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Review

Articular cartilage repair techniques exploiting intrinsic healing capacity – which one is the best?

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List of nonstandard abbreviations:

ACI – autologous chondrocyte implantation
ACT – autologous chondrocyte transplantation
BMS – bone marrow stimulation
CACI – collagen membrane - autologous chondrocyte implantation
CCI – characterized chondrocyte implantation
COI – conflict of interest
MACI – matrix induced autologous chondrocyte implantation
OALT – osteochondral allograft transplantation
OATS – osteochondral autograft transfer system
PACI – periosteum - autologous chondrocyte implantation

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Abstract

In this review article articular cartilage structure and organization is explained, followed by brief discussion on articular cartilage focal lesion development and subsequent endogenous regeneration, which mainly relies on presence of intrinsic healing capacity. In case of full thickness focal chondral defects intrinsic healing ability is insufficient and full spontaneous repair is almost never achieved. In those cases, cartilage repair techniques are indicated.

Currently, the most commonly used articular cartilage repair techniques include three groups of techniques such as: bone marrow stimulation, osteochondral allografting/autografting and autologous chondrocyte implantation. These groups are further divided to specific cartilage repair techniques, discussed in detail and compared to other approaches. The information provided is intended to allow proper critical judgment and to answer the question "Which articular cartilage repair technique is the best for the particular patient?".

INTRODUCTION

Articular cartilage structure

Articular cartilage represents a highly specialized avascular and aneural connective tissue, thick between 2 to 4 mm, which lines the joint surface and provides sophisticated low friction mechanical system allowing smooth joint motion under full weight bearing. It is comprised primarily of water (60-85%), type II collagen (15-22 %) and the proteoglycan aggrecan (4-7%) with addition of other extracellular matrix components including other collagen types (VI, IX, X, XI), small proteoglycans (decorin, biglycan and fibromodulin *(1)*) and glycoproteins (e.g. chondronectin) *(2- 4)*. Only one cell type is present within the cartilage - chondrocytes, constituting only 2% of the total volume of articular cartilage *(5)*. The articular hyaline cartilage possesses well-known zonal architecture, since different distribution of cells, matrix, and mechanical properties are present when observing different cartilage depths *(6)*. Four zones of articular cartilage are: superficial zone, middle zone, deep zone and calcified cartilage zone, underneath which subchondral bone is situated (Figure 1). Within each zone, 3 additional regions can be identified - the pericellular, territorial, and inter-territorial regions *(7)*.

Superficial zone - is the thinnest upper-most cartilage zone, and it is comprised of two layers: a fibrilar sheet covering joint surface and cellular layer of flattened chondrocytes with axes parallel to the articular surface, synthetizing collagen rich matrix with low proteoglycan con-

centration. Superficial zone has the highest water content compared to the other zones (80% of total cartilage mass) *(8, 9)*. *Middle (transitional) zone* is situated under superficial zone, representing transition between the shearing forces of surface layer to compression forces in the deeper cartilage layers. Middle zone is considerably thicker than superficial zone with spheroid cells synthetizing mostly proteoglycan component of the matrix together with smaller proportion of thick collagen fibrils, while water content remains relatively low. This zone accounts for approximately 40% to 60% of the total cartilage volume. *Deep zone* of the hyaline cartilage is situated under middle zone, presenting around 30% of hyaline cartilage volume. In this zone chondrocytes are organized into columns lying perpendicular to the joint surface. This layer provides the greatest resistance of the articular cartilage to compressive forces, since it is rich with proteoglycans and collagen fibrils, which are arranged perpendicularly to the cartilage surface *(7)*. This zone has the lowest water content, compared to the other zones (65% of total cartilage mass) *(3)*. Right underneath the deep zone, *calcified cartilage* is situated and presents layer separating deep zone and subchondral bone. Cells in the calcified cartilage have small volume, while the matrix is rich in collagen X. The tide mark separates the deep zone from the calcified cartilage, and the cement line separates calcified cartilage zone and subchondral bone. The calcified zone has a crucial role in fixation of the articular cartilage to the bone, because the collagen fibrils of the deep zone extend all the way to the subchondral bone and thus serve as anchors *(4,7)*.

Current treatment options in osteoarthritis

Osteoarthritis is among the top-five causes of disability amongst non-hospitalized adults according to estimates from the National Institute of Arthritis and Musculoskeletal and Skin Diseases *(10)*. Osteoarthritis is typically characterized with articular cartilage degeneration, low grade synovitis, and alterations in peri-articular soft tissues and subchondral bone *(11-13)*. Hyaline cartilage is avascular and anerual, and it has limited intrinsic healing capacity *(14)*. In addition, osteoarthritis affects mainly older patients affected with age related articular cartilage changes, which consequently reduce intrinsic regenerative abilities *(15)*. In the case of severe osteoarthritis, the only available treatment option is surgical intervention i.e. joint arthroplasty resulting with pain reduction, improved range of motion within the joint and subsequently improved quality of life. Implants comprised of metal, ceramics and ultra-high molecular weight polyethylene are designed to allow stabile low friction surface with low wear properties. Main disadvantage of joint arthroplasty is extreme invasiveness after which no or little room is left for additional surgical repair in cases when implant failure occurs. Furthermore, it definitely does not represent a good solution for young patients; since those patients have higher physical demands and therefore also higher chance to experience implant failure in their lifetime *(16)*. Several less invasive alternative methods are currently in use, such as various types of osteotomies, interposition arthroplasty, hemiarthroplasty, excisional arthroplasty and joint resurfacing. Although these therapeutical options leave some extra room for further surgical repairs, they should still be considered as an alternative treatment, with articular cartilage repair techniques allowed to become a treatment of choice.

Since osteoarthritis usually affects large areas of hyaline cartilage and occurs in older patients with limited intrinsic healing capacity, it is considered one of the greatest challenges in the area of cartilage repair *(12)*. It could be that effective cartilage repair techniques for focal articular lesion should be developed first, for younger patients who have better intrinsic healing capacity compared to older population. Once such treatment will be established, same/similar concepts could be used to in order to achieve significant improvement in cartilage repair in patients with osteoarthritis. Therefore, the focal articular lesion and the use of new technologies and concepts are in focus of this article.

Articular cartilage focal lesion and intrinsic healing capacity

The response of cartilage to trauma and its potential for repair depends on type of sustained injury and affection of subchondral bone *(17-20)*. Depending on the extent of cartilage damage sustained after acute articular cartilage injury, we can divide the injuries into three basic categories *(21)*. First category is comprised of injuries where extracellular matrix and/or cells are damaged, without visible disruption of articular surface. Usually, no symptoms are present, and injury cannot be detected macroscopically. Cartilage responds to these injuries with synthesis of new matrix molecules and eventually with cell proliferation. Only in cases where basic matrix structure sustains considerable damage, injury may progress. Second category includes injuries where the cartilage is disrupted, with intact subchondral bone, combined with either mechanical symptoms, joint effusions or synovitis. Because of intact subchondral bone, there is no blood clot formation; and healing potential is based on extracellular matrix synthesis and cell proliferation, still insufficient to fill the lesion gap. Third category includes cartilage injuries with underlying subchondral bone disruption (osteochondral fractures). These injuries may cause similar symptoms to those of second category, but in these injuries blood clot is formed, and bone marrow cells are invading the lesion site, finally resulting with formation of the fibrocartilaginous tissue. Similar to the second category, healing capacity and lesion progress depend on lesion location/size and joint characteristics. The full thickness cartilage defect in the joint lacks the intrinsic healing abil-

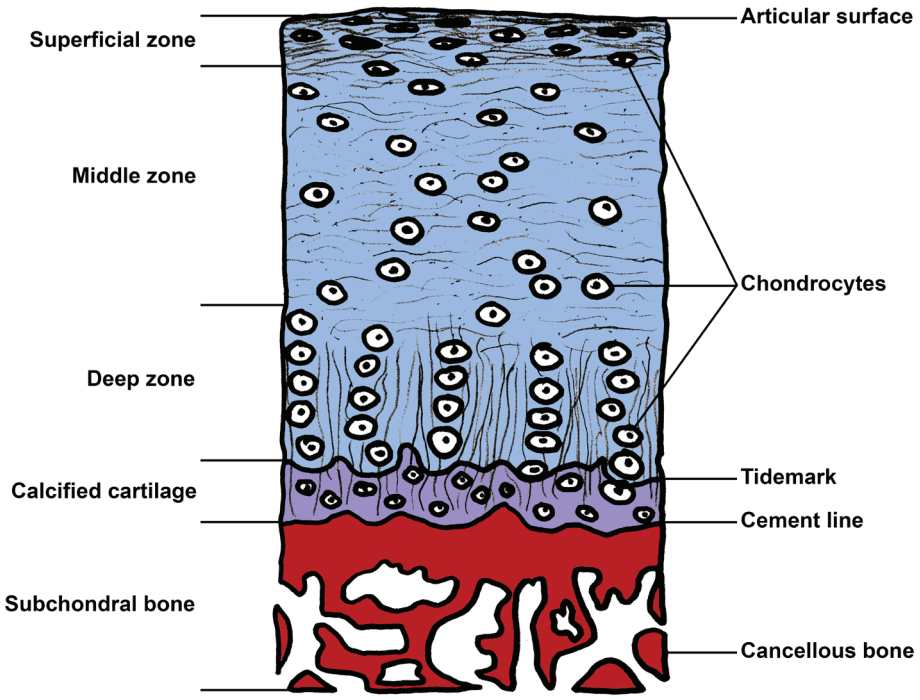

Figure 1. ***Four zones of articular cartilage.*** *Superficial, middle, deep and calcified cartilage can be easily distinguished, based on different distribution of chondrocytes and components of extracellular matrix.*

ity and full spontaneous repair is almost never achieved *(22)*. Furthermore, these defects are considered as important factor for osteoarthritis development; therefore in those patients articular cartilage repair techniques are indicated and should be performed.

ARTICULAR CARTILAGE REPAIR TECHNIQUES

Bone marrow stimulation

Several well established bone marrow stimulation (BMS) techniques were developed so far, including: abrasion arthroplasty, subchondral drilling and microfracture. The basic principle of these techniques is to abrade (abrasion arthroplasty *(23, 24)*), penetrate (drilling *(25)* or microfracture *(26)*) the subchondral bone. These techniques allow *de novo* tissue formation from a bone marrow derived blood clot situated on the lesion site. Among these, microfracture is currently considered as the gold standard technique, and it is currently the most common routinely preformed BMS technique. The surgical goal is to produce microfractures in the subchondral bone perpendicular to the surface and to be able to reach all areas of the joint with the instruments (Figure 2). The microfracture technique has been demonstrated to be an effective arthroscopic treatment for full-thickness chondral lesions. It is cost effective, technically not complicated, has an extremely low rate of associated patient morbidity, and leaves options for further treatment. It is performed using various angled awls (30°, 45°, 90°) and multiple holes, or microfractures, are then made in the exposed bone about 3 to 4 mm apart. Blood and bone marrow start to flow into the damaged area and gradually they create a clot that is known as super clot. The microfracture technique produces a rough bone surface that the clot adheres to more easily. This super clot, which completely covers the damaged area, contains various elements, including progenitor cells, mesenchymal stem cells, cytokines and growth factors that contribute to cartilage repair. Over time this clot matures and slowly transforms into fibrocartilage, which unfortunately is of inferior quality when compared to the original articular cartilage that joints have. However in most cases even this lower quality cartilage is enough for patients to return back to normal day activities and sports *(27)*.

Disadvantage of fibrocartilage is that it lacks desired hyaline cartilage properties i.e. structural, biomechanical and biochemical properties needed to provide satisfying long-term results *(28)*. Indications for microfracture include full thickness (grade IV) focal articular cartilage defect, unstable full thickness lesion and degenerative knee joint lesion (as a concomitant procedure during knee alignment). Contraindications for microfracture treatment include partial thickness defects, uncorrected axial malalignment (knee) and global osteoarthritis. Complications following microfracture treatment include mild

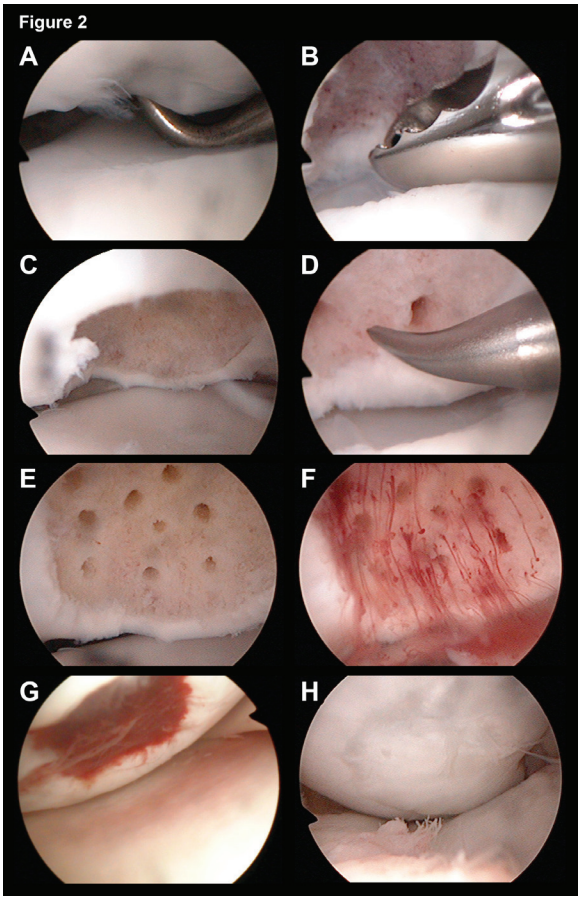

Figure 2. ***Microfracture treatment of osteochondritis dissecans.*** *(A) Probatory instrument identifying osteochondral defect present on the capitulum of the humerus. (B) Debridement of the osteochondral defect using a motorized instrument. (C) Subchondral bone is exposed and ready for microfracture, note that no signs of sclerotic bone are present; (D) Microfracture treatment performed using angled awl; (E) Multiple microfractures situated every 3-4 mm on exposed subchondral bone; (F) After releasing tourniquet blood together with bone marrow start to flow into the damaged area. (G) Super clot formed three days after microfracture treatment on the site of previous osteochondral lesion on medial femoral condyle; (H) One year after initial microfracture treatment fibrocartilage is filling the osteochondral defect on medial femoral condyle.*

transient pain, recurrent joint effusions, especially when beginning to bear weight and decreased range of motion due to scarring *(29).*

Osteochondral autograft/allograft transplantation

Osteochondral autograft transfer system (OATS) and osteochondral allograft transplantation (OALT) represent a transplantation techniques in which living osteochondral tissue is transplanted directly into the defect site. It is the only articular cartilage repair technique in which hyaline cartilage is provided and retained *(30, 31).* Such osteochondral tissue can be derived either from donor (OALT), or the patient itself (OATS). Both graft types are obtained using a sharp harvesting tool and further press-fit into a defect site. OATS grafts are usually harvested from non-load-bearing surfaces of the joint, e.g. intercondylar notch or lateral/medial trochlea above the linea terminalis for knee procedures; or anterior part of the medial or lateral talar facet for treatment of osteochondral lesions in foot and ankle *(32).* On the other side, when obtaining OALT grafts, optimal donor-recipient fit is significantly facilitated since grafts are harvested from anatomically identical area on which lesion is present. Main indications for osteochondral grafting technique are treatments of focal cartilage defects, in particular osteochondritis dissecans *(33-35)* and osteonecrosis *(36, 37).* In general, osteochondral grafting is indicated in cases of larger osteochondral defects, for cases in which bone involvement is greater than 6 to 10 mm deep, or in cases of unsuccessful previous microfracture treatment *(38).* Smaller lesions (up to 2cm^2) are suitable for OATS, while larger lesions (2cm^2 and larger) require use of OALT *(39).* Some authors have put this size limit to lesion diameter of 1 cm, a size under which OATS is used, and above which OALT is recommended. Use of OATS autografts is contraindicated in "kissing" lesions, multiple compartment full-thickness lesions, significant angular changes, history of joint infection, intraarticular fracture and rheumatoid arthritis *(40).* A few relative contraindications for OATS allografts can be fund in the literature, such as: advanced multicompartmental arthrosis, inflammatory arthropathies and the presence of altered bone metabolism (chronic steroid use, alcohol abuse, and smoking) *(41).* Several disadvantages of these techniques were reported so far, such as: limited tissue availability (autografts), donor site morbidity (autografts), questionable chondrocyte viability after storage (allografts), poor lateral tissue integration (both, auto- and allo-graft OATS) and donor to patient disease transmission (allografts) *(42).* In addition, several complications may occur such as: infections, loose body (in cases when graft loosens), graft reabsorption or cartilage degeneration if excessive pressure was applied during graft press fitting. Thromboembolic events and reflex sympathetic dystrophy may also occur *(40).*

Autologous chondrocyte implantation

In the 1970's Swedish doctor Lars Petersen, came to the idea which is nowadays considered as a basic concept in autologous chondrocyte implantation (ACI): to culture autologous chondrocytes and implant them on articular cartilage injury site under the periosteal flap. After verifying his hypothesis on the rabbit model in 1987 *(43),* Peterson et al worked on the development of the same technique for human use. The first clinical study was published

in 1994, showing efficacy of ACI for treatment of deep articular cartilage defects *(44)*. The whole concept is nowadays considered as a revolutionary breakthrough at that time, which has completely changed the cartilage repair concept/strategies.

ACI, frequently also referred as autologous chondrocyte transplantation (ACT), represents a cell-based articular cartilage repair technique in which transplanted chondrocytes are used in order to allow de novo development of the articular hyaline cartilage. Over time, original technique was further developed, following current concepts and trends in cell transplantation and biomaterial science. These modifications of the original ACI technique are popularly known as so-called "ACI generations" *(22, 45)*.

Some types of ACI techniques, regardless of the generation to which they belong, can be indicated as primary treatment choice, but they are also frequently indicated in cases when other techniques have failed. Based on the current evidence, an indication for ACI is given for symptomatic cartilage defects starting from defect sizes of more than 3-4 cm^2, up to 10 cm^2; while in the case of young and active sports patients lower limit starts at 2.5 cm^2. ACI is also frequently indicated in cases of failed previous treatment, such as microfracture or osteochondral grafting. Advanced osteoarthritis, "kissing" lesions and inflammatory arthritis represent the most important contraindications for ACI *(39, 46)*.

The "first generation" of autologous chondrocyte implantation

The classical ACI *"first generation"* is the method originally described by Brittberg et al in 1994, and consists of two stage procedure. In the first stage chondrocytes are harvested from non-load-bearing donor site of the patient and subsequently transferred to the laboratory in which cartilage is digested in order to isolate chondrocytes. The chondrocytes are expanded in the tissue culture until desired number of differentiated cells is achieved and in the second stage the cells are transplanted to the patient. In the original procedure cells were injected beneath the periosteal patch harvested from patient's proximal tibia and sewn over the chondral defect, in order to achieve complete defect filling *(44, 47)*. ACI provides satisfying long-term results with significant benefits for the patient in terms of pain relief, improved function and improvement in life quality *(48)*.

Since periosteal flap is used in the original method, it is also known under acronym PACI (Periosteum - ACI). The initial idea to use periosteum was based on the assumption that it has strong chondrogenic potential, on one side, containing mesenchymal stem cells and on the other side, providing growth factors needed for cartilage regeneration *(49, 50)*. Despite all the beneficial effects of PACI, several complications of the technique were also described, usually related with periosteal patch. They can be divided to early complications: periosteal patch detachment and delamination; and late complications, such as periosteal hypertrophy *(49, 51-54)*. In addition, harvesting the periosteal flap prolongs surgical procedure, requires larger incision and it is frequently associated with pain on the harvesting site *(55)*.

In order to develop ACI technique with fewer complications, periosteal flap was replaced by collagen membrane usually made of porcine derived type I/type III collagen *(56)*. This method is therefore widely known as CACI (Collagen - ACI), the use of which results with lower incidence of graft hypertrophy *(57, 58)*.

Characterized chondrocyte implantation (CCI) is also designated in literature as first generation ACI technique since in the second stage open procedure is performed, periosteal flap is used, under which cultured chondrocytes are transplanted *(22)*. Characterized chondrocytes represent an expanded population of chondrocytes, which expresses a marker profile (a gene score) predicting the capacity to form hyaline-like cartilage in vivo. This marker profiling is used to enhance potency of each chondrocyte batch in a way of optimizing the cell expansion procedures for preserving phenotypic characteristics and biological activity *(59, 60)*. In that way, a higher degree of homogeneity in the cartilage-forming capacity of the individual expanded cell populations is achieved.

The "second generation" of autologous chondrocyte implantation

Both, PACI and CACI require two-stage procedure, and imply the chondrocyte cultivation. Once cultivated and transplanted, chondrocytes may be unevenly distributed within the lesion site, which represents potential problem in optimal cartilage repair *(61)*. Another drawback of both, PACI and CACI, is potential chondrocyte leakage into the articular space *(62)*. In order to overcome these problems, the *"second generation"* of ACI was developed and defined as a two-stage procedure (first stage arthroscopic, second stage open or arthroscopic), with cultivated chondrocytes implantation via cell-seeded, three-dimensional, bio-absorbable scaffolds *(22, 63)*. An example of second generation ACI is a technique of matrix induced autologous chondrocyte implantation (MACI) *(64, 65)*. It is based on utilizing the porcine derived type I/type III collagen (like in CACI) as a scaffold for in vitro cultured chondrocyte seeding, with subsequent autologous serum culture application before seeded scaffold in-vivo implantation. In second ACI generation several different techniques and scaffolds are described and patented. The scaffolds include hyaluronic acid-based scaffold (Hyalograft C, HYAFF-11, Fidia Advanced Biopolymers Laboratories, Padova, Italy) *(66)*; fibrin gel-polymer matrix (BioSeed C, TransTissue Technologies GmbH, Berlin, Germany) *(67)*; a type I collagen gel ma-

trix (CaReS, Arthro Kinetics, Esslingen, Germany); a biphasic chondroitin sulfate-collagen scaffold derived from bovine pericardium (Novocart 3D, TETEC Tissue Engineering Technologies AG, Reutlingen, Germany); a solid agarose-alginate matrix (Cartipatch, TBF Genie Tissulaire, Bron, France); tissue fibrin glue (TissuCol, Baxter, Austria) *(68)*; hydroxyapatite with interconnected pores scaffold, later embedded in 3% type I collagen atellocollagen gel (IP-CHA-atellocollagen gel, Koken, Tokyo, Japan); chondrocyte-pre-seeded fibrin 3D matrix gel (Chondron, Sewon Cellontech Co. Ltd., Seoul, South Korea) *(69)* and chondrocyte-pre-seeded type I/III collagen membrane (ACI-Maix, Matricel GmbH, Herzogenrath, Germany) *(22)*.

The "third generation" of autologous chondrocyte implantation

The *"third generation"* ACI includes one- or two-stage procedures, regardless open or arthroscopic, in which in vitro treated chondrocytes are implanted within chondroinductive and chondro-conductive 3D matrices *(22)*. Example of third generation technique is technique performed in two stages, where chondrocytes processed in bioreactor are further embedded into a type I collagen matrix from bovine origin (NeoCart, Histogenics, Waltham, Massachusets, USA) *(70)*. Another example represents utilization of minced autologous hyaline cartilage spread on a 3D polyglycolic-acid-polycaprolactone scaffold and secured with staples (CAIS - cartilage autograft implantation system, DePuy, Mitek, USA).

Failure, reoperations and complications of ACI

In the literature there is large number of different clinical studies performed, usually proving safety and efficacy, but not many of them dealt with failure occurrence after ACI, prevalence of reoperations after ACI or prevalence and description of the complications after ACI. However, Harris *et al (22)* performed important systematic review and selected 82 studies comparing different generations and ACI techniques regarding postoperative complications, failure and reoperation occurrence. Interestingly, even 90% of the considered studies were rated as poor, according to the methodology score. In addition, in 41% of studies financial conflict of interest (COI) was declared, while in 22% there was no report about potential COI. According to the analysis, 5.8% of the patients experienced failures (1.5-7.7%), with mean of failure being 22 months, suggesting that first two years are critical for the failure development. Failure rates were: 7.7% for PACI, 3.3% for second generation, 1.5% for CACI and 0.83% for all-arthroscopic-stages second generation ACI. Failure rate for all open vs arthroscopic ACI's was 6.1% vs 0.83%. Overall rate of reoperation was 33%, including planned second look arthroscopies. Unplanned re-operation rates PACI, CACI, second-generation, and all-arthroscopic second-generation ACI were 27%, 5%, 5%, and 1.4%, respectively. Highest occurrence observed after PACI was usually caused by development of arthrofibrosis or graft hypertrophy. The number of studies/patients who underwent third generation techniques was too low and adequate analysis couldn't be performed; therefore, we are still lacking clear conclusions on third ACI generation.

ACI vs microfracture

Great debate is present in last couple of years regarding the cost-benefit ratio between the ACI and simpler microfracture method. Knutsen *et al (71)* have reported results of a randomized clinical study comparing ACI with microfracture 5 years after initial procedure. According to that study, both techniques provided satisfactory results in 77% of the patients, without significant difference in the clinical and radiographic results between the two groups. Authors suggested that further long-term follow-up is needed. Later on, relatively recent systematic review was performed and ACI was compared to other treatment options, such as microfracture, mosaicplasty, bone marrow derived mesenchymal stem cells etc. *(72)*. Seventeen studies were included, and according to them ACI shows better clinical outcomes and higher tissue quality compared to microfracture. Interestingly, studies comparing ACI with MACI or bone marrow derived mesenchymal stem cells demonstrated similar results of all these methods. Altogether, in all but 2 studies ACI was demonstrated as superior treatment for cartilage defects compared to other treatment options. The recent systematic review comparing ACI and microfracture by Oussedik *et al. (73)* included 34 articles. All studies showed improvement in outcome scores compared to baseline values, regardless of the treatment modality. Authors have concluded that microfracture appears to be effective in smaller lesions and ACI in larger lesions. PACI has been shown to be associated with symptomatic cartilage hypertrophy more frequently than CACI, while MACI was described as technically less challenging and in lesions greater than 4 cm^2 it has shown to be more effective than microfracture *(73)*.

In addition to above-mentioned debate, a prospective randomized multicentric study was performed, where CCI was compared to microfracture in grade III to IV symptomatic cartilage defects of the femoral condyles. This is one of the rare studies in which group of patients was followed and reported in literature in early-, mid- and long-term follow-up after initial procedure. Saris et al reported that in early follow-up (one year after treatment) CCI was associated with a tissue regenerate that was superior the one present after microfracture technique *(59)*. Later, on mid-term follow-up (three years after initial procedure) clinical outcome was evaluated with serial MRI scans. Results have revealed that treatment of articular cartilage defects with CCI results in significantly better clinical outcome compared with microfracture. Time to

treatment and chondrocyte quality were also shown to affect the final outcome. Namely, patients with shorter period from symptoms onset to initial procedure and higher chondrocyte quality had significantly better results *(74).* Long-term clinical outcome of the same group was performed 5 years after initial procedure, i.e. CCI or microfracture. Clinical outcome 5 years after initial treatment for CCI and microfracture were comparable. However, time to treatment has again showed to affect the final outcome, since in the early treatment group CCI obtained statistically significant and clinically relevant better results than microfracture. Delayed treatment, however, resulted in less predictable outcomes for CCI. Results provide strong evidence that time since onset of symptoms is an essential variable that should be taken into account in future treatment decision making *(75).*

We have to emphasize that second and third ACI generations were developed mainly in last decade, some of which even in last couple of years. Therefore, prospective randomized clinical studies are not performed yet and current results mainly rely on very few (frequently limited) studies, requiring additional long-term high-quality clinical studies to be performed, comparing all the techniques with microfracture treatment, which is still the most widely used and most extensively analyzed articular repair technique.

CONCLUSION

Chondral and osteochondral focal lesions represent a wide spectrum of disorders for which there is no single effective treatment that would fulfill all the requirements needed for adequate restoration of cartilage structure and function. Currently, a great number of established and emerging techniques are present for treatment of such lesions. This review article gives insight into available treatment options together with list of their indications, contraindications and potential complications. Having that in mind, an individualized approach can be created for each patient with a single aim: to prevent development/progression of osteoarthritis under the high mechanical demand present in everyday life of an individual.

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