Chondrocyte transplantation in treatment of the focal chondral lesions

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This graduate thesis was made at Department of Orthopaedics and Traumatology, mentored by Associate Professor Mislav Jelić and was submitted for evaluation 2021

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Summary

Focal chondral lesions are disruptions of the cartilaginous tissue in the body's joint that result in symptomatic knee lesions. The limited ability of the body to repair hyaline cartilage spontaneously, combined with the decreased quality of life of patients suffering from focal chondral lesions have led to development of surgical techniques that aim to repair the damaged chondral tissues and thus, restoring the patients quality of life. The purpose of this study is to review the technique of Autologous chondrocyte transplantation in the treatment of the focal chondral lesions together with the preoperative and postoperative procedures that accompany. Another aim of this study is the presentation of clinical outcomes that compare variations of autologous chondrocyte transplantation among themselves, and relative to other treatment modalities of the focal chondral lesions.

Abbreviations

ACT - Autologous chondrocyte transplantation
ACT-C - ACT-collagen type II/III
IKRC - International cartilage repair society
KOOS - Knee assessment and Osteoarthritis Outcome Score
MACI - Matrix Induced Autologous Chondrocyte Implantation
OATS - Osteochondral Autograft Transplant System
ROM - Range Of Motion
IKCT - Documentation Committee Knee Score
CPM - Continuous Passive Movement

Sažetak: Žarišne hondralne lezije su poremećaji hrskavičnog tkiva u zglobu tijela koji rezultiraju simptomatskim lezijama koljena. Ograničena sposobnost tijela da spontano popravi hijalinsku hrskavicu, u kombinaciji sa smanjenom kvalitetom života pacijenata koji pate od žarišnih hondralnih lezija doveli su do razvoja kirurških tehnika kojima je cilj popravak oštećenih hondralnih tkiva, a time i obnavljanje kvalitete života pacijenata . Svrha ovog istraživanja je pregledati tehniku autologne transplantacije hondrocita u liječenju fokalnih hondralnih lezija zajedno s preoperativnim i postoperativnim postupcima koji prate. Sljedeći cilj ove studije je prikaz kliničkih ishoda koji uspoređuju varijacije autologne transplantacije hondrocita među sobom i u odnosu na druge modalitete liječenja žarišnih hondralnih lezija.

Introduction

Focal chondral lesions are well demarcated disruptions in the chondral tissue of hyaline cartilage lined joints. Focal lesions of the chondral tissue are most commonly caused by trauma to joints containing articular cartilage, and are a common cause of knee pain and other related symptoms. The cartilage's architecture makes spontaneous repair after trauma very unlikely to occur, thus, various surgical techniques were developed to try and restore damaged hyaline cartilage and its physiological characteristics. The developed various techniques can be categorized into three groups, non surgical techniques, marrow stimulation techniques, and transplantation techniques. Autologous chondrocyte transplantation (ACT) is among the transplantation techniques. ACT was first introduced in 1994 by M. Brittberg (23), Brittberg performed the ACT procedure in the patellofemoral and tibiofemoral compartments of the knee joint using a periosteal flap. The following review discusses the preoperative investigations done before the surgery with indications and contraindications, what are the different variations of ACT, postoperative clinical outcomes and how the patient should be treated following the procedure. This review also includes a comparison of postoperative outcome of different ACT variations, and a comparison between ACT and other treatment modalities used in the treatment of the focal chondral lesions.

Structure and function of cartilage

Articular cartilage is a specialized tissue in the human body, cartilage does not have a blood supply, innervation, or lymphatic tissue in it, therefore, nutrition and waste removal from and to the cartilage occurs via diffusion to and from the overlying synovial fluid and from the underlying subchondral bone (1). Cartilage is made of chondrocytes and extracellular matrix that form around 95% of the tissue (1,2). The role of hyaline cartilage in joints is the reduction of friction between two or more articulating surfaces of a joint, and serving as a shock absorber.

Chondrocytes differentiate from mesenchymal stem cells. The chondrocyte is the specialized type of cell that resides in articular cartilage. Each chondrocyte forms a lacuna around itself, the lacuna is an optimal environment from which chondrocytes play a major role in the creation, maintenance, and turnover of the extracellular matrix around themselves and thus, they are essential for the existence of healthy cartilage tissue. The existence of chondrocytes in lacunae, however, means that chondrocytes are physically trapped in them, and therefore they cannot migrate and effectively repair the tissue surrounding them in the case of tissue damage (14). Communication between the chondrocytes and their external surroundings is achieved via mechanical factors, piezoelectric forces, cytokines, and growth factors rather than by adjacent cell to cell communication (3). By volume, chondrocytes make up around 2% of the total cartilage volume (2).

The extracellular matrix is made from; Water that can make up to 80% of the total cartilage by weight. Water serves as a solute for ions and as a medium for the transport of waste and nutrients. A minimum of 15 types of collagen, type II collagen is the most abundant type of collagen in cartilage (95% of collagen). Other types of collagen include types XI, IX, VI, V, IV, I, which help stabilize type II collagen. Collagen serves as a filament that helps stabilize and give cartilage its biomechanical properties (4). Proteoglycans - protein cores with glycosaminoglycans attached to them compose up to 15% of collagen's dry weight, their electrical and osmotic properties allow for the distribution of fluid and electrolytes throughout the cartilage, characterizing collagen with its compressive strength (37).

The fluid and solid phases of cartilage and the interactions between them while under external forces characterize cartilage as a tissue that is very resilient and resistant to high cyclical loads (5).

Mechanisms of cartilage injury

Lesions of the cartilaginous tissue can be categorized into two groups, degenerative lesions being one group, and focal lesions being the other.

Degenerative lesions are characterized as lesions having poorly defined edges, of varying depths. Degenerative lesions are most commonly a result of osteoarthritis. Osteoarthritis is the wearing down of the cartilage lining joints and their underlying bone. Cartilage loss from a joint results in an increase of friction forces inside the joint and a decrease in the ability of the joint to serve as an effective shock absorber. The decreased ability of the affected joint to resist shock and friction forces results in the joint's increased susceptibility to further damage and faster degradation (6). Loeser et al (90). argues that abnormal mechanical forces on a joint will provoke an inflammatory response from chondrocytes, with a resulting release of inflammatory mediators, such as leukotrienes, prostaglandins, cytokines, chemokines, and reactive oxygen species. All these inflammatory mediators stimulate the catabolic activity inside the chondral tissue, leading to further damage of the cartilage. Osteoarthritis is the most common type of chondral lesions in patients over the age of 40 (7). Factors that predispose patients to develop osteoarthritis are an Increase in weight-bearing on the joint that increases the amount of stress inflicted on the chondral tissue (7). Other conditions that predispose to osteoarthritis are loss of supportive structures in the knee joint i.e. ligament damage and meniscal tears that increase the amount of stress on the cartilage (8,9).

The second group of lesions is focal chondral lesions, which are characterized by having well-demarcated edges of varying depths. Accidents and injuries during physical activity are the most common causes for the development of focal chondral lesions in patients before the age of 40 (7). The force of extensive trauma is usually enough to disrupt the cartilaginous tissue and even the underlying bone (7). Another mechanism of chondral trauma is the dislocation of the patella, which exists in about half of the osteochondral lesions found on femoral condyles (10). Osteochondritis dissecans is a condition caused by repeated microtrauma and subsequent ischemia and osteonecrosis to the subchondral bone which in turn, leaves the cartilage susceptible to damage (1,12,37).

Scores and classifications

Classification of the chondral lesions is most commonly done by the Outerbridge classification system. The classification is done by visual assessment of the chondral lesions, with an assignment of a numeric grade from 0-IV based on the results. Grade 0 - normal cartilage. Grade I - softening and swelling of the tissue (require a tactile assessment). Grade II - partial-thickness lesion with a diameter smaller than half an inch. Grade III - lesion extends to the subchondral bone and its diameter is greater than half an inch. Grade IV - subchondral bone is seen (13).

The SF-36 PF score is a useful score when measuring disability in patients (83). The Tegner and Lysholm activity scales provide a symptomatic assessment of patients with a focus on pain, limping, swelling, and other parameters (84). International cartilage repair society (IKRC), is a scoring system used in the assessment of cartilage repair (85). Documentation Committee subjective knee score (IKCT), is a measure of sports activity, function, and symptoms that was proven to be a reliable scoring system in the assessment of patients with knee-related pathologies (86). The Fugl-Meyer score is a reliable scale to measure sensorimotor function (87). Cincinnati knee rating system is a commonly used scoring system by orthopedic surgeons in follow-up assessments (88). The knee assessment and osteoarthritis outcome score (KOOS), is a reliable score that assesses knee-related activity, symptoms, and quality of life of the patient. This score is self-administered by the patient (88).

Treatment modalities for focal chondral lesions.

The avascular nature of cartilage and the reduced ability of chondrocytes to move freely and repair their surrounding extracellular matrix makes the body unable to spontaneously replace damaged hyaline cartilage without external intervention. It is known that damage to the cartilage in a joint may cause focal chondral lesions and thus predispose it to osteoarthritis, a painful condition that reduces a patient's quality of life (18). Thus, the goal of treatment should be fixing the chondral lesion and restoration of the joint's biomechanical properties with minimal symptoms.

The treatment options are; Arthroscopic treatment that consists of debridement and lavage, this technique focuses on mitigating symptoms by debriding residual tissue that may interfere with joint movement, washout of inflammatory mediators, and agents that contribute to cartilage damage and wear. Debridement and lavage can result in a symptomatic relief of symptoms (27,28,34). Dozin et al. (77), demonstrated a significant improvement of symptoms in a group of patients after arthroscopic debridement.

Among the surgical options are transplantation techniques, such as osteochondral autograft transplantation and Osteochondral allograft transplantation, in these techniques, a graft is taken from the patient's osteochondral tissue or a donor, respectively, the graft is transplanted with a tubular chisel to the surgically prepared patient's defect. Fibrocartilage is formed spontaneously in the lesion spaces between the transplanted plugs to fill the defect (29). Mosaicplasty, for example, is an osteochondral grafting technique in which small plugs are used to fill large chondral defects like pieces of a mosaic with the formation of fibrocartilage in the spaces between the plugs (29).Another technique, Osteochondral autograft transplant system (OATS) in which larger plugs are used (30). Allografting and autografting techniques aren't ideal because of the possibility of transmission of infectious agents between donor and recipient and donor site morbidity. Also, the created repair tissue after osteochondral grafting is not pure hyaline-like cartilage and consequently, the created cartilage surface may be irregular (38). The presence of fibrous tissue in the graft makes it inferior to pure hyaline cartilage in terms of durability (75). Autologous chondrocyte transplantation (ACT), a technique in which an autologous suspension culture of chondrocytes is injected into a prepared chondral defect that was previously covered with periosteum, an organic membrane, or filled with a three-dimensional scaffold. ACT aims to substitute cartilaginous defects with hyaline-like cartilage. The procedure is mainly applied to the knee joint (38). The appropriate modality of treatment is chosen based on the etiology and morphology of the defect, the patient's age, patient's compliance with the treatment protocols and their motivation for the rehabilitation process, level of physical activity, and accompanying defects that affect the stability of the joint (14,34). Various algorithms have been proposed to help surgeons decide what treatment modality is best for their patients (22,34).

Available marrow stimulation techniques that include microfracture, drilling, and abrasions. All three techniques rely on the repair mechanism similar to the mechanisms described in microfracture. Microfracture, a technique in which multiple lesions, approximately 3 mm apart are made to exposed subchondral bone to cause bleeding of the area. Blood from the

subchondral bone will enter the joint space, mesenchymal cells and fibroblasts that follow the blood into the defect will eventually deposit fibrocartilage to fill the defect (14,15). The damaged hyaline cartilage is replaced by fibrocartilage. In the long term, replacement of hyaline cartilage with fibrocartilage is not an ideal technique because fibrocartilage is a less durable type of cartilage, and wears out faster than hyaline cartilage (16.17).

ACT vs Microfracture

It is important to mention that performing either procedure results in a significant improvement of the IKRS scores, Tegner, and Lysholm scores and, therefore obtaining a better quality of life if compared to patients that have not undergone any procedure (69). Although microfracture was shown to have the same efficacy as ACT after 1 year (74), when we put the microfracture technique in a direct comparison with ACT, ACT comes out as the superior technique in short and intermediate-term clinical outcomes based on the following studies:

A study published by Kon (67), compared the clinical outcomes between second-generation ACT and microfracture at five years postoperatively using the IKCT subjective and objective scores. The study found out that both the objective and subjective IKCT scores were better in the group that underwent ACT compared to microfracture. At two years postoperatively, the two techniques demonstrated a similar rate of return to sports in patients; this rate declined in the microfracture group after five years while it remained constant in the ACT group.Two studies performed by Knutsen (62,68) et al, demonstrated that at two years postoperatively, patients that underwent ACT had worse SF-36 scores than patients that underwent the microfracture procedure. At five years, the number of postoperative failures in the microfracture group continued to rise until it was equal to the failure rate in the ACT group. It might be argued that the failure rate in the microfracture group will increase with time to be higher than that of the ACT group, however, further follow-up research is needed to prove this assumption.A study by Based et al. (69), compared immediate and 2 years postoperative results in 40 patients that underwent matrix-associated chondrocyte implantation (MACI) versus 40 patients that underwent microfracture. The study used the ICRS objective and subjective scores, Lyshon and Tegner scores with acceptable p-values, and it was concluded that MACI resulted in superior patient outcomes at 2 years postoperatively compared to the group that underwent microfracture.

ACT vs Osteochondral autografts

Bentley(70) et al. demonstrated the superiority of ACT over mosaicplasty. A total of 100 patients were randomized to undergo either ACT or mosaicplasty. 42 patients underwent mosaicplasty while the remaining 58 underwent ACT. The patients underwent two assessments, one was postoperative and the other took place 12 months after the operation. The rating systems implemented were the Stanmore rating system and the modified Cincinnati rating score. Mosaicplasty resulted in excellent or good results in 69% of cases and 34% at 1 year postoperatively, while ACT resulted in good or excellent results in 88% and 82% postoperatively and at the 1 year follow up, respectively. On the other hand, Horas et al (71), treated forty patients with either ACT or autologous osteochondral transplantation. The patients were followed for a duration of two years with the postoperative Lyshon score, Tegner activity score, and the Fugl-Meyer score. The two methods were shown to be equally effective in the treatment of focal chondral lesions although the recovery time after ACT was longer than the recovery time after osteochondral autografting. Interestingly, postoperative histological investigations of the cartilage demonstrated the partial formation of fibrocartilage in the repair tissue after ACT, however, Gikas et al (72) proved a connection between the timing of a biopsy after ACT and the formation of favorable results on the histological investigation i.e. hyaline cartilage. Larger sample size and a longer follow-up time in this study will better illuminate which technique is superior among the two.A meta-analysis conducted by Li (73), concluded that although short-term outcomes don't demonstrate the superiority of one technique over the other, long-term postoperative results may demonstrate the superiority of ACT over OATS.

After osteochondral autografting, the surgeon immediately fills parts of the operated lesion with hyaline cartilage and the rest of the lesion is filled with fibrocartilage after a period of healing. ACT will yield hyaline cartilage after a longer period of rehabilitation compared to osteochondral autografting. . In the short term, osteochondral autografting demonstrates better results than the ACT, however, The superiority of one technique over the other remains to be determined with further research exploring long term postoperative follow up data.

Factors that may influence the decision to choose ACT over other modalities.

The size of the lesion as a factor was compared between ACT and microfracture in two studies using SF-36, Visual analog scale, and Lyshon scores postoperatively (68,69). When the two techniques were compared after two years, results for patients whose lesions were larger than 4cm^2 were better if they underwent ACT. results for patients with lesion size smaller than 4cm^4 were better if they underwent the microfracture procedure. This outcome wasn't shown to persist when the investigation was performed 5 years postoperatively (68). If the size of the lesion is in the range of 4cm^2 - 10cm^2, then MACI is a technique that demonstrates superior results compared to microfracture (69). The age of a patient is an important factor that must be taken into account when choosing the appropriate treatment modality. Postoperative results were taken one year after the procedure in a group of patients that was older than 35 and a group younger than 35, the results were obtained using the Cincinnati knee score. In general, patients before the age of 30 that were operated on with ACT had better outcomes on the SF-36 and Lysholm scores than patients that were operated over the age of 30. The duration in which the patients have been symptomatic before the operation was performed plays an important factor in the clinical outcome. Saris et al. (78), demonstrated better postoperative KOOS scores in ACT compared to microfracture that was performed in a group of patients who have been symptomatic for less than two years, and even better KOOS scores compared to a group that has been symptomatic for less than 3 years. In another study (74), patient groups that were operated on, using either 2nd generation ACT or MACI, demonstrated significantly higher modified Cincinnati scores if the duration of symptoms was less than 50 months compared to patients that were symptomatic for more than 50 months, 70.1 compared with 55.8, respectively. A group of patients who experienced symptoms for less than a year had an even better score of 79.1. The activity levels of the patients were proven to be a considerable factor in the postoperative outcomes of patients both in the ACT and in microfracture in Lysholm, SF-36, and visual analog scale (68). The activity level was not correlated with a better outcome in either technique. It is important to note that if a surgical technique such as microfracture, osteochondral grafting, or ACT was performed on the knee before the current ACT procedure, the chance that a subsequent ACT will fail is threefold. The exact mechanism responsible for this increased failure rate still needs to be discovered (76). There are no studies that have found a relationship between the localization of the defect inside the knee joint, and a better clinical outcome using either ACT techniques or any other marrow stimulating technique (75).

Preoperative investigations before ACT

It is necessary to investigate the patient clinically and radiographically to find out whether they are good candidates for autologous chondrocyte transplantation with other inclusion and exclusion criteria in mind. The physician has to take the patient's history and then perform a complete physical examination with an assessment of the range of motion to better understand the etiology and extent of symptoms (24). Standing lateral radiographs, standing long alignment radiographs of the ankle knee and hip, standing anteroposterior, skyline, and Rosenberg radiographs are all used to identify concomitant conditions that may affect clinical outcome after the procedure if not treated i.e. joint space narrowing, osteophytes, ligamentous instability, meniscal deficiency, and a varus or valgus deformity (25). MRI can also be used as a useful tool in the investigation of the focal chondral lesions in the knee (26).

Inclusion criteria

Several patient factors will favor choosing ACT as a surgical option for the optimal outcome of treatment. Most importantly, the lesion treated has to be symptomatic, and the clinical symptoms need to be correlated with the size and location of the lesions. The range of motion of the joint has to be assessed. Assessment for patellofemoral maltracking needs to be performed because patellofemoral maltracking can pose a mechanical problem after the procedure, especially when the lesions are located in the patella or the femoral trochlea (20). Full-thickness, Outerbridge-grade III or IV chondral lesions located in the femoral trochlea or one of the femoral condyles result in the best outcomes(85% to 90% of patients improved). Lesions on the articular surface of the tibia and the patella result in good outcomes (improvement in 70% to 80% of patients) (19). The size of the treated lesion should be at least 2cm^2 (20) and no larger than 12cm^12 (22). In one study (21), treatment of patients diagnosed with Osteochondritis dissecans resulted in a successful clinical result in 90% of the treated patients. The patient's age has to be between 13-55 for favorable outcomes (22,23). The patient has to be aware of the rehabilitation protocol and comply with it. ACT is indicated when other treatment modalities in the attempt of correcting focal chondral lesions have failed (20).

Exclusion criteria

Because of a high regenerative ability of an open epiphyseal plate, the ACT is contraindicated in patients whose epiphyseal plates have not closed yet, children and adolescents (22). If a patient is older than 55 years of age, a total knee replacement is a preferred treatment for the correction of chondral lesions because of the limited lifespan of a knee implant and the advanced patient's age (23). Failure to address and correct a patient's conditions that can increase the risk for the development of osteoarthritis. For example, osteochondritis dissecans, tibiofemoral valgus, or varus deformities. Loss of more than half of the thickness of the cartilage and the presence of osteophytes imply the presence of a degenerative process and is, therefore, an absolute contraindication. Lesions on the opposing cartilage of the inspected lesion with Outerbridge classification of III or IV (kissing lesions) are absolute contraindications, whereas lesions with the staging of I or II are relative contraindications (14). Inflammatory arthropathies or presence of septic arthritis within the last 12 months, familial osteoarthropathy, avascular necrosis, BMI bigger than 35 kg/m2, narcotic use, and a patient being a smoker, crystal or metabolic disorders are all absolute contraindications (19,20).

Accompanying surgical procedures

Factors that may increase the risk for the development of osteoarthritis must be addressed with corrective procedures for better postoperative outcomes (25). Cruciate insufficiency must be addressed. The cruciate ligament stabilizes the knee joint and prevents excessive shear forces from loading and damaging the cartilage (42). Concomitant or staged surgery will be done when needed to restore the cruciate ligaments function in the knee. The rehabilitation protocol for ACT contraindicates closed kinetic chain exercises for at least three months post-op to prevent injury from increased compressive loads on the knee in that case (25). A varus or a valgus deformity of the knee will be treated with a corrective osteotomy, a stable fixation of the corrected area should be placed. If a stable fixation cannot be placed, the procedure will be a staged reconstruction. Integration of treatment protocols such as range of motion (ROM) and continuous passive movement (CPM) can be indicated when a stable fixation after the correction of the deformity is achieved. Damage to the underlying bone from conditions such as osteochondritis dissecans or osteochondral fractures needs to be assessed with imaging techniques; Plain radiographs, MRI techniques, and CT. If the bony defects that are underlying

the bone are larger than 1-2 cm, the damaged bone will be replaced with a bone graft. During this time, protected weight-bearing and then weight-bearing on the joint hardens the transplanted bone enough until it can serve as a viable subchondral bone plate for the ACT. Bone healing in this procedure takes from 6 up to 9 months, then, ACT can be performed. Patellofemoral maltracking, morphological abnormalities of structures that play an active or passive role in the biomechanics of the knee joint can cause incorrect alignment and tracking of the patella. Incorrect distribution of shear forces and stress can increase the wear on cartilaginous tissue (43). The joint has to be assessed clinically and with CT or MRI imaging studies. Tibial tubercle osteotomy and soft tissue realignment are performed together with the second procedure of ACT to correct any maltracking. A rare condition, congenital trochlear dysplasia, is a possible causative agent of patellofemoral maltracking. In a patient with patellofemoral maltracking, if the knee joint is visualized by CT scans, a convex or flattened superior trochlear capturing entry point can be seen. The condition is treated surgically, a trochleoplasty and re-alignment of the patella, if needed, are performed. Peterson et al (44), demonstrated an excellent outcome in 22 out of 25 knees operated with the technique and a fair or poor outcome in the remaining 3 knees.

Generations of ACT

First-generation ACT

Arthroscopy and biopsy for suspension culture.

Arthroscopy is the final diagnostic procedure done, in which the surgeon will determine whether ACT can be performed. First, a minimally invasive arthroscopic exploration of the knee joint is performed. The area of the chondral defect is to be measured and graded. The opposing chondral tissue is also assessed and graded and cannot be higher than II (Outerbridge classification). Cartilage adjacent to the lesion will be assessed. Intact cartilage surrounding the lesion is needed for fixation of the periosteal graft in place. If there is no adjacent healthy cartilage, the synovial tissue will be sutured as a roof for the defect instead. The knee is assessed for a pathology of the meniscus. When all the mentioned above conditions are satisfactory to indicate the operation, a biopsy is performed (31). A biopsy is taken from non-weight bearing areas in the knee joint, the most common site for sampling is the trochlear

superior medial edge. If there is a patellar facet overhanging the superior medial edge of the trochlea, a biopsy of the lateral intercondylar notch is performed. Another site for biopsy is the superior transverse trochlear margin closest to the adjacent synovial membrane. A minimum of 200-300 milligrams of cartilage is harvested, the biopsy sample is then transferred to a laboratory, chondrocytes are isolated from the cartilage with the usage of enzymatic solutions and are then cultured and multiplied many-fold using proliferation control mechanisms (32,33). The cultivation of cells into sufficient amounts for treatment of the chondral defect takes between 3-5 weeks (25).

Defect preparation and cell transplantation

The aim of this procedure is the closure of the chondral defect. First, the cartilaginous defect is exposed by the surgeon. Next, the defect is debrided to the depth of healthy subchondral bone and the extent of healthy chondral tissue. The cartilage defect is then covered with a periosteal flap that is usually taken from the proximal medial tibia. The periosteal flap is then sutured to the rim of the prepared defect forming a roof over it. The periosteum and its sutures are sealed with fibrin-glue and finally, the cultivated cells from the previous biopsy are injected beneath the periosteum cover. The fibrin glue decreases the likelihood of chondrocytes leaking from the covered defect (24), In 2005, Brittberg (35) demonstrated that in this technique, chondrocytes play a major role in the formation of hyaline-like cartilaginous repair tissue in chondral defects, and the transplanted periosteum enhances the anabolic activity of the chondrocytes via paracrine mechanisms, thus, a good environment for the regeneration of hyaline-like cartilage is formed. It is known that chondrocytes and periosteal cells are producing TGF-Beta. It was speculated that this growth factor may play a key role in the promotion of differentiation of progenitor cells to chondrocytes and increased chondrogenesis in humans by the periosteum. This effect was demonstrated in a review paper in 2007 by Davidson (36). After the procedure, a rehabilitation protocol based on knowledge of the post-operational healing stages is started.

Second generation ACT

The ACT-collagen type II/III (ACT-C), was developed to try and mitigate complications that are characteristic of the first generation ACT, such as periosteal donor site morbidity, delamination, and a longer operation time (41). The ACT procedure in this generation is similar to the one described in the first generation (23). The difference between the two generations is that instead of a periosteal autograft, a commercially available collagen I/III membrane is used to cover the

chondral defect (Bio-Gide, Geistlich pharma; porcine membrane). The membrane, similarly to the osteochondral flap, is sutured to the edges of the cartilaginous defect, forming a roof, and is sealed with fibrin glue to prevent chondrocyte leakage after their introduction into the defect. Unlike the periosteal graft, the membrane is completely resorbed after a few months in vivo (40,41).

Third generation ACT

Further developments in the ACT techniques aimed to reduce the invasiveness of the procedure ,minimize the surgical time required for operation, as well as further decreasing the graft failure and reoperation rates. In this generation of ACT, three-dimensional scaffolds are seeded with cultured chondrocytes. The scaffolds are then trimmed to the size of the chondral lesions that are destined to close and secured to the adjacent cartilage and underlying chondral bone with fibrin-glue. Periosteal flaps or suturing techniques are not used in this method. In this generation of ACT the chondrocytes are not injected into the prepared defect, instead, they are evenly seeded on the scaffolds that are destined to fill the defect.

An example of third-generation ACT is matrix-induced autologous chondrocyte transplantation(MACI). In this procedure, an arthroscopic inspection of the articular cartilage is performed with a biopsy of cartilage from a non-weight bearing part of the knee joint. The harvested material undergoes a process similar to the described process in the first generation ACT, the aim is to form a sufficient quantity of autologous chondrocytes in suspension culture (38). From now on, this procedure differs from the first generation procedure: 3-4 weeks after the chondrocytes are taken for culture, the cultivated chondrocytes are placed on a special three-dimensional type I-III collagen membrane then, a second arthrotomy is performed. First, the chondral defect is prepared and its edges are trimmed to the extent of healthy cartilage and the depth of undamaged subchondral bone, it is important to prevent subchondral bone damage because of the presence of a clot will stimulate the production of fibrocartilage (14,15,38). If the subchondral bone is accidentally damaged, thrombin and epinephrine are used to prevent hemorrhage (38). After the defect is prepared, an outline of the defect is taken, and the seeded collagen three-dimensional membrane is cut according to the outline. The cut collagen-bilayer is placed together with fibrin-glue to close the defect, the range of motion of the knee is tested. Finally, the joint is closed and a rehabilitation procedure can be initiated (38). Various commercially available scaffolds are present; There are hyaluronan polymer Collagen-gel

(Hyalograft, CaRes); Collagen-membranes (ArthroMatrix, MACI, MACT), and polymers (Bio-Seed-C, Novocart3D).

Clinical outcomes

A study published by Peterson et al (81), demonstrated good clinical outcomes after first-generation ACT, in the short term as well as in the long term. The study followed 94 patients for 2 to 9 years. A pathohistological investigation of 37 patients from the study group demonstrated a direct relationship between the formation of a cartilaginous tissue rich in type II collagen fibers having sparse fibrous areas (hyaline cartilage), and favorable clinical outcomes. Good or excellent clinical results were demonstrated in 93% of patients with a single lesion localized on the femoral condyle, 89% of patients with osteochondritis dissecans, 75% of patients with anterior cruciate ligament rupture, and a chondral lesion in the femoral condyle. 67% of patients will multiple lesions in the knee, and, 65% of patients with a chondral defect on the patella.

Gomoll et al. (40), conducted a multicenter study that compared the reoperation rates at 1 year postoperatively between a group of 300 patients that underwent 1st generation ACT, with a group of 101 patients that underwent ACT-C. Only 5% of patients that underwent ACT-C required reoperation compared to 27.5% of patients that underwent 1st generation ACT. The rate of reoperation was 5.1%. In a study published by Steinwachs (41), 63 patients were followed up after ACT-C in time intervals of 6, 18, and 36 months. The post-surgical outcomes were measured with ICRS and the modified Cincinnati score, 87% of the patients were found to have excellent or good results after ACT-C. A study by Haddo et al. (82) found out that no correlation was found between the ACT-C procedure and hypertrophy of the newly formed tissue.

In a systematic review conducted by Brittberg et al. (51), whose purpose was to assess the effectiveness of MACI, found out that patients that underwent the MACI procedure, had improvements in the Lysholm scores, modified Cincinnati score, and a decrease in the visual analog pain scale. Brittberg suggests that MACI is a promising popular variation of ACT and that more research is needed to further establish its efficacy. To further explore this suggestio, a study that compared the clinical outcomes and results for the first generation ACT technique versus MACI was included, using 21 randomized patients using IKDC scores, Tegner and SF-36

scores. Although there were differences in the Lysholm score in favor of the first generation technique, It was demonstrated that the two techniques were comparable in their effectiveness, and that no technique was demonstrated to be superior at 12 or 24 months of follow-up (79). Another study compared arthroscopic ACT with open ACT for 50 and 48 patients, respectively, with a minimum of 5 years follow-up, in the initial 18 months of follow-up. The objective and subjective IKDC scores were initially considerably better in the arthroscopic group; the results for the open procedures continued to improve with follow up. Finally, at the time of the final follow-up, The difference between the scores for the two procedures was insignificant, the open ACT group's scores reached a plateau at 24 months (80). Ergglet et al. published a study where 1051 patients underwent a first-generation ACT and then followed up for one, two, and three years. The majority of the lesions were localized on the femoral condyles and were graded as III/IV Outerbridge score. At 3 years follow up, 73.6% of patients reported improvement in their symptoms, and only 8.8% reported deterioration.

Complications

A performed ACT is considered unsuccessful if two criteria are met, the first criteria is the unsatisfactory clinical improvement or deterioration resulting from the performed ACT, the second, is if the said lesion requires a surgical intervention (65). In ACT, the majority of patients operated with the technique present satisfactory, uncomplicated postoperative outcomes, and the rate of successful procedures is between 70% to 90% (61-65). A study published by Niemeyer (65), found that a clinical examination and MRI imaging of postoperative patients are not sensitive enough modalities to indicate re-operation by themselves, and therefore, revision surgery needs to be performed based on the symptoms experienced by the patients. The proportion of patients that require revision surgery is close to 15% considering all generations of ACT (64,65). Out of all possible complications that are seen, only 4 complications are prevalent in approximately 90% of cases (65). Delamination, breaking off of the layers of the newly formed cartilage from the underlying subchondral bone, is usually caused by a fissure in the cartilage. Delamination is corrected by the removal of the delaminated tissue, and the remaining defect is filled by a surgical technique chosen according to the size of the new persisting defect (65). Hypertrophy, a graft whose surface borders extend beyond the surface of the surrounding cartilage; the smooth continuity of the cartilaginous tissue is disturbed. When hypertrophic grafts are treated with bipolar electrocautery, the best postoperative results follow (65). Hypertrophy

can also be treated by shaving the hypertrophic area. When taking into account the different ACT techniques and the hypertrophy rate for each technique, the highest rate of hypertrophy resulted after treatment of first-generation ACT with 22% of 243 patients. Out of 108 patients treated by the second generation, ACT hypertrophy was found in 6%. Out of 58 patients treated with MACI, 7% demonstrated hypertrophy and out of 50 patients treated with Hyalograft-C, 4% demonstrated hypertrophy. It is important to note that these rates include asymptomatic hypertrophy (75). Inadequate integration of the newly formed tissue with the surrounding cartilage. Usually, this defect is partial, only part of the graft fails to attach itself to the surrounding cartilage. To fill this defect, marrow stimulation techniques are usually used in hope of filling the defect and creating a strong enough connection between the graft and the surrounding cartilage. Graft failure, insufficient hyaline-like cartilage have formed, either by quality or, by quantity. Graft failure can be partial or complete. The volume of the formed tissue may be insufficient or the mechanical characteristics of the tissue are not satisfactory. To overcome graft failure, therapy is chosen based on the defect size. If lesions are smaller than 2cm^2, microfracture of osteochondral grafting is done. If the lesions are larger, ACT should be performed again. Other possible complications that are seen rarely include Deep vein thrombosis, Sympathetic dystrophy of adjacent regions, superficial infection of the wound, and septic arthritis (75). The postoperative success rates of ACT vary between results published in varying studies, on the type of the ACT technique that was applied (61-64) and the location of the chondral defects in the joint, for example, hypertrophy and malfusion are complications that were, more commonly found on the patellar surface (65).

Postoperative graft remodeling and rehabilitation

To understand how to optimize the treatment protocol for patients after ACT, we need to understand the phases and the time course of remodeling for the transplanted graft. The healing process is divided into four phases.

The first phase, the Proliferation phase, can begin as soon as 4 hours postoperatively (46) and lasts approximately from 4 to 6 weeks. In this stage, the transplanted chondrocytes anchor themselves to the adjacent subchondral bone and intact cartilage mainly via type I collagen and II collagen fibers in smaller amounts (25). Production of cartilaginous matrix components is initiated and the defect is filled by new tissue. During this stage, the tissue can be described as

having a jelly-watery consistency, and therefore, it is very vulnerable to damage by shear forces. In the proliferation stage taking place after the surgery, the tissue damaged by the procedure is healing, and a postoperative intra-articular effusion is present. Important goals of the rehabilitation team in the proliferative phase are prevention of graft hypertrophy, intra-articular adhesions, and the decrease of intra-articular effusions, and finally, achieving and maintaining a good range of motion with preserved gait (45). The recommended treatment modalities in this phase are touch weight-bearing, passive ROM, and isometric muscle exercise, as well as CPM can be started as early as 6 hours postoperatively, for 6 to eight hours a day, six days a week, for six weeks (25).

The second phase, the transition phase begins four to six weeks postoperatively and lasts approximately until week 12. In this phase, chondrocytes maintain their production of extracellular matrix components with a higher relative proportion of collagen type II synthesis, a collagen type II framework is being created together with proteoglycans. The newly synthesized matrix components gradually change the tissue's consistency, which can be described as becoming increasingly spongy or gelatinous; the change of the tissue's consistency, of course, signifies its increased ability to resist damage and withstand shear forces. After 8 weeks, if the healing process was without any complications, the transplanted tissue is usually well integrated into its surroundings (51). Therefore, the outcome of possible complications in this stage of healing will be the failure of the transplanted tissue to integrate with surrounding tissue and failure to fully occupy the defect's space. Important goals of the rehabilitation team in the transition phase are achieving a gradual increase in the allowed weight-bearing on the joint and, the increase in the strength of muscles supporting the knee joint, together with restoration of a normal range of motion and the gradual return to normal gait (45). The recommended treatment modalities in this phase are discontinuation of CPM at six weeks and initiation of active ROM exercise, touch weight bearing can be modified to increasing gradual weight bearing until full weight-bearing is obtained (usually by week 12), functional exercises such as walking on a treadmill or a stationary bicycle (25).

In the third phase, the remodeling phase, roughly at months 3-6. chondrocytes continue the synthesis of the extracellular matrix. Many proteins in this matrix cross-link. The transplanted tissue integrates into the adjacent cartilage and underlying subchondral bone (30). These changes contribute to the further maturation of the transplanted cartilaginous tissue, whose consistency is gelatinous at the third month postoperatively, and soft plastic-like after six months. The tissue's resistance to shear stress and injury continues to increase (45). Patients in

this stage of healing usually feel a symptomatic relief and start walking without the use of walking aids. In this phase, complications can result from a premature return to high-impact or high-intensity physical exercise that may disrupt the healing process of the transplanted tissue (25,45). The goal of the rehabilitation team in the remodeling phase is, facilitating full neuromuscular rehabilitation by focusing on improvement of muscle strength, endurance, and the integration of functional training routines.

The fourth phase, the maturation, and stabilization phase lasts until 2 to 3 years postoperatively. The matrix components mature and further integrate into the peripheral tissues. The younger the patient is, the shorter the maturation phase (25). The recommended treatment modalities for the remodeling and maturation phases are removing the usage of assistive devices if the patient tolerates weight-bearing, walking, resistance walking. Running without pivoting of the knee joint can be integrated at months 8-12 if the patient can run, and running with pivoting can be integrated after 14 months (25). The goal of the rehabilitation team is to restore the patient's function as close as possible to their function before the onset of symptoms (45).

Postoperative Treatment modalities

The PRICES protocol (53) is an important treatment protocol that is used in early postoperative care. The purpose of the application of this protocol is the reduction in swelling, hemorrhage, pain, and inflammation. It consists of Protection, Rest, Ice (cryotherapy), Elevation, and Stabilization. Protection is initiated with the patient's education and close follow-up. It is essential to protect the operated joint to prevent graft failure. Rest is essential for the joint in the first week. Immobilizing the joint results in healing with minimal scarring (53,54). Cryotherapy is a therapeutic modality applied immediately after the procedure because it is known that an increase in joint temperature can be harmful to the articular cartilage (45). The subsequent reduction in tissue inflammation, decrease in the tissue's metabolic rate after its use, and the temperature-induced decreased rate of nociceptive signaling, make cryotherapy an effective early treatment modality (52). Compression of the joint is done with an elastic band and it is done to prevent any swelling adjacent to the operated joint. Elevation of the joint above the level of the heart is done to increase the lymphatic and venous drainage of the affected joint and therefore, decrease the local swelling. Stabilization of the joint and its adjacent bones and muscles decreases the stress and tension affecting the joint and therefore, better healing

conditions (54). Hydrotherapy is an active mobilization technique performed when the patient is partially submerged underwater. Because the buoyant force counters the effects of gravity, lower weight-bearing and lower shear forces impact the joints. Therefore, a lower effort is needed to mobilize the affected joints and the patient can return to active mobilization exercises earlier in the course of treatment. Early treatment with hydrotherapy is shown to benefit patients morally, allowing them to move relatively freely underwater, as well as having a positive effect on conditioning, muscle strength, and patient coordination. Sohn et al. (46) demonstrated in a bovine model that anchoring of free chondrocytes depends on gravity, as they sink in the liquid medium they are surrounded by. Thus, anchoring of chondrocytes in the proliferation phase is influenced by the positioning of the joint relative to gravity, therefore, correct early patient positioning may be important immediately after the procedure (49). Active and passive range of motion(ROM) exercises and continuous passive motion(CPM) are integral parts of the rehabilitation process. A paper on animal models, published by Vanwanseele (47), shows that a prolonged time of a joint demobilization will cause a decrease in cartilage thickness and its increased deformation under a load. Hirschmuller et al (45), states that passive range of motion exercises should be started as early as the patient can comply. Passive range of motion modalities include manual mobilization, isokinetic devices, and continuous passive motion. Although early postoperative immobilization of the joint is necessary, Buckwalter et. al. show that mobilization is essential for the healthy joint (55). Active and passive ROM exercises are beneficial for joint healing by increasing the local circulation, prevention of adhesions, and analgesia (55). The repetitive nature of the movements and the movements themselves increases the diffusion of nutrients and waste to and from the chondral tissue, increasing the metabolic rate of chondrocytes, the anabolic activity, and anabolic mediators such as IGF-1 inside the cartilage (54,56). Because it is known that in the early phases of healing, the cartilaginous graft is very vulnerable to shear forces and prone to damage, it is very important to increase weight-bearing and active range of motion exercises in a gradual manner. It is important to instruct patients on how to perform the relevant exercise protocol correctly and how to conduct daily activities without injuring the graft.CPM is a therapeutic technique that aims to increase postoperative mobilization of the joint and decrease the side effects that result from prolonged immobilization. Immobilization causes the adaptation of the transplanted tissue to function in an immobilized joint. A transplant in an immobilized joint will be characterized by decreased range of motion of the joint, reduced resistance to shear forces, and a decreased thickness. A study of 57 patients published by Alfredson (58) concludes that postoperative outcome of treatment of focal chondral lesions with ACT with the inclusion of a passive range of

motion combined with active motion protocol is superior when compared to a protocol where only active motion was implemented. Howard et al (48), proved the beneficial effects in passive range of motion exercises only when they were done as an accelerated protocol. Early on, partial mobilization with partial weight-bearing is allowed on the joint (54). Because the cartilaginous tissue is avascular, and nutrient exchange is done by diffusion, partial weight loading on the joint and its mobilization will enhance the diffusion of nutrients and removal of waste products in the cartilage and therefore, accelerate the remodeling process (1). Orthoses in the rehabilitation process are used as aids that help stabilize the joint and reduce a load of unnecessary shear forces on areas of the joint such as the graft site. The application of orthoses, therefore, is indicated in the early postoperative stages. A special type of orthoses is the functional unloader brace. The functional unloader brace that can be adjusted to the patient (57) is used to reduce weight-bearing from a specific compartment of a joint and increase the joint space at various joint positions while providing stabilization and protection to the joint and to the closed defect and therefore, lower shear forces will be imposed on affected areas of the joint. There are two approaches for bracing after ACT. The first approach is applying a functional unloader brace until the 8th postoperative week. The second approach is the application of a regular brace for at least 3 weeks postoperatively and then, the application of a functional unloader brace. This bracing method demonstrated a lower rate of graft failure (54). Neuromuscular adaptation and the restoration of the proprioceptive sensation. Several studies show that trauma and iatrogenic damage that is imposed on joint capsules interfere with the normal nerve conduction patterns in various joints and can cause an abnormal or a deficient sense of proprioception, as well as any other interference in the function of afferent and efferent neural pathways that were damaged as a result, i.e. motor or somatic sensation (59). Other studies show that even a contralateral joint's proprioceptive signaling can be damaged by an injury to the ACL (60). Neuromuscular exercises focus on performing an exercise with feedback and feedforward approaches that utilize the full possible range of motion movements of the joint. Rehabilitation of proprioception can be achieved with an emphasis on performing balance exercises, for example (54,59).

Discussion

After the introduction of the first generation ACT, further developments of the technique have taken place with the introduction of ACT-C, for example, that aimed to decrease the hypertrophy

and the subsequent postoperative reoperation rate, and was successful in doing so. The introduction of MACI, further aims to decrease the surgical and post surgical complication rate. When we compare clinical outcomes after different ACT techniques, it is known that an arthroscopic ACT approach is superior to an open approach for a faster recovery rate, however, long term clinical outcomes are similar between the two approaches. Furthermore, a study based comparison on the efficacy of clinical outcomes between different generations of ACT doesn't lead us to a clear conclusion whether one generation of the technique is superior over the other. When comparing ACT to other treatment modalities, ACT is known to be superior to microfracture in the long term, as fibrocartilage produced from microfracture is less durable than hyaline cartilage produced from ACT. It is not yet established whether ACT techniques are superior to osteochondral grafting techniques. Even though ACT techniques are promising, based on current studies, More research is needed to determine which treatment modality is superior for the treatment of focal chondral lesions.The ACT technique creates new hyaline cartilage instead of the disrupted hyaline cartilage in the lesion eventually. ACT is considered as an effective and safe therapeutic technique in the treatment of focal chondral lesions and conditions such as osteochondritis dissecans in the knee. ACT was proven to demonstrate very good results, especially when patients possessed patient-specific factors that resulted in better postoperative outcomes. A patient's age and weight within a certain range, the lack of structural or metabolic abnormalities that are related to the operated joint and can potentially disrupt the healing process, specific characteristics of the problematic lesion such as it's size and location, or the presence of kissing lesions are all examples of the factors needed to be taken into account preoperatively when choosing the correct treatment modality. It is important to note that relative to other treatment modalities, a long and demanding rehabilitation process is indicated postoperatively and thus, the patient is required to be instructed and being taken care of by a competent rehabilitation team.

Conclusion

Autologous chondrocyte transplantation has been proven to be an effective and promising treatment method in the treatment of the focal chondral lesions. ACT is a promising treatment method among several other methods that aim to improve symptomatic chondral lesions. Understanding of the efficacy of ACT relative to other treatment methods is still being evaluated and the techniques surrounding all methods continue to improve. The procedure benefits

younger patients that wish to remain active. Although ACT techniques continue to evolve and more information concerning its indications, the procedure itself, postoperative care and complications is available, more research is needed to continue and perfect the technique with the purpose of providing the best possible treatment options to the patient.

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