrocyte Transplantation (ACT) Using a Collagen Membrane

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The treatment of articular cartilage defects is difficult and needs a specialized physician to select the appropriate procedure from a variety of established and new therapeutic approaches. The therapy has to be orientated by the etiology of the cartilage defect. The following categories can be distinguished: degenerative, posttraumatic, inflammatory, metabolic, and vascular toxic cartilage damages. Independent from these categories is the osteochondritis dissecans [22, 51]. The classification of the International Cartilage Repair Society (ICRS) is the standard to describe an articular cartilage defect and is based on the classification of Outerbridge [36]. According to this classification grade III and IV defects have to be treated.

## The Structure of Cartilage

The hyaline articular cartilage shows an unique architecture. A superficial tangential zone with approximately 10 to 20% of the whole volume, a middle zone with 40 to 60% volume, and a deep zone with 30% volume can be distinguished. In the superficial zone the cells and the collagen type II fibers are orientated tangentially. In the middle zone the cells are organized in columns and the collagen fibers show a reticular pattern. In the deep zone the cell-fiber mesh is attached to the subchondral bone. In this area the fibers have a vertical orientation [20, 23, 34]. The use of MRI has simplified the diagnosis of articular cartilage defects. Today, with the help of cartilage-specific sequences (e.g. 3D-flash sequences) excellent images of the joint cartilage and the subchondral bone are possible [2, 6, 32]. However, regular X-ray to determine the axial and patellar position and ligament instability still has to be performed.

## Physiological Cartilage Repair

The therapy of articular cartilage defects is only successful if the concomitant injuries are also treated. In this context, existing varus and valgus deformity and ligament instability have to be considered [7, 10, 28]. The physiological reaction of the organism to a damage of the articular cartilage depends on different factors. The cartilage of growing children has an extremely high regeneration capacity. In contrast, grown man and particularly elderly people have a very low regeneration. Whether this is due to a lower number of MSCs in elderly people is still unclear [8, 9, 49]. The answer of

the organism to a damage of the articular cartilage depends on the patient's age and the type and size of the defect.

Chondral and osteochondral defects have to be distinguished. In the surrounding of chondral defects an increase of mitosis and proteoglycan synthesis has been described in animal experiments. However, a cure of these defects has not been observed [12, 15]. The progress of such lesions to osteoarthritis is proven [1, 30, 33, 35]. Similar reactions are detectable in osteochondral defects with an intact subchondral bone plate but healing can also not be expected [31]. As known for chondral lesions the progress to osteoarthritis is also proven. In contrast, osteochondral defects with access to the subchondral bone show limited regeneration. From the bleeding of the subchondral bone a blood clot with a mixture of progenitor cells and fibrin forms, which over time differentiates to a fibrous-like cartilage repair tissue. However, the biomechanical loading capacity of this repair tissue is markedly lower and the collagen composition is not specific for hyaline cartilage. In the long-term regular physiological loading destroys the repair tissue and leads to osteoarthritis [43, 48].

### Therapy of Cartilage Defects

The low regeneration capacity makes the refixation of a detached cartilage or cartilage bone fragment with resorbable pins necessary. The indications are flake-fractures and the osteochondritis dissecans. The healing process of these osteochondral lesions is determined by the bone fragment. A horizontal integration of the cartilage fragment into the surrounding intact cartilage can not be expected.

An other procedure is a debridement. This shaving technique combines a lavage, the removal of free bodies and degenerative cartilage fragments, and a limited excision of osteophytes. Studies of Kim et al. [27] have shown that a regeneration of the cartilage is not possible using this technique. Osteoarthritis can not be prevented by washing out degenerative enzymes and detached cartilage pieces. The relatively good clinical results (32 to 74%) at one to four years after surgery [11, 44] could be explained by the removal of active metabolic enzymes from the synovia. Therefore, a debridement is only a palliative method to temporarily relieve patients from pain suffering from an osteoarthritic joint. The use of different laser systems is not recommended because of chondrolysis and osteonecrosis.

The Pridie-drilling [40] is one of the marrow-stimulating techniques. In this procedure holes are drilled into the subchondral bone marrow underneath the regions of the damaged cartilage. The generated blood clot contains progenitor cells and fibrin and differentiates into fibrous cartilage. One of the disadvantages is the heat-induced tissue necrosis at the tip of the drill. The technique is indicated for the treatment of small osteochondral defects and osteochondritis dissecans grade IV. Clinical studies suggest that patients get most benefit from this procedure when axial mal-positioning is corrected as well [47].

In the last years Pridie-drilling was increasingly replaced by microfracturing. The technique is a modification of the Pridie-drilling and thus relies on the same biological principles promoting resurfacing by the formation of fibrocartilaginous repair tissue. The very small micro-holes generated with a special instrument (Chondropick)

should be put across the entire cartilage lesion at a distance of 3 to 4 mm and a depth of 4 mm, thus yielding in about 3 to 4 holes per cm<sup>2</sup>. Good clinical results with improved joint function and pain reduction during daily activities in 31 to 69% over 3 to 6 years have been reported [37]. The quality of the repair tissue can be improved significantly using CPM after surgery [41].

Another procedure that was first described by Magnusson [29] is the abrasion chondroplasty. This technique gives surgical access to the bone marrow, which together with other vicinal compartments gets stimulated to form a blood clot. The formed tissue is called bioprosthesis, which is fibrous in nature and not durable. The results show that there is a temporary improvement in 60% of the patients [14], but 99% are restricted in their activities of daily life. After 62 months only 12% of the patients are pain free [24-26].

The autologous osteochondral transplantation (OCT or mosaicplasty) is one of the newer procedures in the treatment of cartilage defects. An autologous osteochondral cylinder is harvested from a low weight-bearing area of the joint on transferred into the osteochondral defect. If positioning of the autograft is correct a good surface reconstruction can be expected. Histological analysis revealed a mixture of hyaline (70 to 80%) and fibrous (20 to 30%) cartilage. Symptomatic relief of pain and improvement in joint function have been reported as good and very good (70 to 90%) after one to six years [4, 5, 16, 17]. The procedure is recommended up to a defect size of 3 cm<sup>2</sup>. With more cylinders harvested, 5 to 20% of all patients have complaints that may be due to donor site morbidity.

The periossteal transplantation is based on a self-regeneration procedure. The biological background of this principle lies in a cambial layer at the back of the transplanted membrane. This special layer contains progenitor cells that are capable to induce the formation of hyaline-like cartilage. Therefore, the back of the membrane with the cambial layer must be placed into the defect area. The group of Homminga [18] reported about 80% good results using this procedure. Frequently occurring problems are incomplete defect filling and calcification of the periossteal membrane.

For autologous chondrocyte transplantation (ACT) a cartilage biopsy is taken from a non weight-bearing area. The chondrocytes are released and cultured in a special laboratory under GMP-conditions. The quality standards of the ACT and the tissue engineering committee under the patronage of the DGOOC and DGU have to be followed [45]. After expanding, the cells are transported in a special vessel to the hospital. Our own investigations have shown an average cell vitality of more than 84% over a time period of 72 hours after leaving the laboratory (Fig. 5.1A). Required is a continuous cell cooling. Under these conditions 93% of all vital cells are adherent (Fig. 5.1B).

In a second surgical procedure the cartilage defect is prepared. A periossteal flap is harvested and sutured waterproof over the damaged area. The cells are injected underneath the periossteal flap. The cells attach to the subchondral bone and form a cell lawn. They start to produce extracellular matrix and the defect gets filled with a high-quality regenerative tissue. A differentiation of the tissue is possible even without weight-bearing for the first 6 to 8 weeks. CMP for 6 hours a day plays an important role in the nutrition and stimulation of the cells to produce cartilage-like tissue. The use of a periossteal flap revealed in 70 to 90% of all cases good and very good results after two to eleven years [39]. The generated tissue also shows good biome-

**A** Average vitality of human chondrocytes *in vitro* (n = 12)  
**B** Average adhesion of human chondrocytes *in vitro* (n = 12)

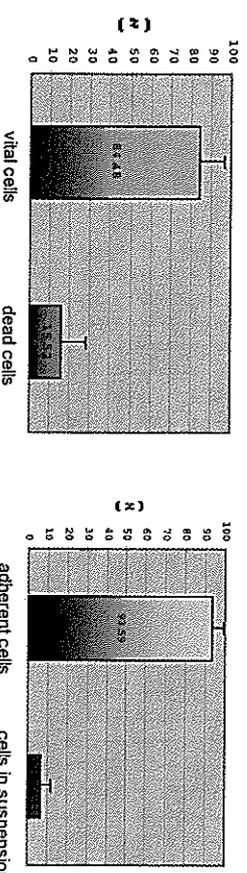


Fig. 5.1A,B. Average cell vitality (A) and cell adhesion (B) of human chondrocytes 24 to 72 hours after leaving the laboratory.

mechanical properties. Stiffness tests revealed average solidity values of 3.08 N for healthy hyaline cartilage compared to 2.77 N for the repair tissue after ACT, and 1.23 N for fibrous cartilage after marrow stimulation techniques [38].

**Function of the Periosteal Flap**

Using periosteum, cartilage formation is promoted by the cambial layer and the injected cells. So far no experimental study has clarified the origin of the cells in the repair tissue. Also, there is no study that has proven a sufficient number of vital cells in the cambial layer of the periosteal flap after cutting the blood supply at the time of harvest. The efficiency of a periosteal graft without ACT could be explained in part because of the bleeding from the subchondral bone and subsequent blood clot formation.

Also, the production of cytokines and growth factors could stimulate the formation of the repair tissue. Our own experiments using periosteal cells have shown a significant synthesis of BMP-2, -4, and -7 but no synthesis of IL-2, IL-6, and IL-8. In 5 to 25% of the cases when a periosteal flap was used a symptomatic hypertrophy has been seen at the repaired surface. Usually the hypertrophic tissue has to be removed in a second intervention. Histologically, the hypertrophic surface is fused to the deep hyaline-like zone [19]. However, especially the hypertrophic surface is fused to the deep importance for the biomechanical properties of articular cartilage [50]. The hypertrophic surface leads to an increased friction and progressive fissuration and splitting between the repair tissue and the surrounding healthy cartilage. The consequence is a delamination with loss of the repair tissue. Hypertrophy is not seen in all cases and this is probably due to the fact that the flap is worn out very early after surgery in some cases. A thick periosteal flap harvested from the tibial head comprises a variety of different cell types (e.g. fibroblasts, precursor cells, osteoblasts, and fat cells) that can mix with the transplanted cells and form an inhomogeneous tissue. It is of special importance that fibroblasts have a significant higher proliferation rate compared to chondrocytes.

**Freiburg ACT Study**  
**Defect localization**

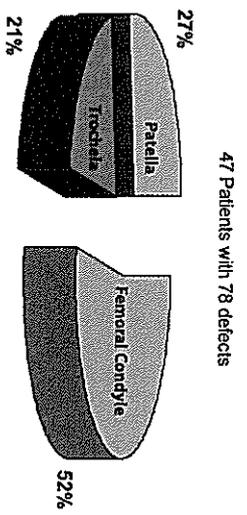


Fig. 5.2. Distribution of the defect localization in the Freiburg ACT study.

**Use of a Collagen Membrane Instead of a Periosteal Flap**

The idea that the main function of the periosteal flap is to cover the prepared defect area has inspired various biotechnology companies to develop different biomaterials for ACT. Collagen is naturally occurring in cartilage and its degradation products are physiological and therefore non-toxic. Due to its good biocompatibility collagen is used in different fields of medicine such as abdominal, plastic or maxillo-facial surgery. The Chondro-Gide® membrane is a bi-layer membrane from porcine collagen type I and III with a smooth outside and a porous inside. The outside has a good mechanical solidity and serves as a barrier, while the inside stimulates through its porous surface the cells to produce cartilage-specific matrix molecules [13]. The membrane is degraded by enzymatic digestion (collagenases). The resulting collagen fragments denature to gelatin and through enzymes such as gelatinase and proteinase to oligopeptides and amino acids.

**Animal Experiments Using the Chondro-Gide® Membrane**

Osteochondral defects with a diameter of 7 mm were set into the trochlea of the adult sheep. A total of 18 animals were divided into 3 groups. Group I had no treatment, group II was treated with an ACT and a periosteal flap, and in group III an ACT with the Chondro-Gide® membrane was performed. After 1 year the defect was examined histologically and biomechanically. There were no significant differences between group II and III. A complete defect filling could be detected in both groups [42].

**Clinical Results**

In a clinical study, 125 patients were treated with ACT. Twenty-six % were treated with ACT/periosteal flap and 74% with ACT/Chondro-Gide®. The mean defect size was 4.35 cm<sup>2</sup> and the mean age 30.9 years. Clinical results after one year turned out to be good or excellent in 89% of all cases. Arthroscopic evaluation after one year revealed

in both groups 80.2% ICRS grade I to II cartilage lesions. There were no significant differences in the defect healing and the clinical outcome [3]. Our own clinical studies showed similar results. Cartilage defects in 47 knees with 78 defects were treated either with ACT/perioosteal flap (Group I) or with the ACT/Chondro-Gide® membrane (Group II). The mean age was 34.1 years and the mean defect size 5.49 cm<sup>2</sup>. The patients underwent 2.88 surgical interventions before the ACT and were examined clinically with the IKDC-score [21] and radiologically after 3, 6, and 12 months.

In 53% of the cases only one defect and in 47% multiple lesions were treated with ACT. The defects were in 21% at the trochlea, in 27% at the patella, and in 52% at the femoral condyle. The medial femoral condyle was involved most frequently with 85%. In both groups, approximately 80% of the patients had grade IV and 20% grade III lesions. The average value in the ICRS score was 3.81 (SD = 0.39) versus 3.85 (SD = 0.36) in the Chondro-Gide® group. After 6 months the following results were found in the two groups.

- ACT/perioosteal flap group: 4.5% grade IV, 53% III, 38% II, and 4.5% grade I.
- ACT/Chondro-Gide® group: 4.8% grade IV, 47.6% III, 47.6% II, and 0% grade I.

The middle score in both groups was 2.57 (SD = 0.66/0.58). After 12 months (Fig. 5.3) the clinical score improved in the ACT/perioosteal flap group to 0% grade IV, 30% III, 55% II, and 15% grade I. The ACT/Chondro-Gide® group revealed after 1 year better results: 0% grade IV, 20% III, 40% II, and 40% grade I. The average score was 2.15 (SD = 0.65, perioosteal flap) and 1.80 (SD = 0.75, Chondro-Gide®). The study shows a time dependent increase of the IKDC score after 1 year. This could be explained with the biological cartilage remodeling and regeneration after ACT.

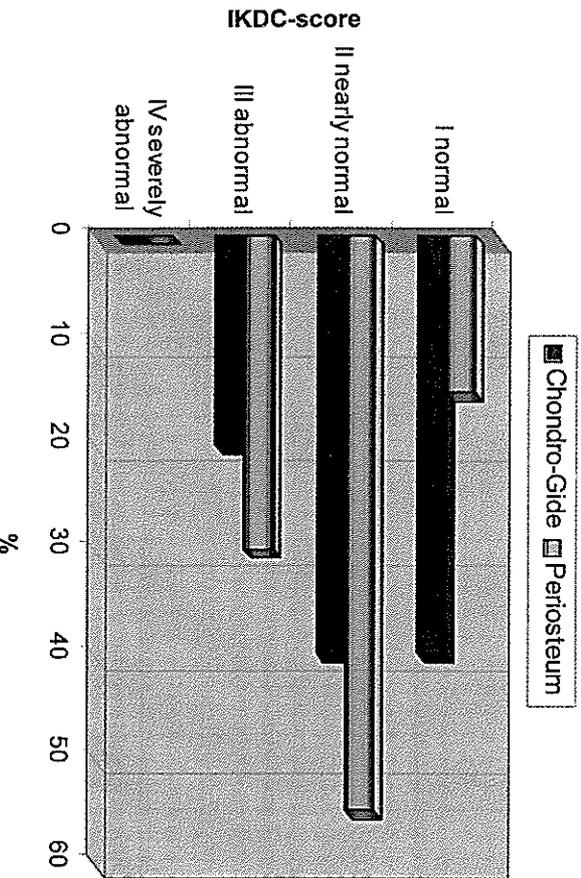


Fig. 5.3. Comparison of the IKDC-score one year after ACT.

**Discussion**

Considering all the advantages and disadvantages of the different resurfacing methods the surgical therapy of a grade I defect seems not to be necessary. Grade II lesions are usually treated with an arthroscopic debridement. Grade III and IV defects have to be treated. The microfracture technique or the Pridie-drilling can be recommended up to a defect size of 2 cm<sup>2</sup>. Good results can be expected for defect sizes between 1.5 and 3 cm<sup>2</sup> with osteochondral autografts. Defect sizes between 3 and 10 cm<sup>2</sup> can be treated successfully only with ACT (Fig. 5.4). The results are good and very good even after follow-up periods of 10 years. There is no other procedure capable to perform an extensive and durable reconstruction of these large cartilage defects. Nevertheless, this procedure has also disadvantages such as hypertrophic changes of the perioosteal flap with consecutive pain. The hypertrophic cartilage has to be removed arthroscopically. Another aspect is the remaining superficial unevenness reflecting a not perfect repair of the uppermost cartilage layer. The use of biomaterials may probably solve this problem (Fig. 5.5). However, the effectiveness of such modifications must be tested in clinical studies. The results of our study show that a significant increase (p < 0.05) of the clinical scores was observed in both groups. No significant differences could be

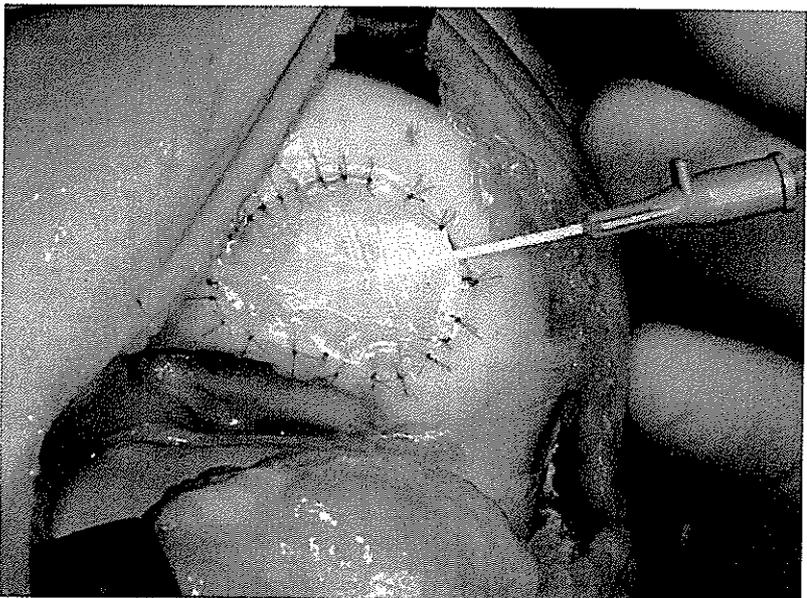


Fig. 5.4. Collagen membrane (ChondroGide®, Geistlich Biomaterials) sutured over the prepared defect area instead of a perioosteal flap.

# Algorithm

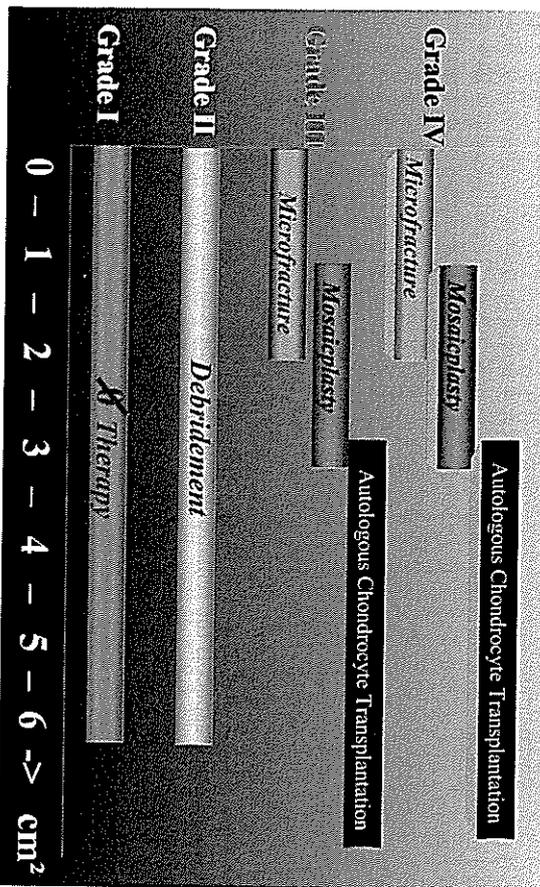


Fig. 5.5. Algorithm for the indication of different surgical techniques in the treatment of cartilage defects.

seen comparing the ACT/perioosteal flap group and the ACT/Chondro-Gide® group. High revision rates by perios hypertrophy (5 to 40% in the literature), large inter-individual quality differences of the perioosteal flap, and an increase of the morbidity by a separate incision are still risk factors in the surgical procedure. According to our clinical results the use of the Chondro-Gide® membrane has the same clinical effectiveness and seems to prevent the complications described above (see Fig. 5.4). The ACT has opened a new dimension in the therapy of cartilage defects. In the treatment of cartilage defects more than 3 cm<sup>2</sup> the transplantation of chondrocytes is the only procedure to generate a biomechanically high-quality regenerative tissue [46]. The procedure should be performed by specialized surgeons and especially in younger patients with cartilage damages of this size. Future developments will provide a wider application of this technology.

## Conclusion

Today, the repair of cartilage defects with hyaline-like repair tissue is possible with 2 methods: the OCT as a one step procedure and the ACT as a two step procedure in the treatment of large isolated defects. For successful ACT a stable bone with an intact tide mark, a high-quality of the chondrocytes, and an exact suture of the flap for closing the bioactive chamber are required. The hypertrophy of the perioosteal flap, observed

in some cases, can be avoided by the application of biomaterials. The future goal is tissue engineering with mesenchymal stem cells and minimal invasive technologies for a faster rehabilitation and good long-term results in the therapy of articular cartilage repair.

## References

1. Aigner T, Glöckert K, Mark K (1997) Activation of fibrillar collagen synthesis and phenotypic modulation of chondrocytes in early human osteoarthritic cartilage lesions. *Osteoarthritis Cartilage* 5:183-185
2. Bachmann G, Heinrichs C, Jürgensen I, Rominger M, Scheiter A, Rau WS (1997) Comparison of different MRT techniques in the diagnosis of degenerative cartilage diseases. In vitro study of 50 joint specimens of the knee at T1.5. *Fortchr Röntgenstr* 166:429-436
3. Bentley G (2002) Autologous chondrocyte implantation (ACI) in the young adult knee: Clinical, arthroscopic and histological results of 125 patients at 18 month follow up. ICRS, Toronto, Canada
4. Bobic V (1996) Arthroscopic osteochondral autograft transplantation in anterior cruciate ligament reconstruction: a preliminary clinical study. *Knee Surg Sports Traumatol Arthrosc* 3:262-264
5. Bobic V (1999) Autologe osteochondrale Transplantation zur Behandlung von Gelenkknorpeldefekten. *Orthopädie* 28:19-25
6. Bohndorf K (1996) Injuries at the articulating surfaces of bone (chondral, osteochondral, subchondral fractures and osteochondrosis dissecans). *Eur J Radiol* 22:22-29
7. Britberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L (1994) Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N Engl J Med* 331:889-895
8. Britberg M (1997) A critical analysis of cartilage repair. *Acta Orthop Scand* 68:186-191
9. Caplan AL, Fink DJ, Goto T, Linton AE, Young RG, Wakitani S, Goldberg VM, Haynesworth SE (1993) Mesenchymal stem cells and tissue repair. In: Jackson DW, Arnoczky SP, Frank CB, Woo SL-Y, Simon TM (eds) *The anterior cruciate ligament: current and future concepts*. Raven Press, New York, pp405-417
10. Erggeleer C, Steinwachs M, Reichelt A (1998) Die Behandlung von Gelenkknorpeldefekten. *Dtsch Arztebl* 95:1397-1382
11. Friedman MJ, Berasi CG, Fox JM, Del Pizzo W, Snyder SJ, Ferkel RD (1984) Preliminary results with abrasion arthroplasty in the osteoarthritic knee. *Clin Orthop* 182:200-205
12. Fuller JA, Ghadially FN (1972) Ultrastructural observations on surgically produced partial-thickness defects in articular cartilage. *Clin Orthop* 86:193-205
13. Fuss M, Ehlers EM et al. (2000) Characteristics of human chondrocytes, osteoblasts and fibroblasts seeded onto a type I/III collagen sponge under different culture conditions. A light scanning and transmission electron microscopy study. *Anat Ann* 182:303-310
14. Goyrann V (1999) Abrasion arthroplasty. *Orthopädie* 28:11-18
15. Grande DA, Pitman ML, Peterson L, Menche D, Klein M (1989) The repair of experimentally produced defects in rabbit articular cartilage by autologous chondrocyte transplantation. *J Orthop Res* 7:208-218
16. Hangody L, Karpati Z (1994) A new surgical treatment of localized cartilaginous defects of the knee. *Hungarian J Orthop Trauma* 37:237-242
17. Hangody L, Kish G, Karpati Z, Szerb I, Udvarhelyi I (1997) Arthroscopic autogenous osteochondral mosaicplasty for the treatment of femoral condylar articular defects. A preliminary report. *Knee Surg Sports Traumatol Arthrosc* 5:262-267
18. Hommiga GN, Bulstra SK, Bouwmeester PS, van der Linden AJ (1990) Perichondral grafting for cartilage lesions of the knee. *J Bone Joint Surg-Br* 72:1003-1007
19. Horas U, Schnetter R, Perinkovic D, Herr G, Aigner T (2000) Knorpelknochentransplantation versus autogener Chondrozytentransplantation *Chirurg* 71:1090-1097

20. Hunziker EB (1992) Articular cartilage structure in humans and experimental animals. In: Kuetner KE, Schleyerbach R, Peyron JG. Articular cartilage and osteoarthritis. Raven Press, New York, 183-199
21. IKDC-Score (1999) International Cartilage Repair Society. ICRS-Newsletter
22. Imhoff A (1991) Kniearthroskopie: Spezielle Diagnostik und Operationstechniken. In: Hempfling H, Burri C (eds) Diagnostische und operative Arthroscopie aller Gelenke. Hans Huber, Bern Stuttgart Toronto, S44-63
23. Jeffrey AK, Blunn GW, Archer CW, Bentley G (1991) Three dimensional collagen architecture in bovine articular cartilage. *J Bone Joint Surg-Br* 73:795-801
24. Johnson LL (1986) Diagnostic and surgical arthroscopy. The knee and other joints. 3rd edn. Mosby, St. Louis
25. Johnson LL (1991) Characteristics of the immediate postarthroscopic blood clot formation in the knee joint. *Arthroscopy* 7:14-23
26. Johnson LL (1991) Arthroscopic abrasions arthroplasty. In: McGinty JB (ed) Operative Arthroscopy. Raven Press, New York, pp341-360
27. Kim HK, Moran ME, Salter RB (1991) The potential for regeneration of articular cartilage in defects created by chondral shaving and subchondral abrasion. An experimental investigation in rabbits. *J Bone Joint Surg-A* 73:1301-1315
28. Löhner J (1999) Autologe Chondrozytentransplantation (ACT) im Kniegelenk. *Arthroscopie* 12:34-42
29. Magnusson PB (1941) Joint debridement surgical treatment of degenerative arthritis. *Surg Gynecol Obstet* 73:1-9
30. Maletius W, Aigner T (1999) Morphologie und Molekularpathologie der Osteoarthrose - Relevanz für Pathogenese und Diagnostik. *Arthroscopie* 12:3-8
31. Mankin HJ (1982) The response of articular cartilage to mechanical injury. *J Bone Joint Surg-A* 64:460-466
32. McCauley T, Disler D (1998) MRI of articular cartilage. *Radiology* 209:629-640
33. Messner K, Maletius W (1996) The long-term prognosis for severe damage of the weight-bearing cartilage in the knee. *Acta Orthop Scand* 67:165-168
34. Metz J (2001) Makroskopie, Histologie und Zellbiologie des Gelenkknorpels. In: Erggelet C, Steinwachs M (eds) Gelenkknorpeldefekte. Steinkopff, Darmstadt, S3-13
35. Mohr W (1998) Morphogenese der Osteoarthrose. *Arthroscopie* 6:195-200
36. Outerbridge RE (1961) The etiology of chondromalacia patellae. *J Bone Joint Surg-Br* 43:752-757
37. Passler HH (2001) Knochenmarkstimulierende Techniken - Mikrofraktur. In: Erggelet C, Steinwachs M (eds) Gelenkknorpeldefekte. Steinkopff, Darmstadt, S83-92
38. Peterson L (1998) Autologous chondrocyte transplantation: 2-10 year follow-up in 219 patients. Annual Meeting of the American Academy of Orthopaedic Surgeons, New Orleans, March 21, 1998
39. Peterson L, Brittberg M, Kiviranta J, Akerlund EJ, Lindahl A (2002) Autologous chondrocyte transplantation, biomechanics and long-term durability. *Am J Sports Med* 30:2-12
40. Pridie KH (1959) A method of resurfacing osteoarthritic knee joints. *J Bone Joint Surg-Br* 41:618-619
41. Rodrigo J, Steadman JR, Silliman JF, Fulsome HA (1994) Improvement in full-thickness chondral defect healing in the human knee after debridement and microfracture using continuous passive motion. *Am J Knee Surg* 7:109-116
42. Russiles et al. (2002) Histological and biomechanical results of 3 different cartilage repair technique in a sheep model. *ICRS 2002*, Toronto
43. Shapiro F, Koide S, Glimcher MJ (1993) Cell origin and differentiation in the repair of full-thickness defects of articular cartilage. *J Bone Joint Surg-A* 75:532-553
44. Sprague NF 3rd (1981) Arthroscopic debridement for regeneration knee joint disease. *Clin Orthop* 160:118-123
45. Stellungnahme der Arbeitsgemeinschaft - Autologe Chondrozyten-Transplantation (ACT) und Tissue Engineering - unter Schirmherrschaft der DGU und DGOOC (2002) *Z Orthop* 140:132-137

46. Steinwachs MR, Erggelet C, Lahm A, Gubke-Steinwachs U (1999) Clinical and cell biology aspects of autologous chondrocytes transplantation. *Unfallchirurg* 102:855-860
47. Tippet JW (1996) Articular cartilage drilling and osteotomy in osteoarthritis of the knee. In: McGinty JB, Caspari RB, Jackson RW, Poehling GG (eds) Operative arthroscopy, 2nd edn. Raven Press, Philadelphia, New York, pp411-426
48. Wakitani S, Goto T, Pineda SJ, Young RG, Mansour JM, Caplan AL, Goldberg VM (1994) Mesenchymal cell-based repair of large, full-thickness defects of articular cartilage. *J Bone Joint Surg-A* 76:579-592
49. Wirth CJ, Rudert M (1996) Techniques of cartilage growth enhancement: a review of the literature. *J Arthrosc Rel Surg* 12:300-308
50. Wong M, Wnetherich P, Buschmann M, Eggl P, Hunziker EB (1997) Chondrocyte biosynthesis correlates with local tissue strain in statically compressed adult articular cartilage. *J Orthop Res* 15:189-196
51. Zollinger H (1977) Indikation und Aussage der Gelenkendoskopie bei der Chondropathia patellae. *Z Orthop (abstract)* 115:617