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Review

Autologous chondrocyte implantation (ACI) for cartilage defects of the knee: A guideline by the working group "Clinical Tissue Regeneration" of the German Society of Orthopaedics and Trauma (DGOU)

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ABSTRACT

Background: Autologous chondrocyte implantation (ACI) is an established and well-accepted procedure for the treatment of localised full-thickness cartilage defects of the knee.
Methods: The present review of the working group "Clinical Tissue Regeneration" of the German Society of Orthopaedics and Trauma (DGOU) describes the biology and function of healthy articular cartilage, the present state of knowledge concerning therapeutic consequences of primary cartilage lesions and the suitable indication for ACI.
Results: Based on best available scientific evidence, an indication for ACI is given for symptomatic cartilage defects starting from defect sizes of more than three to four square centimetres; in the case of young and active sports patients at 2.5 cm^2, while advanced degenerative joint disease needs to be considered as the most important contra-indication.

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Conclusion: The present review gives a concise overview on important scientific background and the results of clinical studies and discusses the advantages and disadvantages of ACI.
Level of Evidence: Non-systematic Review

1. Introduction

Autologous chondrocyte implantation (ACI) was introduced in 1994 by Matts Brittberg and Lars Peterson and has become a recognized method to treat full-thickness cartilage defects in the knee joint [1,2]. Although detailed information on the number of ACI procedures performed globally is not available, the vast number of scientific contributions both in the field of experimental and clinical research demonstrates great interest in this method [3], which is one of the first tissue engineering procedures to be routinely used in clinical orthopaedic practice.

In 2004 the "Clinical Tissue Regeneration" working group of the German Society of Orthopaedics and Trauma (Deutschen Gesellschaft für Orthopädie und Unfallchirurgie, DGOU), has published recommendations for the indications and use of ACI [4]. These were primarily based on the clinical experiences of the members of the working group and on the limited amount of data on the various cartilage repair procedures then available, these recommendations have since been supported by further clinical studies, and have been published in similar form by other authors and professional organisations [5–9]. This paper aims to revise the recommendations published in 2004 by the working group using current research, and adjust them to the best currently available evidence.

Healthy articular cartilage contains up to 80% water and provides congruence to joint surfaces and enables their low-friction movement. The dry substance of its extracellular matrix consists primarily of type II collagen and high-molecular weight proteoglycans, mostly aggrecan. An increase in external pressure through joint loading causes elastic deformation of the molecular structure in articular cartilage and discharge of water into the joint space, which then flows back and is bound to the tissue. The amount of the maximum compensable loading pressure is determined by the interplay between bound and free water, and finally through the integrity and functional capability of the extracellular matrix of cartilage [10].

Tissue architecture, type II collagen and proteoglycan contents, regulating the ability to bind and distribute water, which are both in direct relation to the biomechanical properties of the tissue, are the primary differences between fibro- and hyaline cartilage. Qualitatively poor structural and histological properties of regenerated tissue after cartilage repair are associated with treatment failure or recurring clinical symptoms [11,12].

Articular cartilage is not innervated and, as a bradytrophic tissue, has no blood supply. Transport of oxygen and nutrients to cartilage cells is done through relatively long diffusion paths (supported by pump mechanisms in normal loads); the same applies to the removal of catabolic waste materials. Furthermore, cartilage is a tissue with relatively few cells, whose chondrocytes demonstrate limited mitotic capabilities, and are also enclosed in their extracellular matrix [10]. The sum of these characteristics may explain a phenomenon which has been known for a long time: articular cartilage, especially in adults, has only a limited intrinsic ability to regenerate itself [13].

If cartilage and/or the meniscus is damaged to a larger extent, such as due to trauma, the load per surface area in the joint increases, which can lead to higher pressure loads on the remaining intact cartilage tissue [13]. Of course, this problem increases with the extent of the cartilage damage, whereby the largest loads can lead to shearing forces, especially on the defect edges, and as a consequence to the death of chondrocytes (e.g. through apoptosis) [14,15]. The degree of cell death therefore correlates with the amount and duration of nonphysiological pressure loads [16].

Additionally, it is known from basic research that repeated pressure overloads can induce secondary destructive pathways in articular cartilage which are similar to primary inflammatory joint diseases, and which are accompanied over the course of the disease by the release of pro-inflammatory cytokines and matrix-degrading enzymes [14]. As a consequence, proteoglycans can bind more water, the cartilage tissue swells (chondromalacia), loses elasticity and hardness, which then leads to a further deterioration of load tolerance. This vicious circle can then induce irreversible damage of the extracellular matrix and its chondrocytes, resulting in complete cartilage destruction [10].

There are not many systematically gathered data available in relation to the natural history of untreated primary cartilage lesions, especially for the first few years after the defect has occurred. Since cartilage is aneural and avascular, its damage also in the early stages, may not necessarily be associated with pain or other accompanying symptoms [13,17]. This gives rise to the problem of identifying patients with such damage, and also the consequential difficulty of capturing these in prospective studies [13].

Nevertheless, results from longitudinal studies have been published, in which sequentially conducted magnetic resonance imaging (MRI) results were used to investigate the issue of further consequences of focal cartilage lesions in the knee joint (including asymptomatic defects), in particular as a function of various risk factors (such as the degree of initially observed damage, patient age or increased body mass index (BMI)) [18,19]. In comparison with simple X-ray analysis or arthroscopic joint inspection, the analytic benefit of modern MRI procedures is that they can, among other things, give a significantly more precise quantitative record of existing cartilage volumes in the joint [20]. Over an observation period of two years, an increase in size of the primary lesion was not necessarily seen, but there was a significant loss in total cartilage volume in the affected joint (in the sense of osteoarthritis (OA) development).

Based on the data from clinical studies, and in connection with the aforementioned basic scientific research results, it is widely accepted that focal cartilage defects of the knee, especially when the growth plates are closed, are a risk factor for the development of OA, and that this risk increases with the degree and chronicity of the initial cartilage lesion, despite variability in the natural history of chondral lesions [13,17,20,21]. It is believed that addressing cartilage defect development is an important target for the prevention of cartilage loss and ultimately for the need of total knee replacement [20].

Although clinical studies have shown that even asymptomatic cartilage defects tend to progress, there is still a general consensus that only clinically symptomatic and full-thickness cartilage lesions present an indication for surgical cartilage repair. The ICRS classification is routinely used for cartilage defects [22]. Incidentally discovered asymptomatic defects through MRI, should not be biologically reconstructed for purely prophylactic reasons until further knowledge is gained [17].

The ideal starting point for surgical cartilage repair is presented by painful, full-thickness defects due to trauma, with intact joint surfaces, which are isolated and bordered by surrounding healthy tissue (Figure 1).

Since this diagnosis is more of an exception in regular medicine, it appears justified on the basis of available literature to tend towards an indication for cartilage repair for limited degenerative defects, as long as they are clinically symptomatic and the affected patient shows sufficient compliance [23–25]. However, the possible treatments are limited to the early stages of focal degenerative defects, excluding diffuse lesions.

A dedicated and detailed examination to establish the cause of the defect prior to a surgical cartilage repair intervention must be carried out; this is even more important in degenerative than in trauma-caused

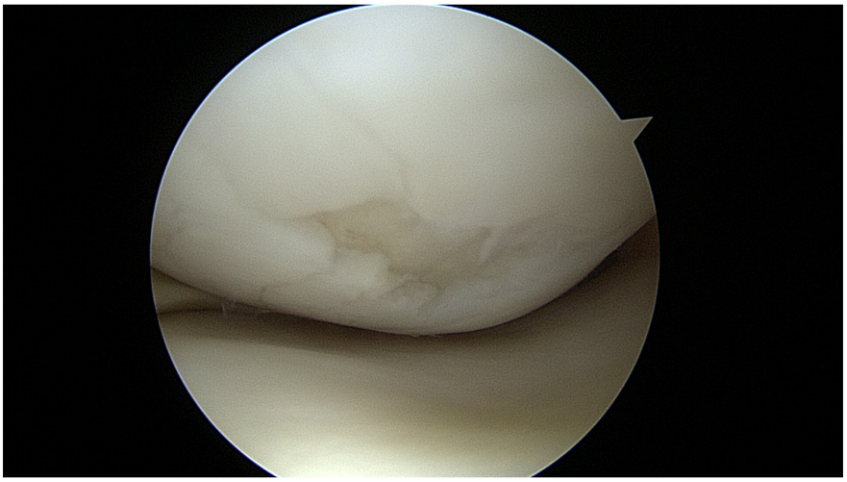

Figure 1. Isolated cartilage defect grades III and IV by ICRS classification, with intact corresponding joint surfaces and intact surrounding cartilage, are a suitable indication for ACI.

defects. This analysis should include morphologic imaging of the cartilage lesion (using cartilage-sensitive MRI sequences) and of the subchondral bone. In addition, an analysis of the alignment of the affected knee with a long leg standing imaging should be performed and, if needed, further additional diagnostics. This basic diagnostic sequence is considered an absolute requirement, as for non-traumatic cartilage lesions, adjuvant treatment is essential to achieve good results. However, further details on this are not subject of the present work.

The currently available surgical options for the treatment of cartilage defects can be divided into transplant procedures and bone marrow stimulation techniques. While autologous chondrocyte implantation (ACI) and osteochondral transplantation (OCT, OATS, mosaicplasty) represent the group of transplant procedures; microfracture, abrasion arthroplasty and drilling procedures are among the techniques used for bone marrow stimulation.

It is our view that abrasion arthroplasty [26] has not been established as a bone marrow stimulation procedure to treat isolated cartilage lesions, and is used more in the context of OA treatment. On the basis of the available literature, arthroscopic microfracture (MFx) is the procedure with the best evidence within the bone marrow stimulation techniques.

Whether the marrow space opening is carried out classically as described by Steadman [27] with conical awls to penetrate the subchondral lamellae, or whether it is advantageous to turn back to the original drilling techniques, or to use newer techniques such as the nanofracture procedure, which is considered to allow the recruitment of cells with a better quality into the defect [28–30], is the subject of ongoing debate, and cannot be finally assessed at this time, since clinical evidence is still missing. Perforation and therefore injury of the subchondral bone plate are criticised by some authors [31].

It is accepted, however, that bone marrow stimulation techniques primarily induce the formation of fibrocartilage. This appears to be inferior when compared with the histological–structural qualities after ACI, the latter resulting in a greater proportion of hyaline-like tissue at the repair site, which may in turn have a beneficial effect on durability [9,32]. A large number of cases are available which clearly point to the clinical effectiveness of MFx. However, factors associated with an unfavourable prognosis include the size of the defect [33,34], and age over 40 years [35].

In addition to the problem of intralesional osteophyte formation, which characteristically and more frequently occurs after MFx, several independent studies have described a worsening of results within a few years; after five years, independent of the size of defect treated [33,34]. Furthermore, in a recently published systematic review certain matrix-associated ACI forms yielded consistently better patient-reported functional outcomes in comparison with MFx over a five year course [8].

In summary, these results suggest a limited durability of typical fibrocartilage after MFx over time. The possible reason for this problem from a scientific point of view has been described above. Similar to osteochondral transplantation [36–38], which must surely be differentiated in the assessment between classical mosaicplasty and transplantation of larger cylinders (e.g. OATS), it seems that MFx is not appropriate to treat particularly larger cartilage defects. This is therefore an indication for ACI in this area.

Whether advancements of the microfracture technique like matrix associated procedures (such as autologous matrix induced chondrogenesis: AMIC) resolve the inherent problems of MFx remains to be seen [30]. Although various authors have described good clinical results in mostly short course times and primarily in small to medium-sized defects using various biomaterials, these results are frequently not confirmed by MRI findings [39–41]. So far it has not yet been sufficiently clarified, if the additional use of a biomaterial, the use of concentrated bone marrow instead of MFx or AMIC plus platelet-rich-plasma gel can significantly improve the quality of the repair tissue. The formation of intralesional osteophytes and fibrous tissue has been observed using these techniques [40–42].

Possibly, there are also differences between various biomaterials with respect to their ability to chondrogenically differentiate mesenchymal cells, especially in-situ. In a randomised controlled trial, the additional use of a gel-type biomaterial improved the 12-month results of MFx as shown by MRI, although no significant differences could be seen in clinical scores between the two groups [43].

A basic problem in the use of mesenchymal stem cells for cartilage repair is seen in their intrinsic differentiation programme reminiscent of endochondral bone formation [44], which has not been observed even with expanded chondrocytes [45].

In summary, at present, the available data are not sufficient to assess the therapeutic value of these relatively new methods in a reliable manner. The same applies to biomaterials which are used cell free (i.e. without accompanying MFx or a bone marrow aspirate) as well as for the use of primary or expanded mesenchymal stem cells or other cell types for the repair of localised cartilage lesions. Further clinical studies are needed in relation to this, in order to compare in prospective, randomised trials for defined indications (e.g. also including the defect size and type) and after longer course times with clinically established and better evaluated methods [30,39,46,47]. This is especially true as some of the new procedures have not yet demonstrated convincing clinical results despite promising preclinical studies [48,49].

Table 1

Indication for autologous chondrocyte implantation of the knee joint
Defect stage: Full-thickness, symptomatic cartilage defect grades 3 and 4 as per ICRS and osteochondritis dissecans stages III and IV as per ICRS-OCD, possibly in combination with subchondral bone reconstruction
Defect size: Minimum: 2.5 to 3 cm^2; Maximum: no limit
Defect localisation: No limitation: Medial and lateral femoral condyle; Medial and lateral tibial plateau; Patellar bearing surface (trochlea); Patella
Age: Typically up to about 55 years of age; higher age is however not a contraindication with relevant defect morphology and primarily intact joint conditions. Children and adolescents possible
Contraindications: Concomitant pathologies which cause it, which cannot be treated in parallel (e.g. misalignment); Advanced arthritis; Subtotal resected meniscus in an impacted compartment; Rheumatoid arthritis with relevant synovitis; Hemophilia-associated arthropathy

2. Indications for autologous chondrocyte implantation

Precise definition of appropriate indications for ACI is the core of this publication (Table 1). ACI is a method with higher procedure-associated costs than MFx or autologous OCT. In addition, ACI is a two-step procedure which requires more patient commitment, as it uses a cell biopsy and retransplantation carried out at a later time, and therefore requires two surgical interventions.

In recent years the available evidence for ACI has significantly improved [6–9,46,50,51]. This is likely related to the changed legal conditions in many countries which have required proof of safety and efficacy through relevant studies for approval of ACI products. A series of prospective, randomised trials have been published in the meantime which compares ACI directly to alternative procedures. These studies deal with a comparison to OCT [52–54], abrasion [55], and particularly arthroscopic MFx [11,32,56–59]. The fact that in all studies comparing ACI to any other treatment, a blinding of the patients to the therapy applied is impossible due to the fact that ACI represents a two-step procedure in contrast to the control group treatments needs to be considered a methodological limitation of all studies.

In assessing most of these studies, it should be noted that various regulatory authorities (such as the European Medicines Agency, EMA, or Food and Drug Administration, FDA), have requested studies to examine the efficacy of ACI products in prospective, randomised studies in comparison with MFx for smaller to medium-sized cartilage defects at a size of up to five square centimetres [32,57,58]. Most of these studies were planned with a "non-inferiority" design and with respect to the defect size treated, more in the indication range for MFx and less for ACI. An extension of trials to include large defects would likely not be approved by most authorities based on the limitations described for MFx, mainly due to ethical concerns.

For this reason, only two trials at the highest level of evidence exist to assess the efficacy and superiority of ACI for larger cartilage defects. After 24 months they demonstrated clinical superiority in the group with matrix-associated ACI using a collagen membrane as a carrier for chondrocytes [59,60].

The other prospective, randomised trials which directly compared MFx with ACI, all reported on patients with smaller defects. With regard to defect sizes, the first comparative study was done by Knutsen et al., averaging 5.1 cm^2 and 4.5 cm^2 [11,56]; and 2.6 cm^2 in the series from Saris and Vanlauwe [32,57,58]. There were no significantly different results found in the study of Knutsen et al. between first generation ACI and MFx.

In the second study, also using periosteum covered ACI, but with characterised chondrocytes, a histological, structural superiority of the repair tissue after ACI was shown without different clinical results after 12 months between ACI and MFx. After 36 months, clinical superiority was found for the ACI group but in the five year follow-up these differences could only be observed in a subgroup of ACI patients with symptom duration of less than three years before treatment. However, in this patient population the differences were considered clinically relevant. The authors came to the conclusion that symptomatic patients should be treated as early as possible [58], a recommendation that is supported by the results of other clinical and preclinical studies [46].

In a prospective, randomised phase II study [61] comparing a matrix-associated type of ACI (using a chondrocyte seeded bovine collagen gel/sponge scaffold with cultivation of the construct in a bioreactor to stimulate the synthesis of cartilage matrix proteins) with MFx (average defect size 2.87 cm^2 and 2.52 cm^2), after six, 12 and 24 months, the outcomes including various clinical scores were significantly better for ACI. Over a 24-month course, improvements were shown in the KOOS score for pain, sports and quality of life, as well as in the International Knee Documentation Committee (IKDC) and Visual Analogue Scale (VAS) scores.

When analyzing results derived from RCT evaluating the effect of ACI in comparison with other techniques, it has also been considered that inclusion criteria have been slightly different not only in terms of defect size but also in concomitant surgeries allowed. While some studies have not considered realignment osteotomies or ACL reconstruction being exclusion criteria, others consequently excluded these patients. Since concomitant surgeries certainly also affect clinical outcome, this might also influence the results of various RCT evaluating the effect of ACI and other cartilage repair techniques.

Further comparative, non-randomised studies with an average defect size of 2.4 cm^2, also showed an improved functional gain in the ACI patient group (using arthroscopic techniques and a chondrocyte seeded biomaterial) in direct comparison with MFx after five years [62]. In the group of patients treated with MFx, a worsening of the results was observed between two and five years, which had also been described by other authors, and may present, as already suggested, a procedure-specific problem for MFx [8,34].

In relation to the various ACI versions, it has been shown in direct, randomised evaluation, but also in retrospective analyses of larger patient populations, a clearly lower complication rate with the use of biomaterials in comparison with first generation ACI techniques using a periosteal flap to cover the defect [46,63].

There are only limited direct comparisons in clinical trials with different ACI products of the second and third generation [64]. In-vitro, sometimes significant differences were found between various biomaterials, even with the use of the same chondrocyte pools [65,66]; whether these become clinically relevant in-vivo can only be established in comparative clinical trials [8,46]. Arthroscopic implantation is not yet widely used, but appears to be advantageous in relation to lower re-operation rates and faster restoration of joint function [46,63].

Analysis of the randomised studies has also been published in sequential analyses of the Cochrane database [67–69], and in addition to this there are several published case series reporting on a relatively large numbers of ACI patients [70]. In the last few years additional work with long term follow-up has been published including results for larger defects and more difficult indications. In these studies a considerable durability of the repair tissue after ACI has been shown with an improvement in joint function when compared to the pre-surgical state (Figure ure 2) [2,71–74]. Given the larger average defect size in these case series the basic effectiveness of ACI has been demonstrated even in large cartilage lesions. An overview of available data can be found in several publications [8,68,75,76].

The frequently observed, sustained efficacy, even in larger lesions, distinguishes ACI to date from other existing and clinically long-term evaluated procedures (such as MFx or mosaicplasty [8,9,77]). On the basis of this data, its status is established for the treatment of larger cartilage defects, as we have already recommended in 2004 [4].

While the recommendation for minimal defect size is based on the critical limits of alternative procedures, and is between 2.5 and four square centimetres (Figure ure 3), it seems difficult to define an upper limit. As mentioned before, the best starting point for the use of ACI is

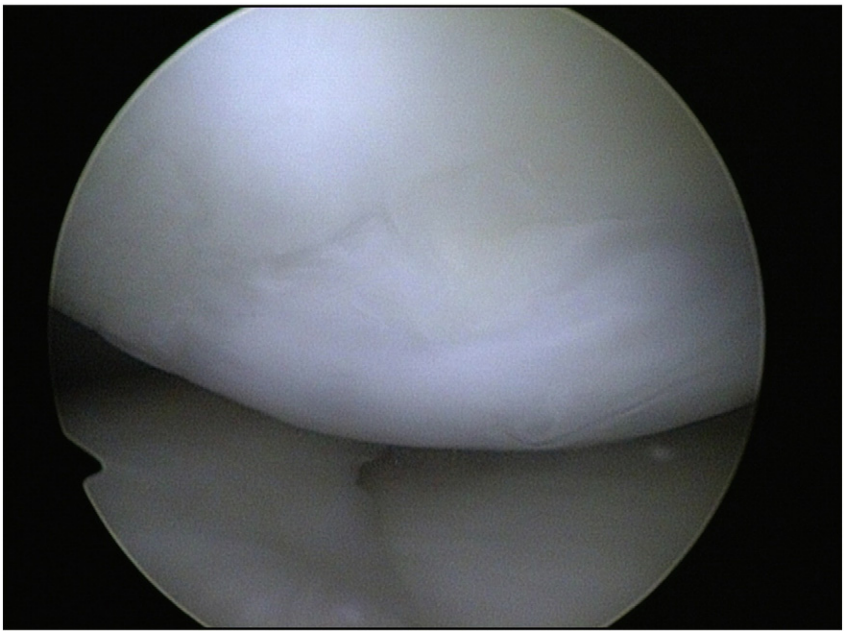

Figure 2. Arthroscopic findings 24 months after ACI in the area of the medial femoral condyle with evidence of well-integrated regenerated cartilage.

a joint with no degenerative changes on the opposing joint surfaces, a functional meniscus and stable ligaments. If the described conditions are present, ACI appears not to be limited in size, because, in particular for larger defects, there is no other suitable autologous repair procedure available. In the context of the discussion of defect size it has to be mentioned, that the vast majority of studies give absolute values for defect sizes. The percentage of the weight bearing affected by a cartilage defect i.e. of a femoral condyle with a lesion size of 2.5 cm^2 might significantly differ in dependence of the size of the patient and respectively joint. These fluctuations might also help to explain why strict limitations for defect sizes are hard to be established based upon scientific evidence. It seems adequate to not only consider defect size in cm^2, but also the relation to the joint and patient size. To evaluate these effects should be part of future scientific studies.

An important aspect which has gained interest recently is the influence of various cartilage repair methods used sequentially. It has been shown by various working groups that the failure rate of ACI is significantly increased after previous failed MFx in comparison with patients who had not been treated beforehand [74,78]. This underlines the need for the best available treatment as soon as possible. Once ACI is indicated, no previous try for a less invasive or cheaper therapy should be performed since this worsens prognosis in the further clinical course.

The functional results of ACI as a "second-line" treatment are worse in comparison with "first-line" treatment, where a long symptom history of the impacted knee joint represents a significant negative predictive factor [58]. With this as a background, early choice of the optimal procedure seems to be decisive for successful cartilage repair. As a change to the recommendations of the working group in 2004 [4] the authors [46] and other groups [5,79] now recommend first line use of ACI for young and athletic patients even with defects <3 to four square centimetres.

One of the important fields in the future with regard to cartilage repair is the extension of the available treatment options in the area of degenerative articular lesions [80]. Even though the first long-term data clearly shows an improvement in joint function after ACI, even for patients in the early arthritic stages [74,77], multiple defects representing developing OA certainly present a limitation to current methods and should only be treated in exceptional cases.

This area requires further research of, among other things, the individual pathophysiological aspects of OA (malalignment, metabolic anomalies, etc.), which should be included in the treatment concepts. It is also necessary, as stated in the recommendations in 2004 [4], that for existing patellofemoral malalignment, a simultaneous correction is carried out in order to ensure healing after ACI or other cartilage repair procedure and to delay the progression of OA.

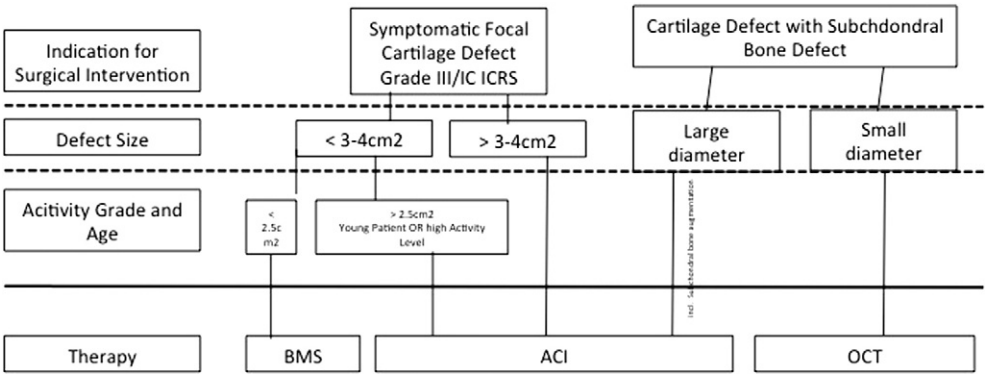

Figure 3. Assistance in making the right choice on the appropriate procedure for biological reconstruction of isolated cartilage defects of the knee depending on various factors (BMS: Bone Marrow Stimulation, e.g. microfracture; ACI, autologous chondrocyte implantation; OCT, osteochondral transplantation).

3. Age and autologous chondrocyte implantation

Initially, ACI was seen as a treatment procedure for patients between the age of 18 and 50. In the meantime, data has been published which shows the efficacy of the method in children and adolescents as well [74,81]. In addition, with the safety evidence provided, there are no basic concerns which argue against the use of ACI in adolescents. The indications are therefore identical to those for young adults [46].

The use of ACI is still controversial in older patients. Since the type of damage is an important indication parameter, and often limiting degenerative joint changes are present in older patients, there are only a few patients over the age of 50 who are suitable for an ACI. In our view, it seems important to determine that a calendar age beyond 50 does not prevent the use of ACI to treat localised full-thickness cartilage defects. Several studies have shown the basic efficacy of the procedure in older patients as well [82]. In a direct matched pair comparison with identical defects and patient-specific parameters, no inferiority was found in the clinical treatment result [83]. This appears to be different from the results reported with older patients after MFx [35].

4. Sports and autologous chondrocyte implantation

Taking up sports again after surgery is a good and comparable parameter to quantify and assess the post-operative functional status of a joint. In addition, it seems important to check whether, and at what point in time, after a surgical procedure, athletic loads are possible in order to include this aspect in patient consultation.

In connection with this, there are several studies which specifically deal with resuming sporting activities after ACI. In order to assess the therapeutic value of cartilage repair methods, especially in athletically active patients, where there are greater joint loads in comparison with less active people, a larger review publication would be helpful in which ACI is considered as well as other reconstructive procedures.

A large meta-analysis from Mithoefer et al. with 1363 patients showed that there were significant differences between different cartilage restoration procedures when restarting athletic activities after surgery [84]. Patients who underwent OCT resumed sports sooner.

Patients undergoing ACI clearly needed a longer recovery, but achieved the highest average level of sports over time. After OCT or ACI the number of patients who resumed a previously practiced sport was higher than after MFx. This disadvantage of MFx has been confirmed in recent review papers [85].

Similarly, Kon et al. described a direct comparison between ACI and MFx in athletes, in which they found a faster return to sports capability after MFx, but the long-term results were better with ACI [86]. The frequently good compatibility between competitive sports and ACI indirectly underlines the weight bearing capabilities of the repair tissue after ACI. In addition, resuming sports seems to have a positive influence on treatment results [87].

5. Post-treatment and autologous chondrocyte implantation

Even though most protocols and recommendations for rehabilitation after ACI primarily rely on expert opinions, available data in recent years has become significantly better [46,88]. Two prospective, randomised studies show a clear trend to more progressive loads after ACI [89,90].

Most authors found that in femoral–tibial defects partial load bearing was recommended for up to six weeks with subsequent increases in load, while in the area of a patellar femoral joint section, limiting flexion was the primary recommendation. In relation to an initial load on the joint in positions near full stretches, there is still no final consensus, but altogether it seems to be possible. A corresponding recommendation on rehabilitation after ACI by the German working group "Clinical Tissue Regeneration" has recently been published [91].

6. Technical aspects and quality assurance

Since its introduction more than 20 years ago, a large number of procedural modifications have been undertaken with ACI, which has led to various "generations" of ACI being entered in the scientific literature [92]. The original technique using cell suspension after prior defect covering with a periosteal flap is the first generation; the use of a cell suspension in combination with a covering collagen membrane is the second generation, and cell-seeded biomaterials are the third generation of ACI. In direct comparison as well as in large case series, 2nd and 3rd generation products show clinical benefits in comparison with the periosteal technique, with a significantly reduced incidence of graft hypertrophies [63,93].

The advantage of the 3rd generation comes from the simple and faster application through the lack of a need for a water-tight seal of the covering membrane, which had previously been necessary to inject the cell suspensions underneath. This change in procedure is not only easier for the application, but also reduces comorbidity through smaller surgical access, and also broadens the indication spectrum to include uncontained defects.

As a result of this, we prefer suitable 3rd-generation ACI products. As already mentioned, there is no final evidence about the optimal scaffold material for ACI. The same applies to the number of cells implanted. This is recommended on the basis of empirical evidence at about one to two million cells per square centimetre of defect area.

Basically, as described in 2004 by the working group [4], for each chondrocyte implant, in addition to sterility and other safety and quality controls, suitable cell and molecular biological tests should be performed. The results of these tests should serve as quality assurance, and also to gain additional scientific knowledge. There is increasing evidence from pre-clinical and clinical studies that the characteristics of the cells used are a factor that has an influence on the histological and clinical results of a cell based therapy [94–97].

7. Autologous chondrocyte implantation and the subchondral bone

In recent times, the significance of the subchondral bone plate has returned to the centre of scientific interest for treatment of cartilage defects [98,99]. Articular cartilage and its subchondral bone should be considered as a functional unit [98–102]. The need for co-treatment of accompanying subchondral pathologies is becoming more understood. It is often difficult to decide, for example in the case of subchondral oedema, whether these changes represent the primary pathology, or are the consequence of overloading the subchondral bone in the area of the cartilage lesion. It is not yet clear whether subchondral oedema is associated with a poor clinical result after cartilage repair. In a trial recently published with matrix-associated ACI, no such correlation was seen at 36 months [103].

Nevertheless it makes sense to differentiate between anatomically localised and generalised oedema, such as those found in osteonecrosis in the area of the femoral condyle. Usually, localised oedema needs no adjuvant treatment in the context of cartilage repair. More generalised oedema, however, must be treated as an independent pathology, and only addressing cartilage pathology would be insufficient here. The same principle applies to osteochondral lesions with subchondral bone defects.

Pure surface bone erosions can be treated solely through transplantation of chondrocytes as part of ACI. Bony substance defects which are more than two to three millimetres deep (after resection of affected bone, such as a sclerotic area in the context of osteochondritis dissecans) require adjuvant defect filling. This can be done with loose, impacted autologous cancellous bone or with cortical–cancellous bone grafts [104–107].

Some authors prefer a one-time procedure in the sense of a so-called "sandwich ACI." Others prefer a two-stage technique, with initial reconstruction of the subchondral bone and subsequent ACI. No evidence-

based statements can be made on the possible superiority of one or the other method [46]. For smaller osteochondral defects, a reliable alternative to ACI is the transplant of an autologous osteochondral cylinder.

In contrast to the abovementioned preexisting pathologies of the subchondral bone, others are directly associated with cartilage repair techniques. Elevation of the subchondral bone and intralesional osteophytes are the most common pathologies occurring in the clinical course following ACI. Although a higher incidence of these problems, which require revision surgeries in a significant percentage of cases, is reported for bone marrow stimulation techniques, elevation of the subchondral bone also occurs in ACI [57]. The idea, that aggressive debridement harming the subchondral bone during surgery leads to increased rate of elevation of the subchondral bone and intralesional osteophytes or if potentially subchondral mesenchymal stem cells with osteogenic potential contribute to this problem remains unclear. Anyhow, resection of these pathologies during revision surgery is generally required.

8. Remarks on the economics of ACI

In addition to evidence assessments, commercial considerations are becoming an increasing area of focus for the commissioners of surgical joint and cartilage treatment. In a study by Wildner et al. [108] in 2000, an incremental cost effectiveness analysis was performed using data from the literature and expert information. This related to the additional costs incurred next to a comparable procedure (e.g. MFx).

In the calculation models it was seen that by 1000 ACI treatments, 310 subsequent arthroplasty operations were prevented, and that in treating 3400 isolated cartilage defects with conventional procedures, 2000 joint replacement operations were required. This number was reduced to half through ACI treatment. The authors came to the conclusion that provided that the amount of evidence for ACI versus the comparable procedure was confirmed in additional trials, the ACI would be economically beneficial. Similar calculations have been published by other authors [109,110].

Since these calculations were done, the available evidence for ACI – for the procedure itself and in comparison with other treatment methods – has continued to improve. As shown above, ACI is at this time the only autologous cartilage repair procedure with sufficient evidence showing good long-term results, even in larger defects and more difficult indications. Since the larger primary cartilage lesions most likely promotes early onset of knee OA, this suggests a risk–benefit evaluation in favour of ACI.

In connection with this, it is worth mentioning the important problem of higher failure rates of ACI after previously failed MFx. Minas et al. [74] showed a graft survival rate of 79% (95% CI, 69–87%) at 15 years when ACI was used as the first-line procedure. When ACI was performed after previously failed MFx this was only 44% (95% CI, 17–68%). Due to this, MFx or mosaicplasty should be carefully considered as a primary treatment option, especially in younger patients with larger defects. If this treatment is not successful, there is an increased probability of OA that will require partial or total knee replacement.

Knee arthroplasty as a result of incorrect defect treatment or early failure of chondral resurfacing may not be a lower-cost alternative, particularly in younger patients. Up to 57% of patients are not fully pain- and symptom-free after arthroplasty, which frequently leads to further consultations and costs [111,112]. Furthermore, in younger patients, the risk of early failure of primary knee arthroplasty is significantly higher than in older patients [113–116]. This means that revision surgery is often necessary in this patient group [111,117] which can also result in higher failure rates [117,118]. Revision of unicompartmental knee replacement also leads to significantly higher subsequent costs in comparison with the implantation of a primary knee prosthesis [119].

From an economic perspective, and particularly in the interest of healthcare commissioners, the early use of knee arthroplasty must be seen in an increasingly critical manner, and avoided as much as possible [111].

The DGOU has established a cartilage register [120] which represents a prospective database involving 90 hospitals in Germany, Austria and Switzerland. All types of cartilage treatments are recorded and outcomes can be studied up to 10 years. This register has an important role in evaluation ACI including matrix-associated ACI and other cartilage repair procedures.

9. Other joints

This position statement relates to ACI in the treatment of cartilage defects in the knee. The evidence for other joints is much less clear. Although ACI (in osteochondral and purely chondral defects) can also achieve functional improvement in the ankle, there are very few controlled studies for this joint [46]. This applies in particular to the size of the defect and/or localisation, and the comparison in regard to this of ACI with other procedures, such as OCT and MFx. For other joints, such as the shoulder or hip, there are only a few individual case reports [46]. For these joints as well, appropriate indications for ACI and outcomes in comparison with other methods should be established, with the assistance of the DGOU cartilage register.

10. Conclusion

Autologous chondrocyte implantation (ACI) is an established treatment and an integral component of cartilage repair techniques for the knee. The safety of the method and its efficacy in terms of functional improvement in patients with isolated cartilage lesions have been demonstrated for this joint in many trials and also over a long period of time (Table 2).

Based on the data available it is suggested that autologous OCT procedures might be more appropriate for lesions smaller than two to three square centimetres. In a prospective randomised study of ACI in focal defects above three to four square centimetres in size clinical 10-year results were significantly better than those of mosaicplasty.

The superiority of ACI vs. microfracture is demonstrated in regard to the quality of the repair tissue, whereas in prospective randomised trials clear functional superiority of periosteum covered ACI over microfracture has not yet been demonstrated. There are now prospective randomised trials that demonstrate superiority for matrix-associated ACI procedures using collagen-based biomaterials. Further assessment of these studies is recommended in order to study the longer-term outcome.

However, at present one should also note that these methods should not be considered as competing procedures, but rather as important pillars in the spectrum of cartilage-related treatments with respective indication-dependent advantages. The modern cartilage surgeon must consider the advantages and disadvantages each method.

The value of ACI is clearly demonstrated in the treatment of larger defects. Using the best available evidence, in our view there is an indication for ACI for defects greater than three to four square centimetres and as a second-line treatment for smaller defects. For athletically active and younger patients, we recommend ACI for defects greater than 2.5 cm^2.

Table 2

Conclusion
Autologous chondrocyte transplantation (ACI) is an established procedure to treat localised cartilage defects of the knee.
Its efficacy even after longer course periods has been proven by a number of studies.
Superiority for some ACI versions against other methods has been shown in the first prospective, randomised trials, but will be confirmed in further studies.
ACI presents a complementary rather than a competitive procedure as compared to microfracture and mosaicplasty. Its significant value is at this time the treatment of larger cartilage lesions.

Conflicts of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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