Present and Future Therapies of Articular Cartilage Defects

Jan P. Petersen, Andreas Ruecker[1], Dietrich von Stechow[2], Peter Adamietz[3], Ralf Poertner[4], Johannes M. Rueger[1], Norbert M. Meenen[1]

Abstract

Background: Until today, no universally successful therapy to treat substantial articular cartilage defects has been available. Numerous therapeutic approaches can only improve clinical symptoms of joint lesions, but cannot stimulate the regenerative and reactive capacity of the biological tissue in the defect, and, thus, cannot restore an articular surface capable of functional load bearing. Some other therapeutic options promised impressing results at the beginning, but did not withstand the process of a closer investigation. Even after laborious, invasive and expensive therapies, patients still complain about pain, joint effusions, restricted movement, or articular blockage.

Established and Novel Therapies: The aim of all therapeutic procedures to treat patients with damaged articular cartilage is to reconstruct the integrity of the articular cartilage surface in order to enable them to live an unrestricted painless professional and private life. This article gives an overview of the clinically established procedures, their indications and the present long-term results, as well as a crucial look on the limitations of each approach. Novel therapies, which integrate molecular biology techniques and tissue engineering into transplantation surgery, are introduced and analyzed in terms of their capability and future potential.

Key Words

Articular cartilage · Defect treatments · Subchondral stimulation · Autologous chondrocyte transplan-tation · (Osteo)chondral transplantation · Tissue engineering

Eur J Trauma 2003;29:1–10

DOI 10.1007/s00068-003-1215-6

Introduction

A cause for lesions or defects of articular cartilage, aside from osteoarthrosis and osteochondrosis dissecans, is the trauma, which plays a significant role, especially when dealing with younger and active patients [48, 79]. Cartilage, as tissue with the exclusively mechanical tasks of reducing relative load transfer by enlarging contact area and providing damping and gliding, has a high sensitivity to mechanical injuries [12].

These injuries and their consequences are relevant especially in the weight-bearing joints of the lower limbs, such as the knee or ankle joints. Trauma can be single or repetitive. Usually, it is not an isolated cartilage defect, but occurs in combination with complex joint injuries of cartilage, bone, ligaments, menisci, and capsule. For example, 20–40% of the anterior cruciate ligament ruptures are combined with cartilage injuries [19, 37, 48, 51, 68].

[1] Department of Trauma and Reconstructive Surgery, Hamburg University School of Medicine, Hamburg, Germany,
[2] Beth Israel Deaconess Medical Center, New England Baptist Bone and Joint Institute, Harvard Institutes of Medicine, Boston, MA, USA,
[3] Institute of Medical Biochemistry and Molecular Biology, Hamburg University School of Medicine, Hamburg, Germany,
[4] Institute of Biotechnology, Technical University Hamburg-Harburg, Hamburg, Germany.

Received: April 3, 2002; revision accepted: January 10, 2003

Cartilage defects > 1 cm^2 are symptomatic with pain, joint effusion, limited range of motion, or even blockage of movement (Figures 1 and 2).

Already in 1743, the surgeon and scientist Sir W. Hunter remarked: "If we consult the standard Chirurgical Writers from Hippocrates down to the present age, we shall find, that an ulcerated Cartilage is universally allowed to be a very troublesome Disease; that it admits of a Cure with more Difficulty than a carious Bone; and that, when destroyed, it is never recovered" [33]. This statement has to be underlined until today.

The hyaline cartilage actually only has a very small potential of self-repair [4, 7, 17, 42]. Superficial cartilage lesions only get smoother but do not heal on account of missing blood supply, differentiated status of adult chondrocytes with very little proliferation tendency and lack of mesenchymal stem cells within this differentiated cartilage tissue [12, 13, 16, 25, 42, 65]. Deeper lesions which reach down to the blood supply of the subchondral spongy bone, are only replenished with a scar tissue consisting of biomechanically and biochemically inferior fibrous cartilage [16, 17, 61, 65, 78]. Experimental data by Jackson et al [35] suggest even nonhealing and progressive resorption processes with deep full-thickness defects. There are different approaches to surgically treat a cartilage damage: small defects (< 1 cm^2) may be treated with a certain success through Pridie drilling, the abrasion arthroplasty or microfracturing techniques, which have the same concept of achieving subchondral stimulation of healing capacity but from there, only fibrocartilage scars can be expected [46]. In the case of larger lesions with profound influence on joint mechanics, transplantation techniques, e.g., osteochondral transplantations, have been established.

Extensive cartilage defects of, e.g., one complete femoral condyle, or a "kissing lesion" on femur condyle and tibial plateau, and generalized osteoarthrosis of the entire joint still require radical substitution of the joint surface by an endoprosthesis. Since, however, artificial joints only have a limited durability, the indication for younger patients is restricted, and, thus, arthrodesis is a possible alternative [44, 60]. The search for procedures to gain ideal mechanical and tissue-adequate repair of the joint surface remains a central topic for all treatment modalities of cartilage defects.

Established Procedures

The following arthroscopic techniques are not able to stimulate cartilage growth and will only improve clinical symptoms resulting from articular cartilage defects.

Lavage

Rinsing with physiological solutions of the affected joint represents one of the oldest and simplest methods of cartilage defect therapy [41]. Jackson [36] describes, that the rinsing of a joint decreases inflammation mediators and removes loose cartilage bodies and fibrin debris. This way, an improvement of the symptoms can be achieved in about 80% of the patients, and this alleviation will last for 3.5 years in 45% of these cases. However, 20% of the patients do not gain any benefit from this method. In particular for young people, this therapy cannot be the definitive solution, since it does not repair the joint damage itself, but only supports temporary improvement of the situation. However, it may be used to, e.g., put off the date for endoprosthetic solutions.

Shaving and Debridement

Destroyed cartilage can lead to mechanical obstacles, which reach up to the complete knee joint blockage. This phenomenon is to be traced back to loose cartilage particles or extensive deposits of fibrin clots in the joint. Beyond that, cartilage fragments can lead to reactive synovitis and joint effusions [50, 75]. Removing injured cartilage through shaving or debridement leads to an elimination of the mechanical hindrance, and removing fibrin clots decreases the accompanying inflammatory reaction. Magnusson [41] reported in 1941 that he

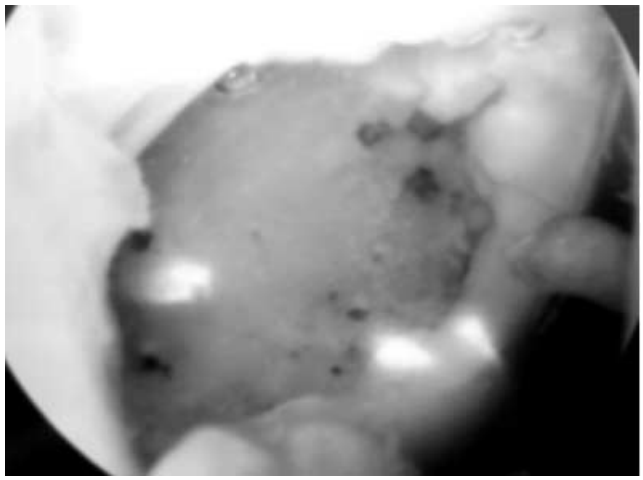


Figure 1. Medial femoral condyle of a 38-year-old man with full-thickness cartilage defect 3.0 cm in diameter after arthroscopic removal of the dissected cartilage layer.

achieved good to excellent results in 70% of his patients with this method. Follow-up trials showed that after carrying out shavings no reparation of cartilage could be witnessed. Beyond that, investigations demonstrate that, on a long-term basis, it even comes to an increased deposit of fibrin after a shaving procedure in the affected joint and that the bordering healthy cartilage shows signs of necrosis in the process [39]. Similar to the lavage, shaving and debridement decrease only the clinical symptoms, but do not lead to sufficient cartilage repair.

Repair Techniques by Subchondral Stimulation

By using these techniques, bleeding from the spongiosa cavities into the cartilage defect is created by punctual and linear perforations of the subchondral bone lamella. Mesenchymal stem cells and vessels migrate into the clot and into the defect. They are able to differentiate to cells of the chondrogenic line and are thus capable of producing extracellular matrix of cartilage. However, as a great number of experimental and clinical studies show, the defect is filled up only with fibrous cartilage consisting of matrix with high content of the inadequate collagen type I, and, thus, of minor quality concerning joint facets.

All of these procedures, that can be performed arthroscopically, have to be combined with intensive physiotherapeutic rehabilitation programs and with limited weight-bearing periods up to 6 weeks.

With the Pridie procedure, named after the primary descriptor [59], multiple holes with an average diameter of 1.5 mm are drilled in the subchondral bone lamella from the joint surface in the area of the cartilage defect. In the investigations of Tippet, who carried out Pride drilling in connection with valgus osteotomy of the tibia, 70.8% of the patients achieved an excellent result over a period of 62 months, 15.4% a good and 6.9% a satisfactory to poor result [72]. Modern therapy concepts still contain this kind of bone drilling [49]. In the case of lesions on less accessible areas (e.g., plateau of the tibia and posterior facets of the patella), a so-called retrograde drilling can also be performed.

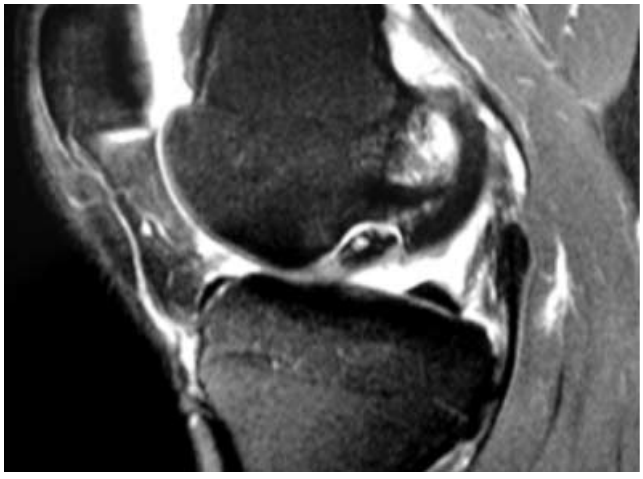


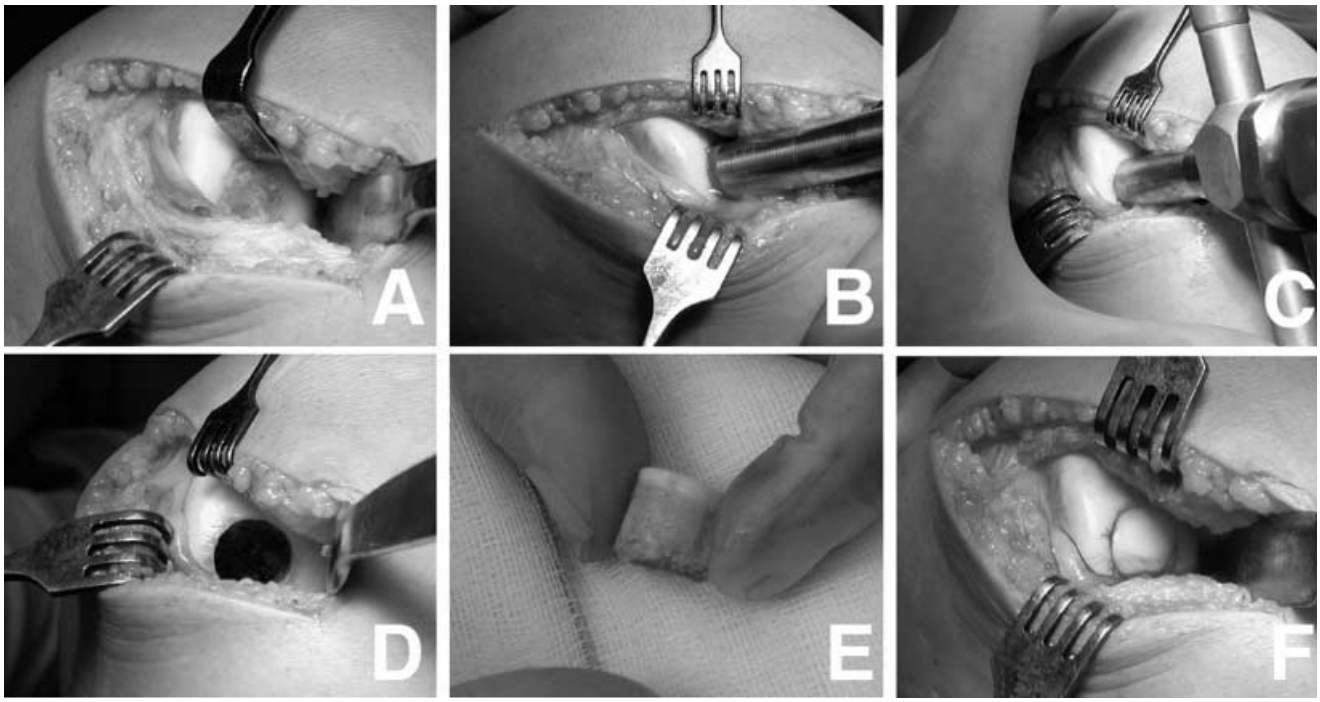
Figure 2. MRT of the same cartilage defect in sagittal view with osteochondrotic necrosis in situ.

With the microfracture technique developed by Steadman et al [69, 70], punctures are hit, with a conical and cranked awl with a tip diameter of 1.5 mm, arthroscopically through the defect into the subchondral lamella which leads to connecting fissure lines (microfractures) between the punctures. Unlike the Pridie drilling, a two-dimensional regeneration field is created. A further advantage of this procedure compared to drilling is the lack of heat-related necrosis of the bone [67]. Moreover, microfractures can also be directly carried out in slightly amenable areas with different cranking angles of the instruments.

In the largest follow-up trial investigating this method on more than 1,200 patients in a period of 2–8 years, Steadman et al [70] report that the patients indicated clear improvements even after 7 years concerning pain symptoms. The authors further state that in histologic investigations, the newly formed tissue contains partly hyaline and partly fibrous cartilage. Other investigations described similar results after microfracture treatment [5, 26, 27, 67].

Transplantation Techniques

On account of the limited ability of spontaneous and induced regeneration of cartilage and the still unsatisfactory results of the aforementioned therapies for more expanded defects, grafting procedures of cartilage and related cells or tissues are performed. It has to be mentioned that grafting of pure articular cartilage alone is of no success, nor is the replantation of isolated cartilage flakes after traumatic dissociation, ablation without a bony support, as cartilage does not heal to bony surfaces nor bone manages cartilage fixation. Only experimental and clinical data from one group suggest some success with fibrin-glue fixation [55–57]. Consequently, cartilage is usually transplanted with the underlying bone plate (= osteochondral grafts). Bone healing has proven to give quick and secure fixation of these osteochondral transplants.



Figures 3A to 3F. Osteochondral transplantation with DBCS® instrumentation in a 45-year-old man with painful cartilage defect.
A) Large cartilage defect in the medial condyle of the right knee.
B) Preparation for resection of the defect zone with the diamond trephine.
C) Removal of cylinder of defective bone and cartilage.
D) Former lacerated zone irrigated and ready for implantation.
E) Osteochondral cylinder transplant taken from a less weight-bearing zone of the edge of the patellar groove.
F) Osteochondral transplantation leads to a homogeneously plane joint surface.

Autologous Osteochondral Grafts

The clinically most successful therapy applied at present is the autologous osteochondral transplantation. With this procedure, first presented by Lexer [40] in 1908, the defective chondral area is replaced by an autologous cartilage-bone block. For this, the damaged cartilage area with it underlying bone has to be milled out. The resulting defect is filled through an intact cartilage-bone block, which is taken from a less loaded area, for example in the knee joint, from the retropatellar facet of the femoral condyles, the dorsal part of the condyles, or from the edge of the intercondylar notch (Figures 3A to 3F).

In 1972, Wagner [76] performed autologous cartilage-bone transplantations. He milled, with a hand-driven steel trephine, a block out of the posterior part of the femoral condyle and fitted it into the anterior defect. 2–5 years after the operation, good results in terms of pain reduction and increased mobility were achieved in 70% of the patients treated with this method. In 30% of the patients, no improvement was obtained. Wagner explained these failures by the insufficient fixation of the transplants, overloading, or the incongruence of the donor and recipient articular areas.

In a current trial [45], after performing cartilage-bone grafting on 52 patients with larger cartilage lesions between 1 and 9 cm^2 conditioned traumatically (n = 15) or in eleven cases by osteochondrosis dissecans, 100% of good and excellent results were achieved until 24 months postoperatively. In 26 cases of osteoarthritis, 76.9% of the patients had good and excellent results. The instruments for this operation are of certain importance for the outcome of the procedure, as a cool and sharp cut will lead to undisturbed bony healing of the transplant. We extract the osteochondral pegs of 2.8–20.05 mm diameter with the aid of an airmotor-driven, diamond-studded and internally chilled milling device combined with cartilage punches of the same diameter (Diamond Bone Cutting System [DBCS®], recently renamed Surgical Diamond Instruments [SDI®]; MedArtis AG, Keltenring 1–3, 82041 Deisenhofen, Germany) developed by Draenert & Draenert [22].

A similar concept of osteochondral grafting is the autologous osteochondral mosaicplasty described by Hangody et al [30]. With a punch, 10–15 mm long blocks are taken out of the retropatellar region of the femur and replanted in a mosaic-like fashion into the articular cartilage defect. The difference to the DBCS® is that the defect is not filled through one or several big cylinders toothed in each other (like a puzzle) but by several small blocks placed side by side. The void area is filled by fibrocartilage only, and the thin implants might dislocate under load (own observations).

In the trial by Hangody et al [30], 8 weeks after the operation the blocks were connected by fibrous cartilage among one another and with the surrounding tissue. In 91% of the patients, good to excellent results concerning pain and range of motion could be found.

The indication for autologous osteochondral grafts are full-thickness articular defects of 1–9 cm^2 in the central loading region of the joint and osseochondrosis dissecans lesions.

A further interesting option, described by Stone & Walgenbach [71], is to place a paste made out of autologous cartilage and bone into the articular defect after microfracturing it, as a combination of the subchondral stimulation concept and transplantation. An autologous condylar block is arthroscopically punched from the notch entry and worked up to a paste. This paste is then pressed into the microfractured and debrided cartilage defect. The presently available results are promising, especially when taking into account, that exclusively athletes were treated. However, extensive rehabilitation programs are an indispensable condition. Histologies proved that the nonstructured graft converts into hyaline-like cartilage.

As drawback of all transplantation techniques, the necessity for donor site defects with coherent joint morbidity has to mentioned. To limit this morbidity, the DBCS® method, for example, fills those defects with bone cylinders from the iliac crest, with adhering periost covering, that converts into fibrocartilage.

Cartilage-Bone Allografts

This method would offer the advantage of an almost exact anatomic reconstruction of an articular defect by the use of a corresponding joint area of an organ donor. Moreover, no donor defect results [77]. Theoretically, the implants are available at any time and in every size. Considering the dangers of transmission of life-threatening infections such as AIDS, hepatitis or Creutzfeld-Jakob disease [11, 18], the implantation of allogenic tissue has to be avoided in our opinion unless there is a vital indication, e.g., liver or heart transplantation. Moreover, the results are not definitely convincing altogether, as allografts will undergo major necrotic changes [2–4, 20, 21, 63].

Periosteum and Perichondrium Grafts

The transplantation of perichondrium into a cartilage defect was proposed by Homminga et al [31]. O'Driscoll et al [52–54] described an analogous procedure, but used periosteum as a graft. Both techniques are based on the consideration that cells which have a potency of chondrogenesis and are fixed in a biological matrix, can be brought into the articular cartilage defect. The periosteum is mostly taken from the tibia and the perichondrium from rib cartilage. The grafts are then fixed via fibrin glue into the defect, or they are stitched on.

In the affirmative case, the graft then fixes to the debrided subchondral bone and the surrounding healthy cartilage. Advantages of this method lie in the use of autologous, cell-containing material. As a disadvantage it is to be mentioned, that only quite small cartilage defects can be treated in such a way and that the operative effort is by far higher in comparison to the procedures with subchondral stimulation, which mostly can be performed arthroscopically.

The fact that periosteum and perichondrium have the ability to give rise to hyaline-like cartilage in the joint was shown in several studies [9, 10, 15, 62]. The first clinical trials showed good results concerning the function of the joints and the symptoms immediately after the operation [31]. Long-term results are yet to come.

Autologous Chondrocyte Transplantation (ACT)

Tested first in 1989 in an animal experimentation, Grande et al [29] took a small biopsy from cartilage of an unloaded joint area, isolated the cartilage cells and proliferated them in monolayer tissue cultures until there was a sufficient amount of chondrocytes available. The chondrocyte suspension was then injected under a periosteal flap, which was stitched over the debrided articular defect. The periosteum was taken from the tibia via the same incision. The authors reported good results with defects filled by cartilage-like tissue.

In 1994, Brittberg et al [7] then published first clinically approved successes on 23 patients using this method. 16 patients achieved good to excellent results.

In the biopsies taken during arthroscopy, hyaline-like cartilage appeared in twelve out of 22 probes. In 2002, Peterson et al [58] reported about 61 patients treated with chondrocyte transplantation. After a period of 5–11 years, 51 patients showed good to excellent results.

Different results were reported by Breinan et al [6] in 1997. In an experimental study with rabbits, they compared empty articular defects covered only with a periosteal flap toward defects containing grafted autologous chondrocytes. The authors could show that the defects were only filled with a mixture of hyaline-like tissue and fiber tissue, but not with hyaline cartilage. However, the reparative tissue in the defects always contained collagen I. As result of a comparative clinical trial, Horas et al [32] preferred osteochondral transplants over ACT because of mainly fibrocartilage repair from the latter.

As a serious disadvantage of this method, only dedifferentiated connective tissue cells of unknown function instead of well-differentiated chondrocytes are grafted into the defect. The possible redifferentiation to cells, the probable production of a cartilage-like matrix, and the mechanical properties of the developing tissue are not under steering control of surgeon and molecular biologist nor is the definitive stop of the stimulated proliferation process.

Tissue Engineering

All therapies mentioned up to now offer no perfect solution dealing with articular defects, and most cases of a cartilage lesions result in progressive degeneration changes. The only procedure which replenishes the defect in the long run with typical hyaline cartilage suitable for joint surfaces is the autologous cartilage-bone grafting, carried out with DBCS® or as mosaicplasty. The great disadvantage of this procedure consists in the fact that the donor defect is as large as the area that has to be repaired or even somewhat larger, as by milling a substance loss of instrument wall thickness follows.

Relevant donor defects do not occur, if a graft of autologous chondrocytes is gained from a small biopsy, cultured in vitro and inserted into the defect covered by a periosteal flap (ACT). Only a small, exclusively chondral defect in marginal articular areas is generated.

The combination of the indisputable advantages of both procedures, i.e., the grafting of well-differentiated and three-dimensionally structured cartilage tissue with leaving only a tiny donor defect, would meet the demands on an ideal procedure to treat articular cartilage defects. The in vitro production of articular cartilage grafts by tissue engineering allows for definitive control over the processes of cell isolation, proliferation, differentiation, and matrix production for a normally structured autologous transplant.

Cartilage is best suitable for in vitro culturing. The articular cartilage merely consists of a single cell type, the chondrocytes. Vessels and nerves are not associated. The nutrition in vivo is obtained by diffusion as in cell-culture conditions. Differentiated chondrocytes are able to produce all typical protein matrix components.

Regarding the aforementioned assumptions, the following method for the in vitro production of cartilage is focused:

First, the biopsy of cartilage tissue is taken, e.g., during an arthroscopy of the injured joint. After isolation of the chondrocytes by enzymatic digestion of the extracellular matrix, the cells are suspended into a culture flask. The cells proliferate with a doubling time of approximately 2 days and to a factor of > 1,000-fold within regular cell culture media supplemented with growth factors [1]. As soon as the cell layer is confluent, the cells are freed from plastic dishes by trypsin digestion and spread into new flasks. After the necessary number of cells has been attained for tissue engineering, the cells are trypsinized again from the culture flasks, and are assembled into a three-dimensional arrangement by several techniques.

In this close contact to each other or with biomaterials (e.g., collagen sponge, polymer fleece, bone substitute material), the cells do not proliferate any longer but start to produce typical extracellular matrix containing glycosaminoglycan and collagen II structured in a more ore less characteristic manner for hyaline cartilage (Figure 4).

This basic concept for tissue engineering was carried out by several authors. Guiding work was done in Boston, MA, USA, by Joseph and Charles Vacanti, Robert Langer, und Lisa Freed. Vacanti et al [73, 74] took cartilage from shoulders of newborn calves, isolated the chondrocytes and seeded them on to different PGA/PLLA-polymeric carriers (PGA: polyglycolic acid, PLLA: poly-lactic acid). Following cultivation, the chondrocytes-polymer complexes were implanted beneath the skin of nude mice. After explantation, it could be observed that the complex had turned into hyaline-like cartilage tissue, which contained glycosaminoglycans and collagen as characteristic ingredients of the extracellular matrix of articular cartilage.

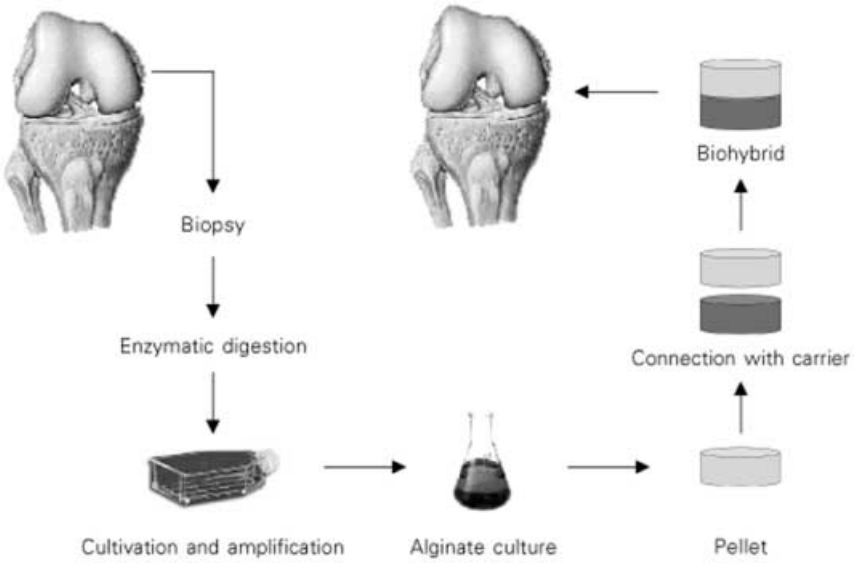


Figure 4. Diagram of in vitro cartilage tissue engineering. After cell isolation from a small biopsy of an unloaded area and amplification in monolayer culture, the cells are seeded into a three-dimensional arrangement on top of a bone-integrative carrier made of calcium phosphate where they produce extracellular matrix, typical of hyaline cartilage. This biohybrid compound with the tissue-engineered cartilage is then transplanted into the defect like an osteochondral graft.

Freed et al [23, 24] took probes from knee and costal cartilage of calves, in another trial rabbit cartilage. The cultivation was carried out on PGA in vitro and implanted in the knees of the rabbits. The polymer-cell complex was macroscopically and microscopically very similar to hyaline cartilage and contained glycosaminoglycan and collagen.

Bujia et al [14] and Sittinger et al [66] used human cartilage from the femoral head. After monolayer cultivation, the cells were given onto the polymers. This cell-polymer complex was then embedded in agarose gel, and cultivation was continued within an automatic cultivating system (bioreactor). An implantation has not been performed to date. Here, also glycosaminoglycan and collagen could be traced in tissue engineering products.

There are further authors who described the method mentioned above. The setup mainly differs in regard to the origin of the cartilage [34, 38, 47, 50], age of the animals, cultivation time, and the carrier.

Different cell sources for cartilage tissue engineering were used by other investigators. For example, Butnariu-Ephrat et al [16] employed bone marrow cells, Martin et al [43] used mesenchymal stem cells. We equally conduct experiments with the scope to substitute differentiated cartilage cells as cellular basis for tissue engineering of articular cartilage with stem cells, as for the proliferation process the differentiated cartilage cells lose the differentiated status and possibly return to stem cell-like situation.

All the above listed setups have in common, that tissue similar to hyaline cartilage is produced in vitro regarding collagen content, proteoglycan composition and three-dimensional structure, a prerequisite for adequate mechanical properties and successful use in joint defects.

Crucial for the process of cartilage tissue engineering is the incapability of the isolated cartilage tissue to fasten onto subchondral bone. Even traumatically originated autologous cartilage flakes are not promising to replant, only in the case of an adhering bone pad, the replantation can succeed. The simple attachment or application of the cartilage pellet into the defect or to the surrounding cartilage would not even satisfy the mechanical requests of the fixation [8]. But there are some interesting ideas for anchoring the cartilage in the bone:

Grande et al [28] used an anchor consisting of PLLA with a PGA fleece connected to it. After culturing chondrocytes in PGA in vitro, the cartilage could be fixed into the subchondral bone with the anchor. The results after 3–6 weeks with sheep showed a good anchorage of the implants and the development of hyalin-like cartilage tissue in the PGA.

Schaefer et al [64] extracted cartilage and periosteum from calves, isolated the cells and cultivated the chondrocytes on PGA, the periosteal cells on foams made of a blend of poly-lactic-co-glycolic acid and polyethylene glycol carriers. After 1–4 weeks the two originated tissues were sutured to each other and cultivated together for another 0–4 weeks. The histologic evaluation showed hyaline cartilage-like and bone-like tissue, but the connection between the two tissues was only moderate.

To obtain a good osseous fixation of tissue-engineered implants, we examine the contact of cultivated cartilage tissue brought onto biodegradable carriers of bone substitute biomaterial. The aim is to achieve a fast and tight contact between the carrier and the bone or the cartilage. Further investigations have to demon-

strate how the degradation of the carrier and the substitution of the basal layer with bone takes place and which influence this bone remodeling has on the overlying cartilage.

Conclusion

All procedures currently in clinical practice are more ore less successful attempts to repair articular cartilage defects. Now it is left to further work and in vivo studies to prove, if in vitro engineered chondral implants integrate, if they can fulfill the mechanical demands on articular cartilage, and if they can achieve a definite cure of cartilage defects under all conditions and in all dimensions.

Acknowledgments

Experimental tissue engineering work was supported by the German Federal Ministry of Education and Research (BMBF) and Biomet Merck, Darmstadt (Grant No. 03N4012). The authors would like to thank Anabel Ruecker, Christiane Goepfert, Brigitte Jeschke, Stefanie Nagel-Heyer, Ditte Siemesgeluess, Jens Schroeder, Frank Feyerabend, Klaus Baumbach and J. Schroeder as members of our TE group for technical assistance.

References

1. Adamietz P. Synergy of transforming growth factor β-1 and insulin-like growth factor in stimulating formation of neocartilage by pig articular chondrocyte pellet cultures. 2nd Fribourg International Symposium on Cartilage Repair, Fribourg, Switzerland, 1997.
2. Asselmeier MA, Caspari RB, Bottenfield S. A review of allograft processing and sterilization techniques and their role in transmission of the human immunodeficiency virus. Am J Sports Med 1993;21:170–5.
3. Beaver RJ, Gross AE. Fresh small-fragment osteochondral allografts in the knee joint. In: Aichroth PMAE, Cannon WD Jr, eds. Knee surgery, current practice. Köln: Deutscher Ärzte-Verlag, 1992:464–71.
4. Bently G. Grafts and implants for cartilage repair and replacement. Crit Rev Biocompatibil 1989;5:245–67.
5. Blevins F, Steadman R, Rodrigo J, Silliman J. Treatment of articular cartilage defects in athletes: an analysis of functional outcome and lesion appearance. Orthopedics 1998;21:761–8.
6. Breinan HA, Minas T, Hsu H, Nehrer S, Sledge CB, Spector M. Effect of cultured autologous chondrocytes on repair of chondral defects in a canine model. J Bone Joint Surg Am 1997;79:1439–51.
7. 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;331:889–95.
8. Brittberg M, Peterson L, Lindahl A, Nilsson A, Olsson C, Isaksson O. Cellular aspects on treatment of cartilage injuries. In: Van den Berg WB, ed. Joint destruction in arthritis and osteoarthritis. . Basel: Birkhäuser, 1993:237–42.
9. Bruns J, Behrens P. Die Transplantation von autogenem Rippenperichondrium zur Behandlung von tiefen Gelenkknorpeldefekten. In: Imhoff AB, Burkhart A, eds. Knieinstabilität – Knorpelschaden, Darmstadt: Steinkopff, 1993:82–8.
10. Bruns J, Kersten P, Lierse W, Silbermann M. Autologous rib perichondrial grafts in experimentally induced osteochondral lesions in the sheep-knee joint: morphological results. Virchows Arch [A] 1992;421:1–8.
11. Buck, BE, Resnick L, Shah SM, Malinin TI. Human immunodeficiency virus cultured from bone. Implications for transplantation. Clin Orthop 1990;251:249–53.
12. Buckwalter JA. Osteoarthritis and articular cartilage use, disuse, and abuse: experimental studies. J Rheumatol 1995;Suppl43:13–5.
13. Buckwalter JA, Mankin HJ. Articular cartilage: degeneration and osteoarthritis, repair, regeneration, and transplantation. Instr Course Lect 1998;47:487–504.
14. Bujia J, Sittinger M, Minuth WW, Hammer C, Burmester GR, Kastenbauer E. Engineering of cartilage tissue using bioresorbable polymer fleeces and perfusion culture. Acta Odontol Scand 1995;115:307–10.
15. Bulstra SK, Homminga GN, Buurman WA, Terwindt-Rouwenhorst E, van der Linden AJ. The potential adult human perichondrium to form hyalin cartilage in vitro. J Orthop Res 1990;8:328–35.
16. Butnariu-Ephrat M, Robinson D, Mendes DG, Halperin N, Nevo Z. Resurfacing of goat articular cartilage by chondrocytes derived from bone marrow. Clin Orthop 1996;330:234–43.
17. Campbell CJ. The healing of cartilage defects. Clin Orthop 1969;64:45–63.
18. Carlson ER, Marx RE, Buck BE. The potential for HIV transmission through allogenic bone. Oral Surg Oral Med Oral Pathol 1995;80:17–23.
19. Coen MJ. The dimpling phenomenon: articular cartilage injury overlying an occult osteochondral lesion at the time of anterior cruciate ligament reconstruction. Arthroscopy 1996;12:502–5.
20. Convery RF, Akeson W H, Meyers MH. The operative technique of fresh osteochondral allografting of the knee. Operat Tech Orthop 1997;7:340–4.
21. Coventry MB, Ilstrup DM, Wallrichs SL. Proximal tibial osteotomy. A critical long-term study of eighty-seven cases. J Bone Joint Surg Am 1993;75:196–201.
22. Draenert K, Draenert Y. A new procedure for bone biopsies and cartilage and bone transplantation. Sandorama 1987;3:254–69.
23. Freed L, Vunjak-Novakovic G, Marquis JC, Langer R. Kinetics of chondrocyte growth in cell-polymer implants. Biotechnol Bioeng 1994;43:597–604.
24. Freed LE, Grande DA, Lingbin Z, Emmanual J, Marquis JC, Langer R. Joint resurfacing using allograft chondrocytes and synthetic biodegradable polymer scaffolds. J Biomed Mater Res 1994;28:891–9.
25. Fuller JA, Ghadially FN. Ultrastructural observations on surgically produced partial-thickness defects in articular cartilage. Clin Orthop 1972;86:193–205.
26. Gill T. The treatment of articular cartilage defects using microfracture and debridement. Am J Knee Surg 2000;13:33–40.
27. Gill T, Macgillivray J. The technique of microfracture for the treatment of articular cartilage defects in the knee. Operat Tech Orthop 2001;2:105–7.
28. Grande DA, Breitbart AS, Mason J, Paulino C, Laser J, Schwartz RE. Cartilage tissue engineering: current limitations and solutions. Clin Orthop 1999;367:176–85.
29. Grande DA, Pitman MI, Peterson L, Menche D, Klein M. The repair of experimentally produced defects in rabbit articular cartilage by autologous chondrocyte transplantation. J Orthop Res 1989;7:208–18.
30. Hangody L, Kish G, Karpati Z, Udvarhelyi I, Szigeti I, Bely M. Mosaicplasty for the treatment of articular cartilage defects: application in clinical practice. Orthopedics 1998;21:751–6.

31. Homminga GN, Bulstra SK, Bouwmeester PS, van der Linden AJ. Perichondral grafting for cartilage lesions of the knee. J Bone Joint Surg Br 1990:72:1003–7.
32. Horas U, Schnettler R, Pelinkovic D, Herr G, Aigner T. Knorpeltransplantation versus autogene Chondrozytentransplantation. Chirurg 2000;71:1090–7.
33. Hunter W. On the structure and diseases of articulating cartilages. Philos Trans R Soc Lond 1743;42B:514.
34. Itay S, Abramovici A, Nevo Z. Use of cultured embryonal chick epiphyseal chondrocytes as grafts for defects in chick articular cartilage. Clin Orthop 1987;220:284–303.
35. Jackson DW, Lalor PA, Aberman HM, Simon TM. Spontaneous repair of full-thickness defects of articular cartilage in a goat model. J Bone Joint Surg Am 2001,83:53–64.
36. Jackson RW. Arthroscopic treatment of degenerative arthritis. In: McGinty JB eds. Operative arthroscopy. New York: Raven Press, 1991:319–23.
37. Johnson DI. Articular cartilage changes seen with magnetic resonance imaging-detected bone bruises associated with acute anterior cruciate ligament rupture. Am J Sports Med 1998;26:409–14.
38. Kawamura S, Wakitani S, Kimura T, Maeda A, Caplan AI, Shino K, Ochi T. Articular cartilage repair – rabbit experiments with a collagen gel-biomatrix and chondrocytes cultured in it. Acta Orthop Scand 1998;69:56–62.
39. Kim HK, Moran ME, Salter RB. 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 Am 1991;73:1301–15.
40. Lexer E. Substitution of whole or half joints from freshly amputated extremities by free plastic operations. Surg Gynecol Obstet 1908;6:601–9.
41. Magnusson PB. Joint debridement. Surgical treatment of degenerative arthritis. Surg Gynecol Obstet 1941;73:1–9.
42. Mankin HJ. The response of articular cartilage to mechanical injury. J Bone Joint Surg Am 1982;64:460–6.
43. Martin I, Padera RF, Vunjak-Novakovic G, Freed LE. In vitro differentiation of chick embryo bone marrow stromal cells into cartilaginous and bone-like tissues. J Orthop Res 1998;16:181–9.
44. Meenen NM. Indikation zur Arthrodese. Hefte Unfallchirurgie 1996;257:607–15.
45. Meenen NM, Rischke B. Autogene, osteochondrale Transplantation. Operat Orthop Traumatol 2003;15:in press.
46. Meenen NM, Rischke B, Adamietz P, Dauner M, Fink J, Göpfert C, Rueger JM. Knorpeldefektbehandlung. Langenbecks Arch Chir 1998;Suppl II:568–76.
47. Mikos A, Lyman MD, Freed LE, Langer R. Wetting of poly(L-lactic acid) and poly(DL-lactic-co-glycolic acid) foams for tissue culture. Biomaterials 1994;15:55–8.
48. Mink JH Occult cartilage and bone injuries of the knee: detection, classification and assessment with MRI imaging. Radiology 1989;170:823–9.
49. Müller B, Kohn D. Indikation und Durchführung der Knorpel-Knochen-Anbohrung nach Pridie. Orthopäde 1999;28:4–10.
50. Newman AP. Articular cartilage repair. Am J Sports Med 1998;26:309–24.
51. Noyes FR, Bassett RW, Grood ES, Butler DL. Arthroscopy in acute traumatic hemarthrosis of the knee: incidence of anterior cruciate tears and other injuries. J Bone Joint Surg Am 980;62:687–95.
52. O'Driscoll SW, Keeley FW, Salter RB. The chondrogenic potential of free autogenous periosteal grafts for biological resur-facing of major full-thickness defects in joint surfaces under the influence of continuous passive motion. An experimental investigation in the rabbit. J Bone Joint Surg Am 1986;68:1017.
53. O'Driscoll SW, Keeley FW, Salter RB. Durability of regenerated articular cartilage prduced by free autogenous periosteal grafts in major full-thickness defects in joint surface under the influence of continous passive motion. A follow-up report at one year. J Bone Joint Surg Am 1988;70:595.
54. O'Driscoll SW, Recklies AD, Poole AR. Chondrogenesis in periosteal explants. J Bone Joint Surg Am 1994;76:1042–51.
55. Passl R, Plenk H. Über die Einheilung replantierter chondraler Fragmente. Unfallchirurgie 1986;12:194–9.
56. Passl R, Plenk H. Die Fibrinklebung von Knorpelflächen. Beitr Orthop Traumatol 1989;36:503–7.
57. Passl R, Plenk H, Radaszkiewicz T, Sauer G, Holle J, Spängler HP. Zum Problem der reinen, homologen Gelenkknorpeltransplantation. Verh Anat Ges 1976;70:675–8.
58. Peterson L, Brittberg M, Kiviranta I, Akerlund EL, Lindahl A. Autologous chondrocyte transplantation. Biomechanics and long-term durability. Am J Sports Med 2002;30:2–12.
59. Pridie KH. A method of resurfacing osteoarthritic knee joints. J Bone Joint Surg Br 1959;41:618–9.
60. Rand JA, Illstrup DM. Survivorship analysis of total knee arthroplasty. J Bone Joint Surg Am 1991;73:397–409.
61. Reigstad A, Gronmark T. Osteoarthritis of the hip treated by intertrochanteric osteotomy. A long-term follow-up. J Bone Joint Surg Am 1984;66:1–6.
62. Ritsilä, VA, Santavirta S, Alhopura S. Periosteal and perichondral grafting in reconstructive surgery. Clin Orthop 1994;302:259–65.
63. Schachar NS, Novak K, Hurtig M, Muldrew K, McPherson R, Wohl G, Zernicke RF, McGann LE. Transplantation of cryopreserved osteochondral dowel allografts for repair of focal articular defects in an ovine model. J Orthop Res 1999;17:909–19.
64. Schaefer D, Martin I, Shastri P, Padera RF, Langer R, Freed LE, Vunjak-Novakovic G. In vitro generation of osteochondral composites. Biomaterials 2000;21:2599–606.
65. 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;75:532–53.
66. Sittinger M, Bujia J, Minuth WW, Hammer C, Burmester GR. Engineering of cartilage tissue using bioresorbable polymer carriers in perfusion culture. Biomaterials 1994;15:451–6.
67. Sledge SL. Microfracture techniques in the treatment of osteochondral injuries. Clin Sports Med 2001;20:365–77.
68. Spindler KP. Prospective study of osseous, articular, and meniscal lesions in recent anterior cruciate ligament tears by magnetic resonance imaging and arthroscopy. Am J Sports Med 1993;21: 551–7.
69. Steadman JR, Rodkey WG, Rodrigo JJ. Microfracture: surgical technique and rehabilitation to treat chondral defects. Clin Orthop 2001;391:362–9.
70. Steadman JR, Rodkey WG, Singleton SB, Briggs KK. Microfracture technique for full thickness chondral defects: technique and clinical results. Operat Tech Orthop 1997;7:300–7.
71. Stone KR, Walgenbach A. Surgical technique for articular cartilage transplantation to full thickness cartilage defects in the knee joint. In: Fu F, ed. Operative techniques in orthopaedics. Philadelphia: Saunders, 1997:305–11.
72. Tippet JW. Articular cartilage drilling and osteotomy in osteoarthritis of the knee. In: McGinty JBE, ed. Operative arthroscopy. New York: Raven Press, 1991:325–39.
73. Vacanti CA, Kim W, Schloo B, Upton J, Vacanti JP. Joint resurfacing with cartilage grown in situ from cell-polymer structures. Am J Sports Med 1991;22:485–8.
74. Vacanti CA, Paige KT, Kim WS, Sakata J, Upton J, Vacanti JP. Experimental tracheal replacement using tissue-engineered cartilage. J Pediatr Surg 1994;29:201–5.

75. Vellet AD, Marks PH, Fowler PJ, Munro TG. Occult posttraumatic osteochondral lesions of the knee: prevalence, classification, and short-term sequelae evaluated with MR imaging. Radiology 1991;178:271–6.
76. Wagner H. Möglichkeiten und klinische Erfahrungen mit der Knorpeltransplantation. Z Orthop Ihre Grenzgeb 1972;110: 705–8.
77. Wagner H. Die Klinik der Knorpeltransplantation bei Osteochondrosis dissecans. Hefte Unfallheilkd 1976;25:118–25.
78. Wakitani S, Goto T, Pineda SJ, Young RG, Mansour JM, Caplan AI, Goldberg VM. Mesenchymal cell-based repair of large, full-thickness defects of articular cartilage. J Bone Joint Surg Am 1994;76:579–92.
79. Wojtys E, Wilson M, Buckwalter K, Braunstein E, Martel W. Magnetic resonance imaging of knee hyaline cartilage and intraarticular pathology. Am J Sports Med 1987;15:455–63.

Correspondence Address
Norbert M. Meenen, MD
Professor of Surgery
Department of Trauma and Reconstructive Surgery
Hamburg University School of Medicine
Martinistraße 52
20246 Hamburg
Germany
Phone (+49/40) 42803-2450, Fax -4512
e-mail: meenen@uke.uni-hamburg.de