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CURRENT CONCEPTS REVIEW

Repair of symptomatic cartilage lesions of the knee
The place of autologous chondrocyte implantation

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An increasing number of patients with cartilage defects of the knee are being treated with autologous chondrocyte implantation (ACI). To date, no clear guidelines exist for the use and indications of this technique. The BVOT and SOBCOT have established a working group to review the clinical results and the cost-effectiveness of the various treatment modalities and particularly of ACI. This group has formulated recommendations and presents a treatment algorithm based on an in-depth review of recent European and American literature, on peer-reviewed opinions of leading investigators in the field and on a comparative analysis of the clinical results and health-economic aspects of current cartilage repair techniques.

Keywords : knee ; cartilage defects ; autologous cartilage implantation.

Cartilage defects and their implications

A large number of patients consult an orthopaedic surgeon because of a joint problem related to damage to the articular cartilage. A chondral lesion was found in 63% of 31,516 arthroscopies retrospectively analysed by Curl *et al* (*29*) in 1997 ; almost 20% of the lesions were Grade 4 (Outerbridge Scale) and were mainly located on the medial femoral condyle. Four percent were single lesions in patients under 40 years of age (*29*). Similar data were reported in two more recent publications by Hjelle *et al* (*52*) and Aroen *et al* (*3*). The real prevalence or incidence of cartilage lesions is not known. There is a variety of underlying causes, and the time to onset of clinical symptoms markedly varies. Unrecognised or untreated cartilage defects in younger age as a result of sports injury or other physical activity may lead to an increased risk of developing osteoarthritis later in life (*60*). A Johns Hopkins prospective cohort study of 1321 former medical students who were followed for a

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median of 36 years, concluded that young adults with knee injuries run a considerable risk to develop osteoarthritis (OA), 10 years earlier on average than the group without cartilage defects in young age (*41*). OA is one of the most common disabling disorders, affecting more than 10% of of the Western population. In the USA, the "Arthritis Foundation" (www.arthritis.org, March 2005) estimated the cost to the US economy at nearly $86.2 billion per year in terms of direct expenses, lost wages and production.

Cartilage defects need to be treated early

Since Hunter (1743), we know that cartilage has a limited capacity for repair. This originates in its specific structure and anatomy, and is clearly linked to age (*22*). Healthy adult articular cartilage is a unique tissue in the human body, providing joints with almost frictionless continuous gliding motion. It can resist loading forces that are a multitude of the individual's body weight. It absorbs mechanical shock and spreads the load over the underlying subchondral bone plate to reduce extreme loading conditions. Under normal physiological conditions, articular cartilage continues for a lifetime to exert these essential biomechanical functions. Chondrocytes are responsible for synthesis and maintenance of the cartilage extracellular matrix (ECM). These metabolically active cells respond to various environmental stimuli including soluble mediators, matrix composition, mechanical load and hydrostatic pressure. Cartilage basically consists of a high amount of water bound within a fine mesh of collagen fibers and proteoglycans (aggrecans). This highly specialised architecture provides the tissue with resilience, biomechanical resistance and tensile strength, to withstand the forces in the joint, and to reduce the thickness variations under load to a remarkable extent. A minor breach within this proteoglycan architecture causes a substantial decrease in the mechanical properties of cartilage (*17*). Because of a lack of inflammatory response, a cartilage lesion without damage to the subchondral plate usually does not heal. When the subchondral plate has been penetrated, repair tissue can form but it mainly consists of collagen type I as in mature scar tissue and will deteriorate over time. Chondrocyte cell death (apoptosis), insufficient synthesis of new macromolecules and the release of inflammatory mediators and catabolic enzymes characterise the course of cartilage degeneration. This may eventually lead to destructive osteoarthritis (*22*). Restoration of the normal homeostasis in the joint must be the main purpose for reconstructive biological procedures. Existing axial malalignments, damage to menisci or ligaments and synovitis should also be addressed. The importance of early biological reconstruction of symptomatic lesions was highlighted by Mithoefer *et al* (*76*). They found that return to pre-injury sporting level correlated with a shorter duration of preoperative symptoms and a lower number of prior operations. All adolescents with preoperative symptoms of 12 months duration or less returned to pre-injury level athletics, compared with 33% of those with time intervals longer than 12 months (*79*).

Treatment options for cartilage lesions

Several surgical biological reconstruction options exist for the treatment of ICRS (International Cartilage Repair Society) grade 3 and 4 cartilage lesions in the knee. Arthroscopic lavage and debridement is meant to clean out debris and potentially harmful catabolic substances that cause deterioration of the cartilage matrix and inflammation of the joint (*8, 12, 42, 58, 59*). Marrow stimulation recruits bone marrow stem cells from the underlying bone marrow through abrasion of the subchondral plate, drilling or microfracturing (*12, 58, 82, 89, 94*). These cells within their blood clot will reorganise into a repair tissue covering the original cartilage defect that was debrided back to stable borders. These techniques lead to the development of predominantly fibrous scar tissue (*56*) that does not show the biomechanical load bearing capacity of healthy articular cartilage (*21, 23*). Different variations of osteochondral grafting techniques exist to fill cartilage defects in a joint. Hangody *et al* (*45, 47, 48*) developed mosaicplasty using small autologous osteochondral plugs, Bobic *et al* (*15, 16*) developed the OATS system (osteochondral autograft transplant system) which uses

larger plugs. Osteochondral allografts can be used in salvage operations (*42*). Owing to the risk of disease transmission and infection, allograft cartilage/bone transplantation should be restricted to cases where size or depth of a defect make alternative procedures impossible (*24, 25, 42*).

Simple transplantation of periosteum or perichondrium cannot be recommended anymore, because of its predominantly poor short and mid-term clinical outcome (*2, 67*).

Autologous Chondrocyte Implantation (ACI) is another established and promising technique for the repair of cartilage lesions in the knee.

Clinical results of the current treatment options

The early optimistic results of lavage and lavage combined with debridement (*32, 36, 55*) are the subject of much controversy, especially since a recently published prospective randomised and placebo controlled trial by Moseley *et al* (*78*). Hubbard (*55*) reported an 80% success rate with debridement after one year, decreasing to 59% at 5 years, in a randomised controlled trial comparing debridement and lavage alone, in patients who had not undergone previous operations. Ogilvie-Harris and Fitsialos (*80*) reported similar results.

Bert reported that the fibrocartilage repair tissue resulting from arthroscopic abrasion arthroplasty for cartilage lesions in otherwise healthy joints lasted only up to 4 years (*12, 13*). Nehrer *et al* (*79*) examined failed abrasion treatment and reported a mean time to failure of 21 months. Examination of the failed repair revealed soft, fibrillated tissue, frequently with central degeneration. The short term clinical results with microfracture are mostly good (*61, 82*). Steadman *et al* (*93*) published good long term (7 to 17 years, mean 11.3 years) retrospective results in a selected patient population with small to medium sized defects (2.77 cm^2). Concomitant pathology was not described and the publication did not include large and deep osteochondral defects (*93*). Marrow stimulation techniques have much less favourable results once the fourth decade has passed (*49, 93*). A study by Mithoefer *et al* (*77*) showed that microfracture can result in significant functional improvement at a minimum follow-up of two years. The best short-term results are observed with good fill grade, low body-mass index, and a short duration of preoperative symptoms. The worst results were seen in patients with a body-mass index of > 30 kg/m^2 ($p < 0.05$). On magnetic resonance imaging, the fill grade correlated with the knee function scores (*77*). A longer follow-up of the patients showed a weaning effect of the repair tissue and similar findings were reported by Kreuz *et al* who found a gradual degradation of the ICRS scores after 18 months (*62*). Brown looked at the repair cartilage overlying the microfracture which generally was depressed with respect to native cartilage. There was a marked propensity for bony overgrowth with loss of adjacent cartilage evident with progressive follow-up (*21*).

The results of mosaicplasty are generally good in small and medium size defects (*46, 48, 57*). The applicability of this method remains limited due to the restricted donor surface area, donor site morbidity and problems in achieving satisfactory surface congruence, thickness and filling. Hangody *et al* advise to restrict indications to defects 4 cm^2 or less, based on their results in a large group of patients with a follow-up up to 10 years (*46*).

The role of allograft tissue transplantation for post-traumatic defects has been reduced to defects larger than 3 cm in diameter and 1 cm in depth owing to recent advances in other techniques for cartilage repair and resurfacing (*4, 6*).

ACI has now been used worldwide in approximately 15000 cases. In a clinical evaluation of 244 patients followed for two to ten years, subjective and objective improvement was seen in a large number of patients with an ICRS grade 3 or 4 femoral condylar lesion or osteochondritis dissecans (*20*). The percentage of good to excellent results was high (84% to 90%) for patients with different types of single femoral condylar lesions, whereas it was lower (mean : 74%) for those with other types of lesions (*84, 85*). In order to study the long-term durability of autologous chondrocyte transplantation, 61 patients were followed for 5 to 11 years (mean : 7.4 years) after the surgery. At 2 years, 50 of the 61 patients had a good or excellent result. This increased to 51 of the 61 patients at

the 5 to 11-year evaluation. The total failure rate was 16% (10 of 61) at a mean of 7.4 years. All failures of ACI occurred in the first 2 years, so a high percentage of the patients who had a good to excellent result at 2 years retained this result at the time of long-term follow-up. Knutsen *et al* (*61*) studied 80 patients who had symptomatic focal cartilage lesions of the femoral condyles measuring 2 to 10 cm^2. The patients were treated at four hospitals and were randomised into two groups : those treated with autologous chondrocyte implantation and those treated with microfracture. At 2 years, the outcomes were slightly but not significantly better in the patients treated with microfracture than with ACI, but both groups had acceptable short-term clinical results (*61*). ACI and mosaicplasty are both claimed to be successful for the repair of articular cartilage defects in the knee but there have been only two comparative studies showing conflicting results. Bentley *et al* (*10*) published a randomised controlled trial comparing mosaicplasty with ACI in 100 patients with a mean age of 31.3 years (range : 16 to 49) and with a symptomatic lesion of the articular cartilage in the knee which was suitable for cartilage repair. Most lesions were post-traumatic with a mean defect size of 4.66 cm^2. The mean duration of symptoms was 7.2 years. The mean follow-up was 19 months (range : 12 to 26). Functional assessment using the modified Cincinatti and Stanmore scores and objective clinical assessment showed that 88% had excellent or good results after ACI compared with 69% after mosaicplasty. Arthroscopy at one year demonstrated excellent or good macroscopic repair in 82% after ACI and in 34% after mosaicplasty. In this prospective randomised clinical trial, ACI has shown superiority over mosaicplasty for the repair of articular defects in the knee. The results for ACI are comparable with those in other studies, but those for mosaicplasty are less favourable in larger lesions (*10*). Horas *et al* (*54*) performed a prospective clinical study to investigate the two-year outcome in forty patients with an articular cartilage lesion of the femoral condyle who had been randomly treated with either transplantation of an autologous osteochondral cylinder or implantation of autologous chondrocytes. Both treatments resulted in a decrease in symptoms. However, the improvement obtained with ACI lagged behind the improvement achieved by osteochondral cylinder transplantation. Histologically, the defects treated with ACI were primarily filled with fibrocartilage, whereas the osteochondral cylinder transplants retained their hyaline character, although there was a persistent interface between the transplant and the surrounding original cartilage. Limitations of this study included the small number of patients, the relatively short (two-year) follow-up, and the absence of a control group (*54*). Krishnan *et al* (*63*) identified a number of favourable factors for ACI with a collagen membrane (ACI-C) : younger patients with higher pre-operative modified Cincinnati scores, a less than two-year history of symptoms, a single defect, a defect on the trochlea or lateral femoral condyle and patients with fewer than two previous procedures on the index knee. Revision ACI-C in patients with previous failed ACI and mosaicplasty produced significantly inferior clinical results. Gender ($p = 0.20$) and size of the defect ($p = 0.97$) did not significantly influence the outcome (*63*).

Autologous chondrocyte implantation

ACI consists of a two- step procedure. In the first step, which is arthroscopic, a small cartilage biopsy is taken from a lesser weight bearing area of the affected joint. About 200-300 milligram of cartilage is harvested from the joint and sent to a dedicated laboratory where the cells are enzymatically released from the cartilage tissue and brought in monolayer culture to expand the number of cells under cGMP (current Good Medical Practice) conditions. After approximately four to five weeks of cell culture, cells have multiplied sufficiently to be collected. The second step of the procedure requires an arthrotomy to inject a suspension of articular chondrocytes (approximately 1×10^6 cells per cm^2 defect surface), without carrier material, underneath a periosteal flap or collagen membrane.

The second step is followed by a patient tailored rehabilitation program.

To consistently obtain expanded chondrocytes, able to produce a stable cartilage *in vivo*, cultures

have to meet the highest standards of quality, safety and efficacy (*11, 31, 38, 102*). The purity of each delivered cell product, including the number of viable cells, the identity of the cells (i.e. chondrocytes) and the absence of contaminants have to be guaranteed.

In vitro expansion of articular chondrocytes normally results in dedifferentiation and loss of *in vivo* cartilage formation. A newly developed "potency assay" using molecular markers monitors the capacity of expanded articular chondrocytes to form stable cartilage *in vivo* and their ability to withstand mineralisation, vascular invasion and replacement by bone. The evaluation of the cartilage-forming ability *in vivo* may be informative for successful cell-based joint surface defect repair protocols (*31*).

Criteria for ACI

At this moment ACI is indicated for biological reconstruction of post-traumatic ICRS grade 3 and 4 cartilage defects in the knee (table I). Before ACI is applied for the treatment of degenerative/early focal osteoarthritic cartilage lesions, the results of ongoing clinical trials have to be awaited.

The current general principles for ACI are :

1. Children have high intrinsic regenerative capacities and ACI should not be applied as a first line treatment, before radiological closure of the epiphysis (*39*). The upper age limit is approximately 50 years. There is no absolute upper age limit, because calendar age does not always reflect the biological age or the condition of the afflicted joint. Thus in patients over 50, cartilage cells can be expanded and implanted (*5, 31, 50, 85*).
2. A total defect size of 2 cm^2 up to 12 cm^2 is a good indication for ACI. Clinical results in the treatment of joints other than the knee are promising, but no recommendations can be given yet for the application of ACI. The optimal indication is a full thickness defect with an intact subchondral plate. For deeper osteochondral defects and adult osteochondritis dissecans, exceeding a depth of more then 6 to 8 mm, a bony reconstruction is needed (*84*).
3. Before ACI is scheduled, the internal structures of the knee are best visualised with MRI. Cartilage specific sequences are essential in the evaluation of the joint surface. Arthroscopic inspection remains the gold standard to evaluate the lesion and confirm the need for ACI or an alternative resurfacing methods.
4. Results of previous surgery on the cartilage should be awaited first. There should be a period of at least 6 months between a failed marrow stimulation technique and any new surgery to allow initial healing of the subchondral plate.

Chondrocyte implantation technique

Surgical technique for defect preparation

In most cases, an arthrotomy of the knee is necessary to reach the defect. In some instances a mini-arthrotomy or arthroscopy can be used. Defect preparation itself must be very thorough. The defect has to be brought back to stable hyaline cartilage borders, perpendicular to the surface. The defect bed can be debrided back to the subchondral bone, ideally keeping the calcified layer intact. A breach in (or damage to) the subchondral plate must be avoided as much as possible. Bleeding can

Table I. — Intra-articular status as criteria for ACI

1.	Intact corresponding joint surface (maximal ICRS grade 2 damage : see website. International Cartilage Repair Society www.cartilage.org).
2.	Intact load bearing capacity of the surrounding cartilage.
3.	Functional meniscus (partial resection to maximum 50% of the total volume is allowed).
4.	Maximally two separate defects.
5.	Full range of motion.
6.	Intact (repaired) ligaments, physiologically correct(ed) lower limb axis.

be stopped using adrenaline soaked sponges, fibrin glue or gentle impaction of the bone. All fibrocartilage present in the bottom of the defect has to be cleaned out (*75*).

Defect coverage

Currently two methods to cover the defect are used in Europe (*7, 43*) : 1) A periosteal flap procured from the ipsilateral proximal tibia ; 2) A tested and approved collagen membrane with CE-mark (Chondro-Gide®, Geistlich AG, Switzerland).

Periosteal flap

Normally this flap is taken from the proximal tibia below the pes anserinus. Because of shrinkage it must be larger than the size of the defect (2 mm in all directions). This flap is sutured into the defect using atraumatic and resorbable suture material. With precise size match and adequate technique a watertight closure of the defect is achieved using separate stitches or a running suture. The suture knots have to rest on the periosteal flap. At the proximal pole of the defect a small opening is left to host a venous catheter of usually 14 Gauge. Water tightness is tested first with saline. If there is still leakage of fluid, additional suture points can be added. Ideally only after water tightness is attained, fibrin glue is applied and the joint is taken through a range of motion to check stability of the construct. After re-aspiration of the saline, the cell suspension is injected beneath the flap. First the cell suspension is reconstituted by gently shaking and rolling the vial in both hands. Then the cells are aspirated from the vial using a tuberculin syringe with a 14 Gauge catheter. Repeated aspiration and re-injection in the vial has to be avoided to prevent shear forces and rupture of the cell membranes. After injection a last suture point is placed at the injection site and the wound is closed in layers without suction drainage (*19, 97*).

The most frequently reported complication in ACI as applied so far is implant hypertrophy. According to current insights this is coming from the periosteal flap and leads to additional surgery in 10 to 25% of cases (*43, 51, 101*). The extra skin incision for prelevation of the periosteal flap causes extra morbidity for the patient. Early loosening of the periosteal flap can lead to failure of the implant (*79*).

Recent developments

Through the development of appropriate biomaterials for implant coverage, the reported problems with traditional ACI can hopefully be solved and the indications can be broadened (*34, 96-98*). Several biomaterials of natural or synthetic origin are under clinical evaluation at his time and the first encouraging results have been reported (*34, 43, 70, 83, 90*). Steinwachs *et al* and Bentley *et al* (*7, 95*) both have published encouraging results of ACI using a collagen type 1/type 3 membrane.

Matrix coupled ACI

Implantation of isolated chondrocytes encapsulated in different artificial scaffolds such as synthetic polymers [carbon fiber (*18*), polylactic acid and polyglycolic acid (*37*) or biological matrices [demineralised bone matrix (*14*), collagen (*26, 91, 98, 99*), hyaluronan (*70, 83, 92*), fibrin (*53, 97*), alginate (*1, 28, 30, 33, 64, 71, 98*) for chondral and osteochondral lesions has been reported. Examples are MACI (Matrix associated ACI) and Hyalograft C (FAB, Bologna, Italy) both are under investigation (*6, 70*), but prospective randomised trials are needed before advocating a broader use.

The artificial matrices should be biodegradable at the appropriate rate and biocompatible to allow the cells to colonise the scaffolds. The chondrocytes must be capable of multiplying and maintaining their original phenotype with the production of cartilage-specific matrix components such as aggrecan and type II collagen. The artificial matrices offer the advantage of an initial support to the chondrocytes, making the implant in theory initially biomechanically superior to the original technique of injecting the cells as a suspension under a periosteal flap.

Allogeneic chondrocyte implantation

When allogeneic chondrocytes are used, the surgical procedure can be performed in one step, but

Table II. — Exclusion Criteria

Local	Systemic
Osteoarthritis (ACR criteria) Joint stiffness Arthrofibrosis Malalignment if not corrected Resection of meniscus more than 50% Ligamentous lesions Patello-femoral malalignment if not corrected Implanted carbon rods Inflammatory joint diseases	Chronic infectious diseases Tumors Metabolic arthropathy Auto-immune disease Borreliosis Severe neurological disease Obesity Alcohol or Drug Addiction Psychiatric conditions with reduced complicance Pregnancy

the long term safety of the use of allogeneic cells is not known, and therefore their use needs to be restricted to experimental treatments in well-defined patient populations and using patient consent forms.

Follow-up and rehabilitation

In the early phase the graft needs protection. Training principles and guidelines specific for cartilage repair need to be identified more closely in the future (*44*). The primary goals of rehabilitation are stimulating local adaptation/remodelling of the repair and return to previous function. Within the wide array of rehabilitation schedules in the literature, there is an overall agreement that controlled weight bearing for graft protection is a necessity. The way this is achieved though, varies substantially.

There is no standard rehabilitation schedule for mobilisation and functional strength training, in other words, rehabilitation must be tailored to the individual patient.

Most important is the localisation of the repair site and its size. For a defect in the tibiofemoral joint immediate full range of movement (FROM) is allowed with very gentle build up. Weight bearing is allowed two weeks after implantation with 10 kg weekly increments, to reach full weight bearing at 8 to 10 weeks. Additional physiotherapy measures are useful (e.g. closed kinetic chain exercises). Sports activities that do not cause overload of the knee are allowed after three months, e.g. swimming and stationary bicycle. Circulation exercises for the knee are crucial for nutrition of the newly forming tissue (*44, 95*).

In patellofemoral defects immediate weight bearing is allowed as tolerated. Range of motion is restricted in the first six weeks and only then is FROM allowed.

Other factors are age, previous activity level, concomitant surgical procedures and patient compliance. Continued patient motivation over a longer time is crucial, due to the extent of the rehabilitation over time.

Evaluation of results after ACI

It is important for the evaluation of ACI to capture and report adverse events, peri-operative complications and failures in combination with their probable cause (e.g. cell quality, indication, clinical outcome, etc). This guarantees good clinical outcome and in the end the quality assurance of this method (*9, 101*). At this moment we advise a prospective follow-up of the patients using validated clinical scoring systems (e.g. Knee injury and Osteoarthritis Outcome Score (KOOS) or ICRS) preoperatively and at least once a year after implantation. The evaluation has to capture subjective and objective parameters. The simultaneous use of disease specific and generic scores (Lysholm, Tegner, Cincinati, SF 36) is an adjunct. Morphological control of defect regeneration is advised using MRI with cartilage specific sequences, also at least at one year and yearly thereafter. Recommended sequences are T2, proton density, 2D Fast Spin Echo and 3D Gradient Echo (ICRS imaging recommendations : www.cartilage.org) (*72, 73, 86*).

Second look arthroscopy

Second look arthroscopy is only recommended in case of justifiable complications or in individual cases that are ethically defendable for scientific reasons, only after a thorough and full explanation to the patient (informed consent procedure).

Histological and MRI evaluation

To increase the validity of histological evaluation at least two independent experts in the field have to examine the biopsy. The biopsy, a 1 cm long cartilage-bone plug, is collected using a cannula of maximum 2 mm diameter. The analysis is best classified according to ICRS standards (*68*). The major limitation of a biopsy is that it only constitutes a momentary view of a certain zone of the repair tissue. In a study of 94 patients with 2- to 9-years follow-up, Peterson *et al* found that the results differed depending on the defect location. Histological analysis of 37 biopsies of those patients showed a correlation between hyaline-like tissue and good to excellent clinical outcome (*85*). Roberts *et al* (*87*) looked at 10 biopsies between 9 and 30 months and saw a continuous remodelling from an initial fibro-cartilaginous matrix via enzymatic degradation and synthesis of newly formed type II collagen. The findings of this study indicate that ACI is not only capable of cartilage repair but in some cases also capable of regeneration.

Evaluation of the repair site by other means than a biopsy is a necessary next step in the study of treatment results. The role of MRI in the evaluation of cartilage lesions has been the subject of controversy. Gelb *et al* (*40*) in 1996 concluded that MRI had low sensitivity for chondral lesions, whereas Roberts and colleagues in 2003 found better results (*40, 88*). Interestingly, Roberts *et al* also noted that the quality of cartilage inproved over time. Brown *et al* found in a non-randomised controlled trial, that sensitive MRI techniques show better results with ACI than with microfracture (*21*). Marlovits *et al* (*72*) in 2005, studied the validity and reliability of MRI in the assessment of autologous chondrocyte implantation (ACI) in the knee joint 2 years after implantation. Nine pertinent variables were analysed with high-resolution MRI, including filling of the defect, integration of the border zone to the adjacent cartilage, the subchondral lamina, the subchondral bone, signal intensity of the repair tissue. An intra-class correlation coefficient (ICC) of more than 0.81 for 8 of the 9 variables showed an "almost perfect" agreement. The correlation between clinical outcome (Visual Analogue Scale and Knee injury and Osteoarthritis Outcome Score) and MRI variables as "filling of the defect", "structure of the repair tissue", "changes in the subchondral bone" and "signal intensities of the repair issue" was statistically significant (*72*).

Health-economic aspects of ACI

The clinical results obtained in the aforementioned strict indications, convinced the international orthopaedic community about the safety and efficacy of ACI. More and more evidence is coming forth that ACI, when compared to other biological procedures, can be economically beneficial. To obtain reimbursement of expenses this is the third important criterion, next to safety and efficacy. Health-economic analyses of longer term prospective data became available only recently. Minas *et al* in a study of 44 patients, concluded that ACI improved the Quality Of Life (QOL) and was a cost effective method in circumscribed cartilage lesions (*74*). Lindahl *et al* (*65*) have examined the total direct economic burden in 57 patients with full-thickness chondral lesions of the knee. They saw a dramatic reduction in costs for absenteeism (SEK 9,508 = € 991) and medical treatment (SEK 7,050 = € 734), compared to the 10-year period prior to ACI (SEK 982,457 = € 102339 and SEK 47,000 = € 4895 respectively). Forty-nine of the 57 patients improved clinically as a result of ACI treatment. A German Cost Effectiveness Analysis of ACI based on review of the literature concluded that per 1000 ACI treatments, 310 total knee replacement operations and 3 surgery-related deaths can be avoided. The authors concluded that cost-effectiveness of ACI appears to be superior to conventional treatment options (*100*). More recent mid and long term studies, prospective randomised trials and better insight in the natural history of cartilage lesions bring support to this conclusion (*41*). ACI today is the only reliable biological reconstruction method for localised cartilage defects of 4 cm^2 or more. Without biological reconstruction cartilage injuries predispose to disabling osteoarthritis, a huge socioeconomic burden to society. Increasing incongruence of a joint surface,

which in time becomes a larger defect zone, has been shown to be an important risk factor in the development of osteoarthritis (*81*). ACI helps to deter costs of reiterative surgery, frequent absenteeism and early joint replacement and to postpone definitive surgery (*27*).

However, results from a large prospective randomised trial comparing chondrocyte implantation with microfracture must give better insight in the place of both techniques in the treatment of cartilage defects.

Future developments

Since the original description of ACI in 1994 many new techniques and technique modifications have been reported (*19*). To guarantee the continuous improvement of biological effectiveness and to ensure the safety of any new or modified procedure to treat cartilage defects (such as matrix implants, growth factors, etc) research has to be conducted following these four subsequent steps :

1) *In vitro* research on growth and differentiation behaviour of chondrocytes and mesenchymal stem cells.
2) Experiments in *adult animal models* to explore growth and differentiation behaviour of chondrocytes, with full documentation on safety and efficacy, long term (> 6 months) examination of the implant histology and mechanical testing of the regenerative tissue.

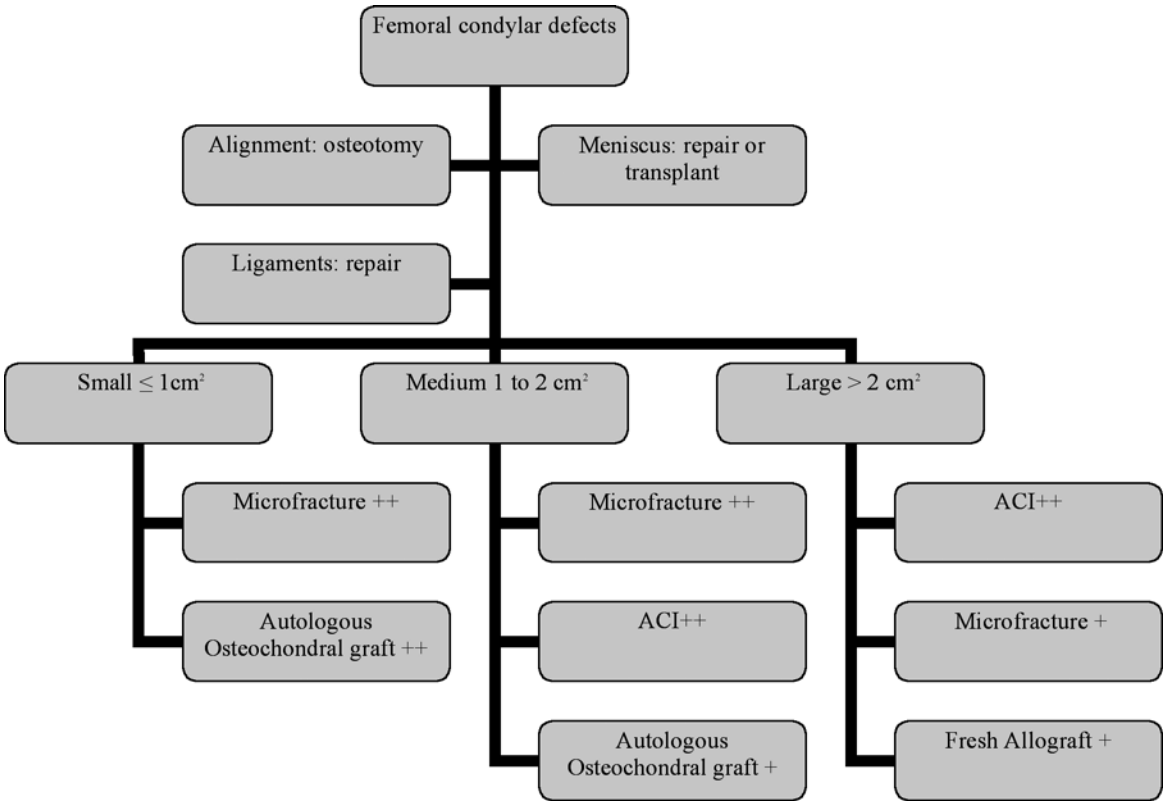

Fig. 1. — Femoral cartilage treatment algorithm

Treatment algorithm for cartilage lesions on the femoral condyles. In the treatment of these defects, alignment, ligaments and meniscus have to be corrected adequately to increase the long term success rate. In the larger lesions microfracture remains an alternative depending on patient age, concomitant ACL lesion, time to return to sports and site of the lesion on the condyle.

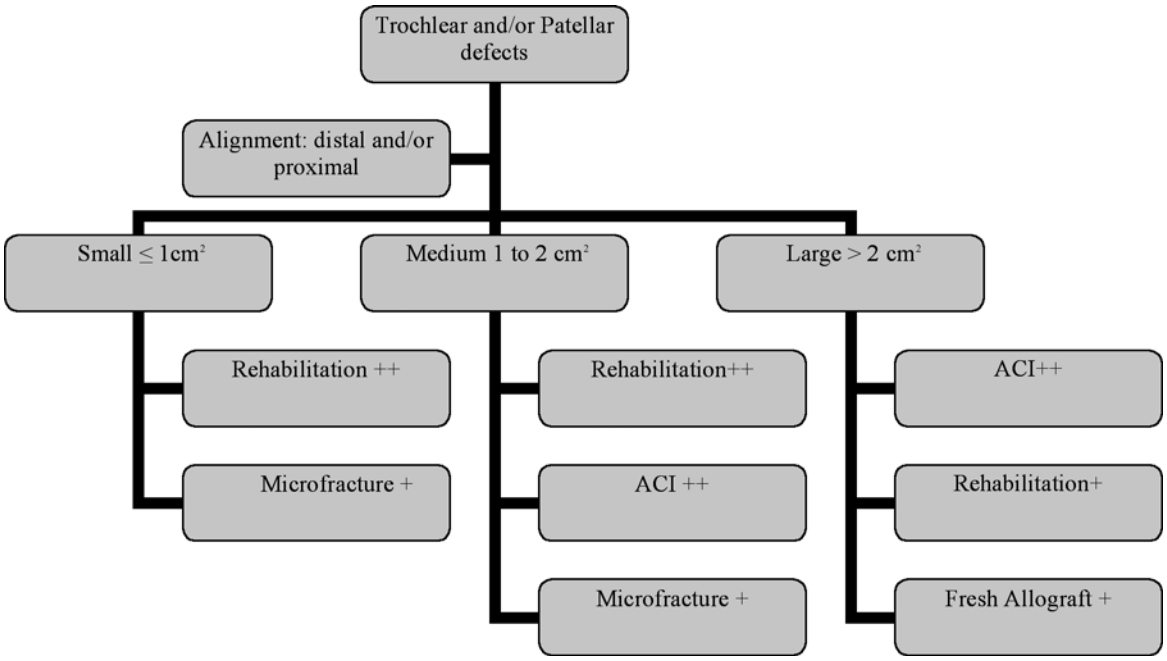

Fig. 2. — Patellar and trochlear cartilage treatment algorithm

Treatment algorithm for patellar and trochlear cartilage lesions. Alignment of the extensor apparatus has to be corrected to increase the chances for a good long term clinical outcome.

3) *Exploratory human studies* preferably using less invasive methods, long term examination of the implant (> 12 months), thorough evaluation of safety and toxicity and unforeseen events, examination of the immunological response (cartilage specific antigens), if possible in a prospective randomised controlled way.
4) *Confirmatory human prospective randomised studies* for long term follow-up of the clinical results through regular contact with patients. Results have to be validated, documented and published.

CONCLUSION

The working group of the Belgian Orthopaedic societies on cartilage repair in the knee recommends the following treatment modalities :

1. Lavage and debridement are mostly indicated in degenerative arthritis with mechanical symptoms.
2. Microfracture is still the most widely used treatment option for small full thickness lesions (< 2 cm^2) of the femoral condyles and the patella.
3. For larger lesions (> 2 cm^2) ACI should be part of the treatment strategy. Increasing evidence from recent studies shows that microfracture repair tissue has a limited lifespan. Results from a large prospective randomised trial comparing chondrocyte implantation with microfracture might give better insight in the place of both techniques in the treatment algorithm.
4. OATS as a “single plug” treatment is a good option next to microfracture, for smaller lesions on the femoral condyles, especially in a young and sportive population. It is not advised for treatment of patellar lesions. Mosaicplasty and OATS are good second line options for full thickness cartilage lesions of less than 3 cm^2.
5. In larger lesions fresh osteochondral allografts can be considered although availability of

viable allografts and disease transmission might be a problem.

6. Any new and emerging treatment should be scrutinised against standard treatments before generalised use as outlined in the recommendations above.

The treatment algoritms presented in fig. 1 and 2 adapted from the guidelines presented at the AAOS in 2005 (*69*). According to AAOS the lower limit is 2 cm^2.

These guidelines also apply to adult OCD. In adolescent OCD, conservative treatment is first choice (*35, 66*). In a grade 3 lesion, re-fixation of the fragment or removal and microfracture of the defect bed are first line treatments. Microfracture of the lesion bed will cause a "moving up" of the bone front (*21*) and can obviate the need for a bone graft in larger lesions where ACI treatment is likely to follow in a second stage, provided the bony lesion is not deeper than 6 to 8 mm (*84*).

Arthroscopic lavage and debridement and marrow stimulation techniques provide only temporary symptom relief due to the limited durability of the repair tissue. This may change with the advent of ACI, showing durable repair tissue and promising long term results.

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