Original Articles

The operative treatment of full thickness cartilage defects in the knee joint with autologous chondrocyte transplantation

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ABSTRACT

Objectives: The high clinical and socio-economical impact of cartilage defects and chondral degeneration is well-known. After trauma or without a known etiology, often young patients suffer from pain and a loss of function leading into a decrease of physical activity and, more severe, into long term disability and unemployment. The clinical use of autologous chondrocyte transplantation was introduced in 1994 reporting the data of a pilot study. The objective of this study is to evaluate the efficacy of this method of surgery.

Methods: Autologous chondrocyte transplantation has been established in our department since 1995 for the treatment of large, full thickness cartilage defects which can be completely covered with hyaline-like cartilage without harming the subchondral bone plate. Our first patients (n=24) all showed Grade IV lesions and an average defect size of 6.27 cm^2. All but 4 of the patients had at least 1 cartilage defect related operation on the knee.

Results: The patients and the clinicians rating indicated an increase of a modified Cincinnati Knee score from 3.6 point pre-operation to 6.9 points after 6 months and 8.1 points at 12 months on a scale from 1 (bad) to 10 (excellent). These results support the data of an international multicenter study with almost 2000 patients. The 5 year results described by the originate authors are good to excellent in 85%-95% with an adverse event rate of 5%.

Conclusion: Autologous chondrocyte transplantation has to be considered a safe and effective method for the treatment of large full thickness cartilage defects. Alternative treatments are symptomatical: drilling, abrasion, lavage, chondroplasty, or osteotomies. The short term results are promising but a lot of patients have to be treated for osteoarthritis as a consequence of failure with total joint arthroplasty. Osteochondral transplantations have the disadvantage of limited harvesting sites and the impairment of the subchondral bone plate.

Keywords: Cartilage defect, autologous chondrocyte transplantation.

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Defects of the joint cartilage are of enormous medical and socio-economic impact. Joint function is majorly impaired due to pain and limitation of motion. This leads to professional and private loss of performance. All synovial joints of the human body can be affected, but knee joints as well as ankle and elbow are in the center of attention. Cartilage defects caused by polyarthritis and related syndromes as well as osteoarthritis are not discussed in this article. The high rate of operations for knee joints or meniscus lesions or both (e.g. Germany 1996, 116,680 plus 100,000 out-patient procedures) reflects the eminent incidence of cartilage defects. Meanwhile, it is widely acknowledged that untreated cartilage defects lead to an early onset of osteoarthritis. It is well known that hyaline cartilage in the joint has only a limited capacity of regeneration.[1] Superficial defects can stay stationary

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over years or get deeper and more extensive due to mechanical and enzymatic irritation. Full thickness defects with a broken subchondral bone plate (SBP) are covered by fibrous cartilage synthesized by in growing fibroblasts.[2] The long-term effects of this kind of repair tissue on the joint cinematics, as well as its mechanical stability, is still controversely discussed. In the last 10 years, modern biochemical and cell biological techniques have opened new horizons for the treatment of cartilage defects. Joint cartilage presents almost always as hyaline cartilage which reaches a thickness of 5 or more millimeters in the knee joint. Its unique and complicated construction enables mechanical load distribution and low friction gliding of the corresponding joint surfaces. The histological picture (Figure 1) shows 4 different layers which divide by composition and organization of the tissue components. In a thin, superficial layer the chondrocytes appear to be lying in high numbers with a limited intercellular space. In the transition zone the chondrocyte population is not as dense with a variable orientation of cells. The radial or deep zone is characterized by a low number of chondrocytes surrounded by large areas of matrix. With a sclerotic zone the cartilage is attached to the SBP. Normal hyaline cartilage contains up to 80% water whereas chondrocytes represent only 1% of the tissue volume. The remaining fractions are composed of macromolecules (proteoglycanes and collagen fibers) with approximately 20-40% volume. Chondrocytes synthesize the matrix of hyaline cartilage. Collagen fibers (Figure 2) represent the largest fraction of the macromolecules (approximately 60% dry weight). Mainly type II Collagen forms the framework of hyaline cartilage whereas collagen type IX, X, XI represent only smaller fractions. Collagen fibers give hyaline cartilage the unique capacity of elastic resilience. Proteoglycanes (Figure 2) are responsible for the balance between water uptake and dehydration of the cartilage.

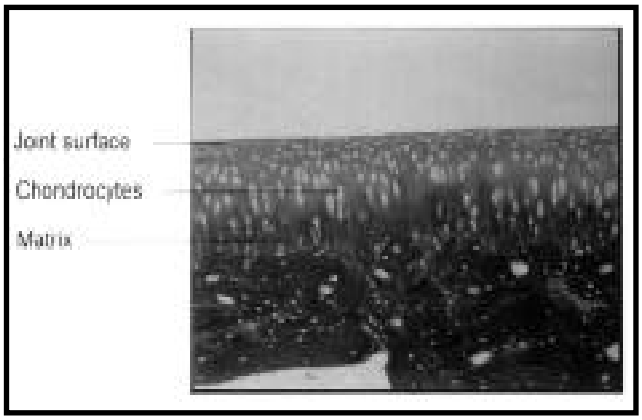

Figure 1 - Histology of hyaline cartilage.

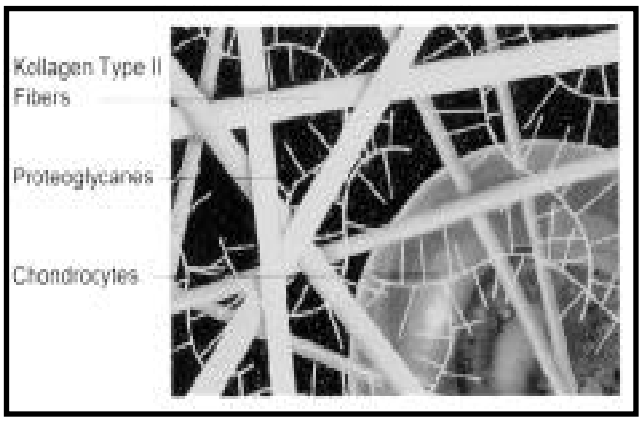

Figure 2 - Construction of hyaline cartilage.

Methods. Between March 1997 and December 1998, 24 patients with full thickness cartilage defects (Figure 3) in the knee were treated with autologous chondrocyte transplantation (ACT). The indication was set up based on clinical symptoms and examination as well as magnetic resonance imaging (MRI) results. Adapted from the recommended technique of Brittberg[3] a cartilage biopsy was taken during an arthroscopy from a less weight bearing area, usually the medial or lateral rim of the trochlea. The chondrocytes were isolated and cultivated under GMP (good manufacturing practice) environment to increase the number of cells by the factor 10 to 15. At the implantation procedure the knee is opened by a standard parapatellar incision and, if necessary a lateral luxation of the patella. The defect is then debrided down to the SBP without damaging it

Figure 3 - Arthroscopic view of a large grade IV cartilate defect on the femoral condyle.

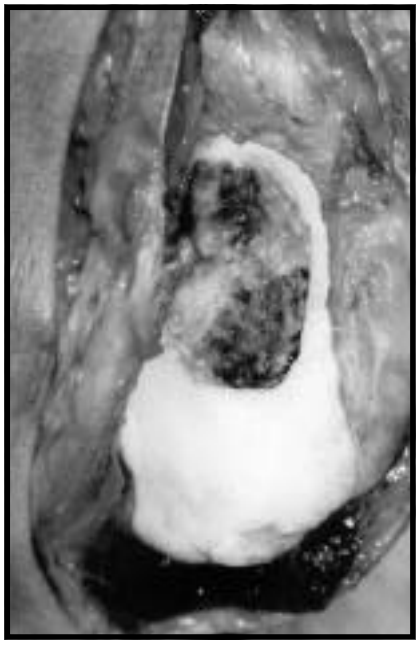

Figure 4 - Well debrided cartilage defect with sharp edges prepared for autologous chondrocyte transplantation.

Figure 5 - The periostal flap sutured onto the defect.

Figure 6 - Injection of the chondrocyte suspension under a periostal flap for the treatment of full thickness cartilage defects with autologous chondrocyte transplantation.

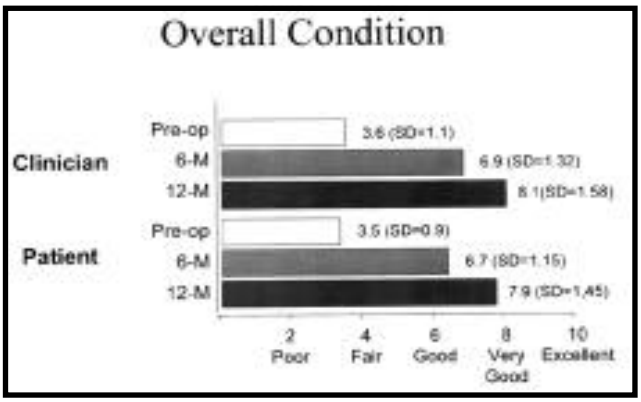

Figure 7 - Mean rating based on a modified Cincinnati Knee scale.

Table 1 - Modified Cincinnati rating scale for overall condition.

Grade		Description
Poor	2	Significant limitations affect activites of daily living.
Fair	4	Moderate limitations affect activities of daily living, no sports.
Good	6	Some limitations with sports but participate; I compensate
Very good	8	Only a few limitations with sports
Excellent	10	Able to do whatever I wish (any sport) with no problems

(Figure 4). If bleeding occurs it has to be stopped e.g. with epinephrine. Using a template, a defect-sized periosteal flap is harvested at the ventral aspect of the tibia or the distal femur. This flap is then sutured on the defect with the cambium layer facing the bone and then sealed with fibrin glue creating a 'bioactive chamber' (Figure 5) in which the suspension with the chondrocytes is injected (Figure 6). After drainage of the lateral compartment the wound is closed. The rehabilitation program starts immediately after the operation with CPM. Range of movement (ROM) is unlimited unless the patello-femoral joint is affected. In this case flexion is limited to 60° for 2 weeks to reduce the initial retropatellar pressure. Full weight bearing is allowed after 6 weeks. Swimming and cycling is encouraged after 2-3 months post-op and running not before the 6th post-op month. We recommend to refrain from contact sports for one year but sometimes there is a conflict with professional interests. For the follow up, the patients were assessed pre-op, at 6 and 12 months and yearly thereafter. For the clinical evaluation a modified Cincinnati knee score was used with a scale from 0 (very bad) - 10 (excellent) (Table 1). Parallel to the clinical examinations MRI was performed. Statistical analysis was carried out by descriptive measure and the SAS (Statistical Analysis System) software package.

Results. Twenty four patients (16 men and 8 women) aged 17 to 48 years (mean = 33.7) with an average weight and height of 71kg and 176 cm were operated 9 times on the left and 15 times on the right knee. A total of 29 defects were treated with a double location in 5 cases. Mostly the medial femoral condyle was affected; n=18 vs n=4 on the lateral femoral condyle. In almost all cases defects of the trochlea (n=4) and the patella (n=3) were combined with lesions on the condyles. The average size of the defect was calculated at 6.27 cm^1. Only Grade IV defects according to the Outerbridge classification were found. All but 4 of the patients had at least 1 cartilage defect related operation on the knee (1-5 operations). The mean time between onset of symptoms, (6 patients acute and 18 patients gradual), and biopsy harvesting was 40 months (3-83). Concurrent operation was performed 6 times: ACL-reconstruction (n=1), osteochondral transplantation (n=2) and high tibial osteotomy (n=3). Preoperatively the clinical score averaged 3.6 (2-6) assessed by the clinician and 3.5 defined by the patient. At 6 months post-op the score increased to 6.9 (3-8) and 6.7 (n=13). Twelve months after the operation the score values were measured with 8.1 (5-10) and 7.9 (n=8) (Figure 7). The 2 patients at 24 months after implantation are doing excellently (9.5 and 9). Range of motion was limited more than 10° preoperatively in 7/24 knees (flexion x 5, extension x 1, extension and flexion x 1) and postoperatively in 7/13 knees after 6 months and 1/8 knees after 12 months. Persistent effusion of the knee was eminent in 4 knees at 6 months but was gone at 12 months. However, prolonged swelling of the knee for 3-4 months post-op was prominent in more than 50% of the patients. Standard MRI indicated in all cases, and at all times, an increasing restoration of the subchondral bone but an inconsistent structure of the regenerated cartilage (Figure 8a and 8b). Exact data is part of a separate prospective study and subject to later publication. Four out of 24 patients underwent a

Figure 8 - (a) Magnetic resonance imaging showing a focal cartilage defect on the lateral femoral condyle. (b) Magnetic resonance imaging of the knee joint 12 months after autologous chondrocyte transplantation of a full thickness cartilage defect.

Table 2 - Overall condition of femoral condyles at 24 and 36 months post-operation.

Patient condition	24 months post op		36 months post op	
	Clinician Evaluation	Patient Evaluation	Clinician Evaluation	Patient Evaluation
Improve	79%	74%	85%	85%
Same	13%	16%	8%	7%
Worsen	8%	10%	8%	7%

reoperation: 2 as a diagnostic second look arthroscopy and 1 for a partial resection of the periosteal flap. On an additional patient, an open synovectomy had to be performed due to persistent synovitis. There was no treatment failure.

Discussion. The treatment of cartilage defects has always been a high-priority subject for orthopedic surgeons although the long-term outcome of various treatment methods was as inconsistent as the permanent promise of success was consistent. Autologous chondrocyte transplantation represents the first clinical application of a new generation of regenerative treatment options in orthopedic surgery. Hyaline cartilage can be created to resurface chondral lesions e.g. on femoral condyles. Our results show a significant ($p<0.001$) increase of the Cincinnati knee score at 6, 12 and 24 months, this means, that the average patient improves from 3.6 ('Severe' to moderate limitations affecting activities of daily living, no sports') to 8.1 ('Only a few limitations with sports') within 12 months. The range of motion was still impaired after 6 months in 7 knees, probably due to ongoing rehabilitation. Reoperation was necessary in only 2 cases.

In support of our very promising preliminary data, the originating authors were able to present a follow-up of 2-10 years. A cohort of 213 patients experienced a significant increase in various scores. Nineteen independently evaluated histologies from femoral condyles presented hyaline cartilage in 14 cases and a composite hyaline/fibrous tissue in 5 cases. There was a strong correlation between repair tissue that stained positive for the characteristics of hyaline cartilage and a positive clinical outcome for the patient. Electromechanic indentation testing in 46 second-look arthroscopies demonstrated a stiffness equivalent to 2.7 N (newton) compared to 3.1 N for hyaline control and 1.2 N for fibrous cartilage. In a prospective international multicenter study the demographic and outcome data of 1051 cases of ACT is collected and evaluated under the supervision of a medical advisory board.[4] Five hundred and eighty three surgeons from the US and from Europe reported on 2876 patients with indication for ACT and performed the cartilage harvesting procedure for mostly grade IV defects (76%) with an average size of 4.6 cm^1. About 80% of the patients improved after the procedure (Table 2). Adverse events possibly related to ACT (4.8%) mostly adhesions, hypertrophic changes and detachment/delamination of the graft were described. The method requires a high degree of surgical skill, two operations and additional logistic and financial efforts for the culturing of the chondrocytes, but it offers durable chances for severe cases especially in young patients. Long-term data is necessary to define the value of regeneration vs. reparation of joint cartilage.

What are the alternative options? Mobile flakes after fresh osteochondral fractures should be anatomically refixated. Arthroscopic techniques with resorbable screws or pins are available. In the case of a purely chondral delamination the chances of a positive outcome are inferior but sometimes, especially in young patients, it is worth a try, otherwise the fragment has to be removed. Various authors describe a dramatic decrease of symptoms after arthroscopic lavage even in cases with severe cartilage defects. This can be explained by the fact that mobilized cartilage molecules such as collagen fibres and proteoglycanes act as inflammatory mediators to the synovial tissue of the joint. The same mechanism applies to cartilage debridement (shaving, trimming etc.) where the superficial, fibrillated layers of the cartilage are carefully resected with a motorized shaver system. The SBP should not be violated by this procedure. Hubbard concluded in 1996[5] that the long-term results of a debridement are better than those after isolated lavage. In a prospective study with a mean follow-up of 4.5 years 19 of 32 patients were pain free after 5 years post debridement and only 3 out of 26 after lavage. Other authors judge the long-term outcome of those only symptomatic methods less optimistically.[6,7] The deleterious effect of unphysiological load distribution in cases of e.g. varus/valgus deformity is unquestioned for the prognosis of cartilage defects. Factors for a poor outcome after osteotomies are overweight, over or under correction, instability and postoperative limitation of motion.[8]

The term 'bone stimulating techniques' summarizes techniques which reflect the idea of activating intrinsic repair mechanisms by perforating the SBP. As a result, the medullary bleeding carries proteins and stem cells into the defect, starting a cascade of physiological cell differentiation. In many cases, with the predominant existence of fibroblasts in those conglomerates the development of fibrous cartilage is described.[9] Other studies did not support this theory.[5,10] Various techniques are reported pioneered by the simple perforation of the SBP with

a drill or a k-wire in 1959 by Pridie.[11,12] Motorized shaver systems enable the resection of the superficial sclerosized layer of the SBP to expose the healthy spongious tissue (abrasion chondroplasty).[13] The popular microfracture technique is authored by Steadman using a specially designed pick to perforate the subchondral bone without substantial bone loss. Following multiple clinical trials the results are promising, others are questionable.[14,15] For none of the described techniques a reproductable quality of repair tissue is proven but a wide variety of clinical outcome is noticed. Even a placebo-effect should not be underestimated.[16] A fairly new technique is described by Stone who harvests osteochondral bone plugs with healthy hyaline cartilage and impacts a pluripotent paste into the defect after morselisation of the plugs. This method combines transplantation and microfracturing. Long-term results are still pending.

The transplantation of cartilage tissue as part of an osteochondral unit is experimentally and clinically widely acknowledged, especially in a post-traumatic situation. It has to be differentiated between autologous and allogenic transplants. Especially in the anglo-american countries, where allografts are much easier to obtain, this technique is backed up with solid data.[17] The use of fresh autologous transplants for the treatment of circumscribed cartilage defects was first described in the 50s and 60s. The results were variable.[18] Today modern and newly designed instruments with very thin and short cutting edges replace the traumatizing drill bits and enable the gentle harvesting of osteochondral plugs. With arthroscopic instruments this technique is widely spread. Bobic[19] and Hangody[15] were able to prove both clinical and histological results of the so-called mosaic plasty. The defect size accessible by osteochondral transplantation is probably limited by the circumscribed donor site for the transplants. Another factor deserving future research is the only subtotal filling of the defect with hyaline cartilage and the ingrowth of fibrous tissue between the plugs. The long-term influence on the joint cinematics due to the damaged SBP is still unknown.

The large amount of various therapeutical methods for the treatment of cartilage defects as a single entity emphasizes the fact that most of the surgeons are rather insecure in their decisions for a specific treatment. A golden standard does not exist, and a therapy is oriented following the empiric experiences of the doctor. Superficial lacerations of the joint cartilage do not have a tendency towards self healing but seem to stay stationary in many cases. Full thickness cartilage defects down to the SBP or beyond have a proven tendency toward progression and therefore require a specific treatment. Post-traumatic flake fractures should be reattached. If this is not feasible the mobile fragment has to be removed, followed by a subtotal debridement of the defect. Prior to any resurfacing measure the complete restitution of the subchondral bone has to be awaited. The same applies for defects deeper than 0.8 - 1 cm post-traumatic or after refixation with pins or screws when chondroplasty is indicated. Then a restitution time of a minimum of 6 months has to be planned. Fairly good joint function and mobility frequently masks a serious cartilage defect if a perifocal solid cartilage shoulder protects the lesion itself. Mechanical ulcerations of the corresponding joint surface and enzymatic reactions induce a progredient degeneration of the surrounding intact cartilage. Since joint instability and unphysiological joint axes have been proven to be co-factors for cartilage lesions, deformities have to be corrected prior to a cartilage-specific treatment, which means that it might be necessary to combine an osteochondral transplantation by mosaic plasty with a high tibial osteotomy or ACL reconstruction or both. Since lavage, debridement and shaving represent only a symptomatic approach of cartilage treatment, they should be reserved for those patients who are not accessible for other therapies due to age or medical problems. The various techniques which promise a defect repair are described in the literature with “70-80%” studies which means that in 70-80% of the cases good or excellent results are found. Design, follow-up, population and defect localization and size, are all factors which prohibit a comparison of those studies. Nevertheless, it is a proven fact that Pridie-drilling, abrasion chondroplasty, and microfracture induce a defect repair with fibrous tissue. The inferiority regarding long-term stability and resilience of fibrous tissue in comparison to hyaline cartilage is well-accepted. Whether this repair tissue is sufficient for the resaturation of impaired joint function is an intensely debated question. Additionally, it should be mentioned that bone stimulating techniques create an osteochondral defect out of a purely chondral lesion. The elasticity of the SBP is unquestioned and protects the onlying cartilage from hyperpressive damage. Even with a meticulous operation technique and a skilled surgeon, treatment failures do happen and do matter. Therefore, they should be incorporated into the therapeutic planning: After a failed cell or soft tissue transplantation with an intact SBP a mosaic plasty is still possible and can be performed with good success. The induction of fibrous tissue is still possible as a third-step procedure. Today, defects due to advanced stages of osteoarthritis cannot be addressed yet with regenerative techniques but it is possible to culture chondrocytes from arthritic cartilage.[20]

In conclusion, the treatment of full thickness cartilage defects still requires very differentiated therapeutical planning[21] which should include autologous chondrocyte transplantation as indicated by our data. It should be the goal of every cartilage surgeon to select the right procedure for the right defect since cartilage does not forgive wrong treatment.

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