Modern Approach to Treatment of Knee Articular Cartilage Injuries – from Conservative Methods to Regenerative Medicine

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Abstract

This article presents the anatomical and pathophysiological basis of cartilage injuries, their clinical presentation and diagnostic approaches, with particular emphasis on treatment options, primarily in the knee joint. Following an overview of the anatomy and biomechanics of articular cartilage, the pathophysiology and mechanisms of injury, and the clinical features and diagnostic methods, the main focus is placed on treatment possibilities, especially surgical and biological-regenerative therapies. Surgical options include bone marrow stimulation techniques (microfracture and nanofracture), bone marrow stimulation combined with three-dimensional scaffolds, autologous chondrocyte implantation, minced autologous cartilage implantation, osteochondral transplantation, patient-specific metal implants, and corrective osteotomies. We also present a novel method using a temporary knee joint distraction device. Among biological-regenerative approaches, therapies with mesenchymal stem cells (MSCs), platelet-rich plasma (PRP), gene therapy, and bone morphogenetic proteins (BMPs) are discussed. Given the limited regenerative potential of cartilage tissue, treatment strategies must be carefully individualized and tailored to the anatomical, biomechanical, and pathophysiological characteristics of the injury. While conservative methods often provide symptomatic relief without structural restoration, surgical and biological approaches such as microfracture, autologous chondrocyte implantation, minced cartilage implantation, osteochondral transplantation, MSC therapy, PRP, gene therapy, and BMPs show promising results in functional restoration and slowing lesion progression, although their long-term efficacy and standardized protocols remain subjects of ongoing research. Ultimately, a multidisciplinary and personalized approach integrating biomechanical correction, biological stimulation, and targeted rehabilitation is crucial for optimal management of cartilage injuries and preservation of joint function.

Keywords: articular cartilage, cartilage injuries, biological therapies, surgical treatment, cartilage regeneration

Sažetak:

Suvremeni pristup liječenju ozljeda zglobne hrskavice koljena – od konzervativnih metoda do regenerativne medicine

U ovom članku prikazuje se anatomska i patofiziološka osnova problema ozljeda hrskavice, klinička slika i dijagnostika, s naglaskom na mogućnosti liječenja ozljede hrskavice prvenstveno u zglobu koljena. Nakon prikaza anatomije i biomehanike zglobne hrskavice, potom patofiziologije i mehanizma ozljede

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zglobne hrskavice, zatim prikaza kliničke slike i mogućnosti dijagnostike, glavnina članka je usmjerena na mogućnosti liječenja ozljeda hrskavice i to prvenstveno operacijskog liječenja i biološko-regenerativnih metoda liječenja. Od operacijskog liječenja prikazuju se metoda stimulacije koštane srži (mikrofrakture i nanofrakture), zatim tehnike stimulacije koštane srži uz upotrebu trodimenzionalnih nosača, autologna implantacija hondrocita, implantacija usitnjene autologne hrskavice, koštano-hrskavična transplantacija, individualizirani metalni implantati te korektivne osteotomije koljena. Također prikazujemo i novu metodu primjene privremenog distraktora koljena. Od biološko regenerativnih metoda opisuju se terapija mezenhimalnim matičnim stanicama (MSCs), plazma bogata trombocitima (PRP), genska terapija i primjena koštanih morfogenetskih proteina (BMPs). Zbog ograničenoga regenerativnog kapaciteta hrskavičnog tkiva, pristupi liječenju moraju biti pažljivo individualizirani i temeljeni na anatomskim, biomehaničkim i patofiziološkim specifičnostima hrskavične ozljede. Konzervativne metode često nude simptomatsko olakšanje, no ne dovode do strukturalne obnove. S druge strane, operacijske i biološke metode, uključujući mikrofrakture, autolognu implantaciju hondrocita, implantaciju usitnjene autologne hrskavice, koštano-hrskavične transplantacije, terapije mezenhimalnim matičnim stanicama, plazma bogata trombocitima, genska terapija i koštani morfogenetski proteini pokazuju obećavajuće rezultate u funkcionalnoj restauraciji i usporavanju progresije lezije, iako su dugoročna učinkovitost i standardizacija protokola još predmet intenzivnog istraživanja. U konačnici, multidisciplinarni i personalizirani pristup koji integrira biomehaničku korekciju, biološku stimulaciju i ciljanu rehabilitaciju ključan je za optimalno liječenje ozljeda hrskavice i očuvanje zglobne funkcije.

Ključne riječi: zglobna hrskavica, ozljede hrskavice, biološke metode liječenja, operacijsko liječenje, regeneracija hrskavice

Introduction

Articular cartilage injuries represent a significant clinical problem due to the limited regenerative capacity of cartilage tissue. Despite the development of numerous therapeutic approaches, no method has yet been able to restore hyaline cartilage with identical biomechanical properties fully. In clinical practice, lesions in younger, active individuals present a particular challenge, as the goal of treatment is not only symptom relief but also the preservation of long-term joint function and the prevention of osteoarthritis development. The aim of this review paper is to present the anatomical and pathophysiological basis of cartilage injuries, their clinical presentation and diagnostic methods, with an emphasis on current treatment options. (1–12)

Anatomy and Biomechanics of Articular Cartilage

Articular cartilage is a specialized tissue of mesenchymal origin that covers the ends of long bones and forms an integral part of all synovial joints. Its primary function is to provide a smooth, low-friction surface, enabling efficient and unrestricted joint movement. In addition, it transmits mechanical forces to the subchondral bone and absorbs significant shear and compressive stresses generated during motion. Cartilage behaves as a biphasic material composed of a fluid phase, which includes water and electrolytes, and a solid phase consisting of the extracellular matrix and cells (chondrocytes). This biphasic structure allows resistance to compression due to the interaction between proteoglycan aggregates and interstitial fluid. Under loading, the pressure of the interstitial fluid increases, preventing the immediate outflow of fluid from the matrix and maintaining mechanical stability. When the load is removed, the fluid returns into the cartilage, allowing elastic adaptation to repeated loading. Hyaline cartilage consists of chondrocytes embedded in lacunae within the extracellular matrix, which constitutes the majority of the tissue volume and contains water (65–80%), type II collagen, and proteoglycans. In addition to type II collagen, types VI, IX, X, and XI collagens are also present, along with important glycoproteins such as matrilin and fibronectin. These components collectively provide structural support, load resistance, and regulation of regenerative processes. Articular cartilage lacks a perichondrium and is neither vascularized nor innervated, which greatly limits its regenerative potential. Although chondrocytes make up only about 2% of the total tissue volume, they play a key role in synthesizing and maintaining the extracellular matrix and respond to mechanical and biochemical stimuli by regulating cartilage homeostasis. Structurally, articular cartilage consists of four functional zones: the superficial, middle, deep, and calcified zones. The superficial zone contains the *lamina splendens*, a thin layer of finely organized collagen fibers that facilitates low-friction gliding. Chondrocytes in this zone are flattened and oriented parallel to the surface. In the middle zone, the cells are

oval and randomly distributed, and the matrix contains more proteoglycans and less collagen. In the deep zone, chondrocytes are arranged in vertical columns, and the concentration of proteoglycans is highest, while collagen content is lower than in the superficial zone (Figure 1).

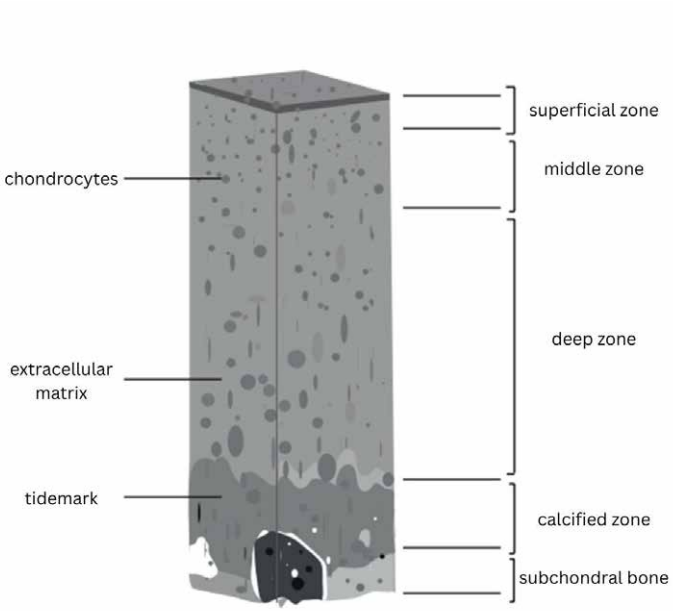

Figure 1. Depiction of the ultrastructure of hyaline cartilage by functional zones from the surface layer to the subchondral bone. (13)

Synovial fluid plays a crucial role in the lubrication and nourishment of articular cartilage. It contains hyaluronic acid, lubricin, and phospholipids, which together enable boundary lubrication and protect the articular surface from wear. In addition, the cartilage matrix has low permeability, which prevents rapid fluid extrusion during loading, thereby maintaining volume and ensuring mechanical stability. Despite its exceptional biomechanical properties, such as elasticity, resilience, and a low coefficient of friction, damaged cartilage has a very limited capacity for spontaneous healing. Studies have shown that cartilage lesions are present in up to 60–70% of individuals undergoing arthroscopy, highlighting their high prevalence and clinical significance. Cartilage lesions rarely occur in isolation and are often associated with concomitant injuries to the meniscus and ligaments. Partial-thickness defects generally do not heal, whereas in full-thickness lesions, reparative processes originate from the subchondral bone, which serves as a source of progenitor cells. These cells migrate into the defect area and contribute to the formation of new tissue. However, the repair tissue is predominantly fibrocartilaginous in nature, exhibiting inferior biomechanical properties compared to native hyaline cartilage and is susceptible to accelerated degeneration. (14,13)

Pathophysiology and Mechanisms of Cartilage Injury

Articular cartilage injuries most commonly result from acute trauma or chronic mechanical overload, particularly in younger and physically active individuals. In contrast to degenerative lesions that develop in osteoarthritis, traumatic injuries in an otherwise healthy joint usually present as localized chondral or osteochondral defects. Mechanical causes include direct impact, torsional forces, patellar dislocation, anterior cruciate ligament rupture, and contact sports injuries. These lead to disruption of the extracellular matrix structure, loss of proteoglycans, collagen rupture, and chondrocyte death, all of which compromise the biomechanical stability of the cartilage and predispose it to further damage. (15–17) Superficial injuries that do not extend into the subchondral bone fail to elicit a reparative response, as progenitor cells from the bone marrow cannot access the defect site. Conversely, injuries that penetrate the subchondral bone allow the influx of blood and marrow-derived stem cells; however, the resulting repair tissue is predominantly fibrocartilage(1), which is biomechanically inferior to native hyaline cartilage and more susceptible to degeneration (Figure 2). At the cellular level, mechanical trauma induces chondrocyte apoptosis and activates inflammatory mediators such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α), which further degrade the extracellular matrix. (1,18–20) Malalignment of the joint axis, such as valgus or varus deformities of the knee, uneven load distribution, and delayed management of ligament injuries also significantly contribute to lesion progression and the development of post-traumatic osteoarthritis. (15,16)

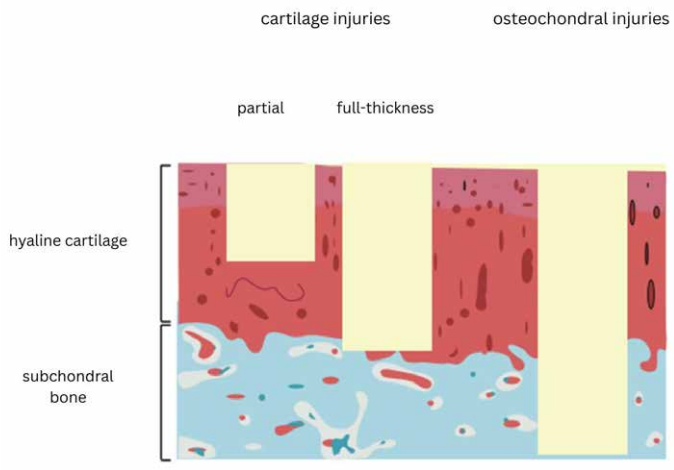

Figure 2. Depiction of cartilage and osteochondral damage according to the depth of involvement of the damaged tissue (13).

In athletes, articular cartilage injuries occur as a result of a combination of acute trauma and chronic mechanical overload, particularly in sports that involve high-energy movements such as jumping, rotation, sudden deceleration, and direct contact such as football, basketball, gymnastics, and skiing. Cartilage lesions in athletes most commonly develop due to repetitive microtrauma, which causes microcracks in the extracellular matrix, loss of proteoglycans, disruption of the collagen network, and chondrocyte apoptosis. (15,21,22) In addition to acute traumatic events such as patellar dislocation, anterior cruciate ligament (ACL) rupture, or osteochondral fractures, chronic factors including meniscal lesions, ligamentous instability, and premature return to play also represent significant risk contributors. (16,22) Studies have shown that cartilage lesions occur in up to 50% of athletes undergoing ACL reconstruction and in nearly 95% of cases following patellar dislocation.(15,21,23) Among professional football players, the incidence of symptomatic knee cartilage injuries reaches up to 36%, while magnetic resonance imaging (MRI) studies in asymptomatic basketball players demonstrate a prevalence of cartilage lesions of up to 50%. (24) Repetitive loading beyond the biomechanical threshold of cartilage disrupts homeostatic balance and triggers cartilage degradation processes mediated by metalloproteinases and cytokines, resulting in increased hydration, fissure formation, and progressive lesion expansion. Over time, these processes lead to a loss of cartilage volume and elasticity, elevated contact pressures, and progressive weakening of the cartilage matrix, rendering the tissue unable to adapt to physiological loading and increasingly susceptible to degeneration. This phenomenon is particularly pronounced in athletes with unrecognized or untreated lower limb malalignment, which further exacerbates uneven load distribution across the joint and accelerates lesion progression. In adolescents and young competitive athletes, osteochondritis dissecans is most commonly observed as a consequence of repetitive microtrauma in areas of limited vascularization, whereas in older athletes, traumatic focal defects predominate, typically occurring during high-energy movements. (1,16,22,24,25)

Clinical Presentation and Diagnostics

The clinical presentation of articular cartilage injuries varies depending on the location, depth, and extent of the lesion, but commonly includes knee pain, a sensation of instability, joint swelling, and mechanical symptoms such as catching, locking, or crepitus during movement. Although cartilage itself is avascular and aneural, pain may occur due to increased loading of the subchondral bone, particularly in osteochondral lesions. Before selecting the optimal surgical treatment, a comprehensive diagnostic evaluation is essential. This includes high-quality magnetic resonance imaging (MRI), which is considered the gold standard for the assessment of cartilage lesions. High-resolution imaging is essential for accurate evaluation and subsequent therapeutic decision-making. Diagnostic protocols typically employ specialized equipment with high-resolution sequences such as T2-weighted or Gradient Echo Imaging (GRE). The Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scoring system is also frequently used for the quantitative assessment of repaired cartilage tissue. MRI evaluation should always be complemented by weight-bearing radiographs of the lower limbs to detect possible angular deformities (varus or valgus). In the knee joint, load-bearing axis deviations greater than 5° are an indication for concomitant corrective osteotomy, which is planned together with the selected cartilage reconstruction procedure (e.g., autologous chondrocyte transplantation combined with proximal tibial osteotomy). After obtaining a detailed medical history, performing a clinical examination, and acquiring all relevant imaging studies, the final therapeutic plan should be determined on an individual basis, taking into account any concomitant injuries, including ligament damage. (2,13,21,26–31)

Treatment of Cartilage Injuries

Conservative Treatment Approaches

Conservative management of articular cartilage injuries is based on symptom control, preservation of joint function, and slowing the progression of damage. The main approaches include patient education, activity modification, physical therapy, pharmacological interventions, and the use of orthopedic aids. (16) Patient education is essential for understanding the nature of the injury and the importance of reducing load on the affected joint. Patients are advised to avoid high-impact activities that generate substantial axial forces, such as running, jumping, and sudden rotational movements, while low-impact activities like swimming and cycling are recommended. (29) Physical therapy involves targeted kinesitherapeutic exercises aimed at strengthening the periarticular musculature, improving proprioception, and maintaining the range of motion in the joint. (32) Particular emphasis is on strengthening the quadriceps in cases of knee cartilage lesions, as this reduces axial load on the damaged areas. (27) The pharmacological approach of conservative treatment most commonly includes the use of nonsteroidal anti-inflammatory drugs (NSAIDs) to control pain and inflammation. Medications such as ibuprofen and diclofenac help alleviate symptoms, although they do not promote cartilage regeneration. In cases where NSAIDs are contraindicated, paracetamol is recommended as a safer option for pain management. (16,29) Orthopedic aids, such as knee braces or specialized insoles, are used in cases of lower limb malalignment to optimize force distribution across the joint and reduce progressive cartilage damage. (33) Additional methods, including cryotherapy and manual therapy, can further help reduce pain and inflammation while improving joint mobility, particularly in the acute phase of injury. Although conservative measures can provide significant symptom relief and improve joint function, they do not result in structural

regeneration of damaged cartilage tissue. Therefore, in patients who continue to experience symptom progression or functional deterioration despite conservative therapy, surgical or regenerative treatment options should be considered. (17)

Surgical Treatment Methods

Temporary Knee Joint Distraction

Treatment of knee osteoarthritis through temporary joint distraction lasting approximately six weeks using distraction devices has shown a high success rate among treated patients, with significant and long-lasting symptom relief. However, most of the devices currently used for this purpose are designed in such a way that the knee must remain fully extended during treatment, without the possibility of movement while the distraction is applied. As a result, once these fixed devices are removed, patients frequently experience loss of normal knee mobility, requiring up to six months of intensive physical therapy to restore the preoperative range of motion. The first to use distraction for the treatment of knee osteoarthritis was Ilizarov, after whom four additional distraction devices were developed, of which two were articulated. However, these articulated distractors allowed only one or two degrees of freedom, flexion and extension.

Professor Mislav Jelić, from the Department of Orthopaedic Surgery, University of Zagreb School of Medicine, at the University Hospital Centre Zagreb, developed a novel distractor that replicates the same degrees of freedom as a natural knee joint, naming it FlexiOscar – Flexion Osteoarthritis Cartilage Repair Device. This innovative distraction device for the treatment of medial compartment knee osteoarthritis aims to temporarily separate the damaged articular surfaces for a period of six weeks, thereby unloading the affected joint area while simultaneously allowing normal knee motion. This approach prevents postoperative stiffness and loss of mobility that typically occur after the removal of rigid distractors (Figure 3).

The FlexiOscar allows the knee all six degrees of freedom of movement, enabling full range of motion from complete extension to at least 90 degrees of flexion during distraction. The device is designed as an external fixator, temporarily positioned on the medial side of the knee for a duration of six weeks. Patients treated with this method ambulate with crutches during the distraction period and simultaneously undergo physical therapy. Treatment with this innovative distraction technique developed by Mislav Jelić often completely eliminates or significantly delays the need for total knee arthroplasty, in many cases for several years. The device is protected by an international patent. (34,35)

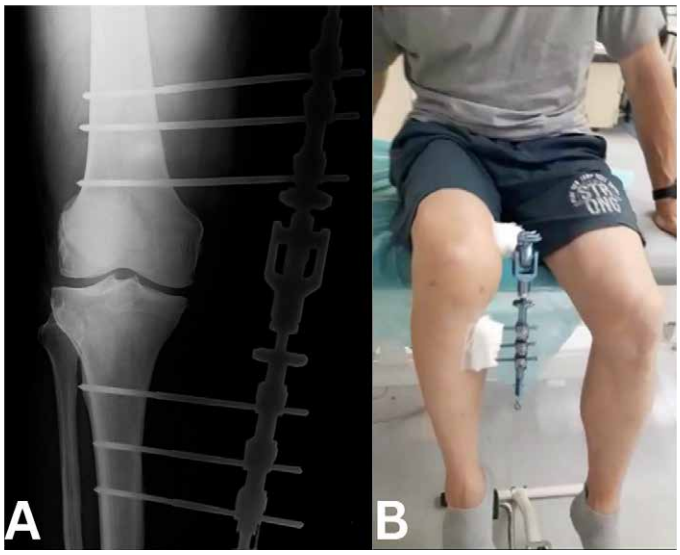

Figure 3. X-ray of the distraction device with separated articular surfaces of the medial compartment of the knee (A) and native photo of the patient during rehabilitation with 90 degrees of flexion of the knee (B) (Fig. by Mislav Jelić) (34,35)

Surgical treatment methods include many procedures aimed at restoring or replacing damaged cartilage, with the choice of technique primarily depending on the type and size of the cartilage defect. Using the example of knee cartilage injury management, the recommended treatment algorithm for femoral condyle cartilage lesions is presented, depending on the size (surface area) of the defect (Figure 4). (2)

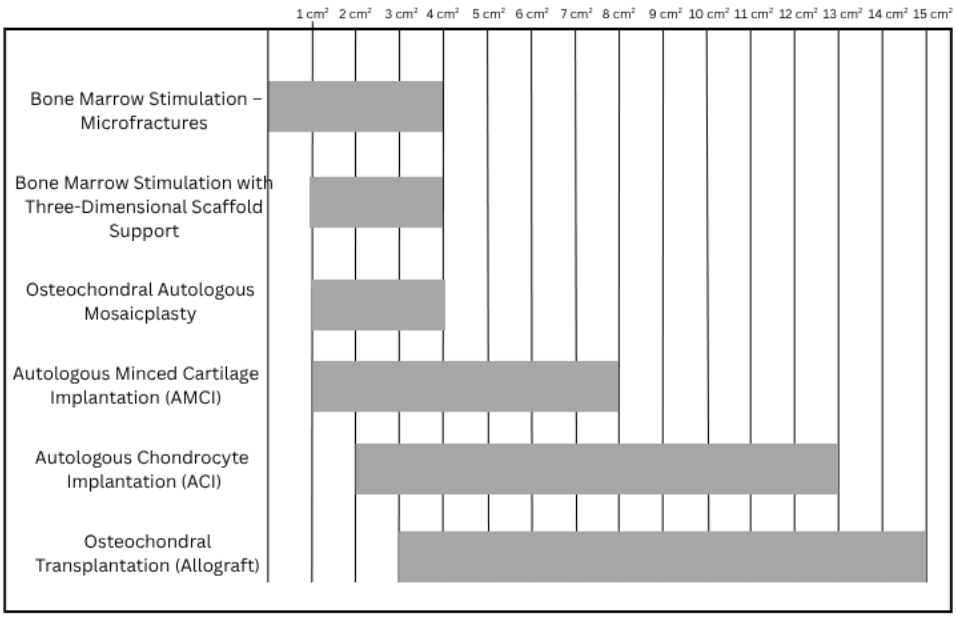

Figure 4. Recommended algorithm for treating femoral condyle cartilage injuries depending on the size (cross-section) of the lesion. (2)

Bone Marrow Stimulation

The bone marrow stimulation technique, including microfracture and nanofracture, is a minimally invasive procedure developed for the treatment of full-thickness cartilage defects and was popularized by Steadman in the late 1990s. (36,37) The technique involves creating small perforations in the subchondral bone using an arthroscopic awl, allowing the release of bone marrow elements rich in mesenchymal stem cells into the cartilage defect. This process results in the formation of fibrocartilaginous repair tissue (Figure 5).(30,37–40) Microfracture is particularly effective for small defects (up to 2–4 cm²) and in patients younger than 40 years. (17,33) Short-term outcomes often demonstrate significant improvements in joint function and pain reduction, with return-to-sport rates ranging from 44% to 77%, and approximately half of the athletes returning to their previous level of competition.(36,41)

However, the fibrocartilage formed through this technique is biomechanically inferior to native hyaline cartilage, which leads to a gradual deterioration of clinical outcomes, particularly after two to five years. (42) Factors such as lesion size, time from injury to surgery, activity level, and the presence of concomitant joint lesions significantly influence treatment outcomes. Recent innovations have aimed to enhance the microfracture technique through adjunctive methods, including the use of scaffolds (e.g., BST-CarGel, chitosan–glycerol phosphate) or the application of growth factors such as TGF-β3 and BMP-7, with the goal of improving the quality of the repair tissue and increasing clot stability. (40)

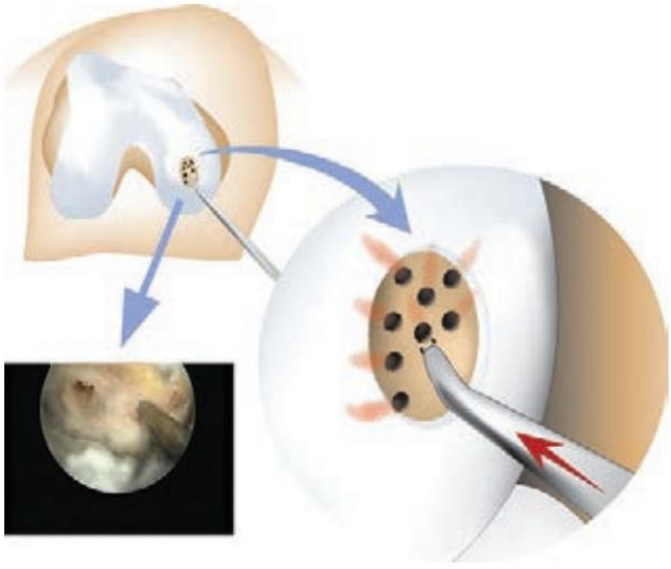

Figure 5. Schematic representation and arthroscopic image of microfracture procedure. (13)

Bone Marrow Stimulation Techniques with the Use of Three-Dimensional Scaffolds

Bone marrow stimulation techniques combined with three-dimensional scaffolds represent a significant advancement in the treatment of chondral and osteochondral knee lesions, particularly in cases involving larger defects. These scaffolds in the form of collagen membranes, hyaluronic acid matrices, or synthetic multilayer implants serve as a three-dimensional framework that stabilizes the blood clot formed after microfracture or subchondral bone drilling and guides the differentiation of mesenchymal stem cells into chondrocytes. Collagen scaffolds and hyaluronic membranes have demonstrated superior defect filling, more stable clinical outcomes, and longer-lasting results compared to isolated bone marrow stimulation techniques. More recent thermogels further enhance the volume and stability of the clot within the defect, promoting better adhesion and proliferation of regenerative cells. (2,39,43–46)

Autologous Chondrocyte Implantation (ACI)

Autologous chondrocyte implantation (ACI) represents the first biological restorative technique in which chondrocytes are harvested from a healthy, non-weight-bearing area, expanded in vitro, and subsequently implanted into the defect beneath a periosteal flap. The introduction of ACI in 1994 marked the beginning of the first effective biological therapy for deep cartilage defects. Later innovations, such as Matrix-Assisted Chondrocyte Implantation (MACI), further optimized clinical outcomes. In the MACI technique, cells are embedded within three-dimensional scaffolds, which simplifies implantation and improves cell distribution within the defect. Recent studies have demonstrated excellent results with MACI, reporting a mean five-year graft survival rate of approximately 90%, confirming the long-term effectiveness of the method (Figure 6). Indications for ACI/MACI include larger cartilage defects ranging from 2 to 13 cm², and the technique is particularly recommended for younger, physically active patients as well as professional and recreational athletes. As with microfracture techniques, a well-structured rehabilitation protocol plays a crucial role in treatment success, with return to sports typically expected around one year postoperatively. Despite its high success rate, the ACI/MACI approach faces certain challenges, including the need for two surgical procedures (biopsy and implantation), high costs, complex graft preparation, limited availability of specialized laboratories, a restricted defect size suitable for treatment, and the risk of chondrocyte dedifferentiation during the cell culture process. (2,13,26,47)

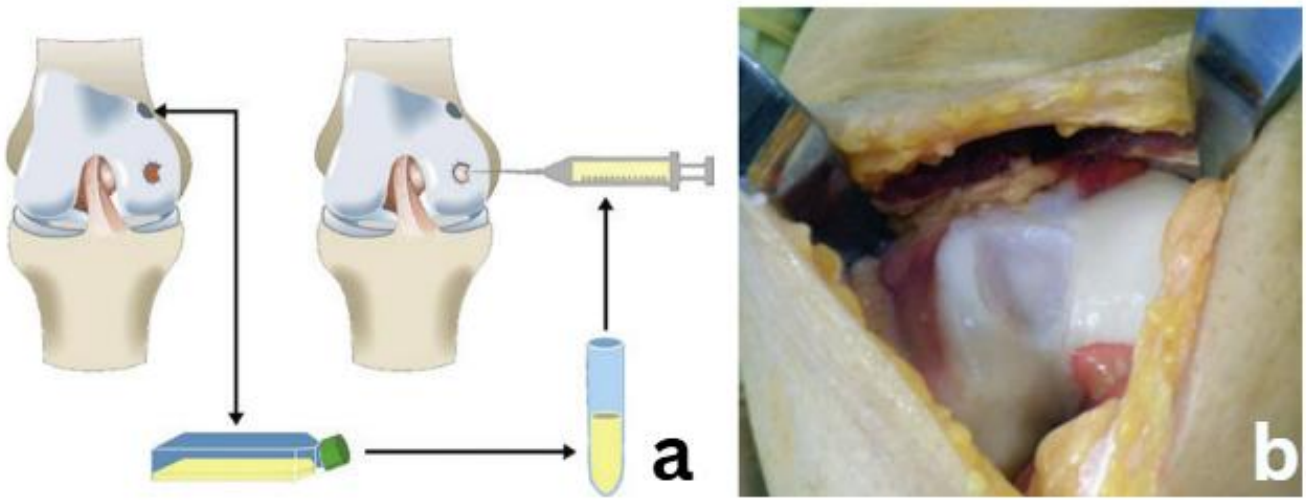

Figure 6. Autologous Chondrocyte Implantation – ACI: a) scheme of the implantation procedure; b) intraoperative image of application of autologous chondrocyte implantation using the MACI method. (13)

In addition to the ACI/MACI method, a novel and innovative approach known as Nose2Knee has recently been developed, utilizing chondrocytes derived from the nasal septum for the regeneration of knee articular cartilage (Figure 7). A promising variant of this approach is N-TEC (*Nasal Chondrocyte-based Tissue Engineered Cartilage*), a tissue-engineered mature cartilage construct which has demonstrated superior outcomes in clinical trials compared to the N-CAM (*Nasal Cultured Autologous Cartilage*) technique. After two years of follow-up, patients treated with the N-TEC method achieved significantly better clinical outcomes, as assessed by the Knee Injury and Osteoarthritis Outcome Score (KOOS), particularly in cases involving larger defects and revision surgeries. Radiological findings also confirmed higher quality cartilage regeneration. These results indicate that the Nose2Knee approach, and particularly its N TEC variant, represents a promising biological therapy for the treatment of complex cartilage defects of the knee. (11,48,49)

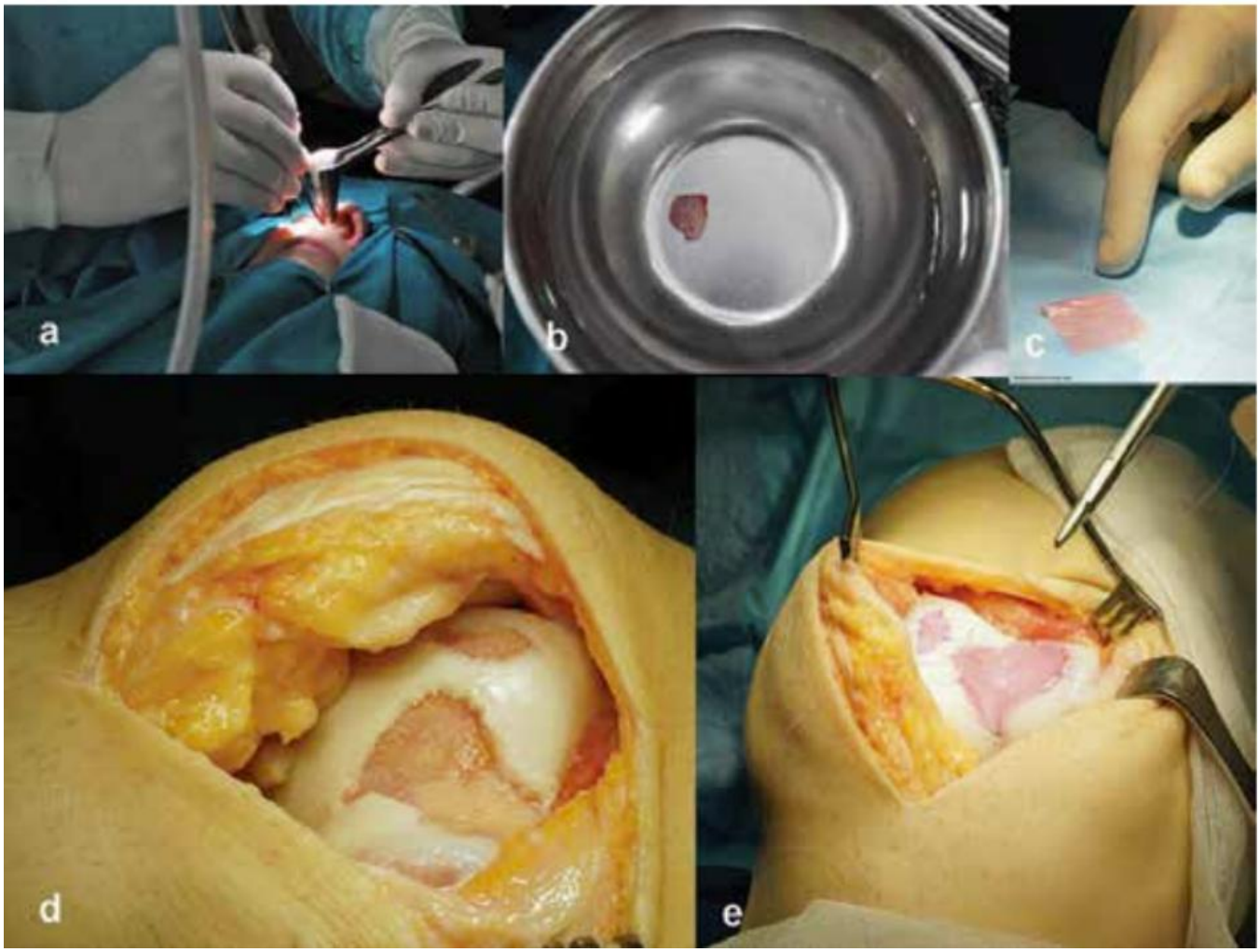

Figure 7. Autologous Chondrocyte Implantation using the "nose-to-knee" method: a) biopsy of cartilage from the nasal septum, b) piece of nasal septum cartilage from which new cartilage for implantation will be grown, c) grown cartilage, d) cartilage lesion to the femoral condyle e) implanted cartilage sutured to the edges of the lesion. (13)

Autologous Minced Cartilage Implantation – AMCI

Autologous Minced Cartilage Implantation (AMCI) represents a simple and cost-effective method of transplanting a patient's own cartilage. The procedure is performed in a single step, without the need for laboratory processing of the sample or the use of allograft material, which significantly reduces costs and simplifies regulatory requirements. The minced cartilage contains activated, undifferentiated autologous chondrocytes, providing high biological potential for regeneration. This technique can be applied in the treatment of both small and large chondral and osteochondral lesions.

Cartilage samples are harvested from the peripheral, mechanically less loaded areas surrounding the lesion, taking care not to damage functionally healthy tissue. The obtained sample is then minced, mixed with platelet rich plasma (PRP), and applied to the defect area (Figure 8). For additional stabilization of the graft, autologous fibrin is used to initiate the coagulation cascade, and the final step involves applying fibrin glue over the implanted material. Although this is a relatively new technique with a limited number of available clinical studies, current results show very good functional outcomes, and due to its simplicity and accessibility, the method is rapidly growing in clinical practice. (2,4,13,50–57)

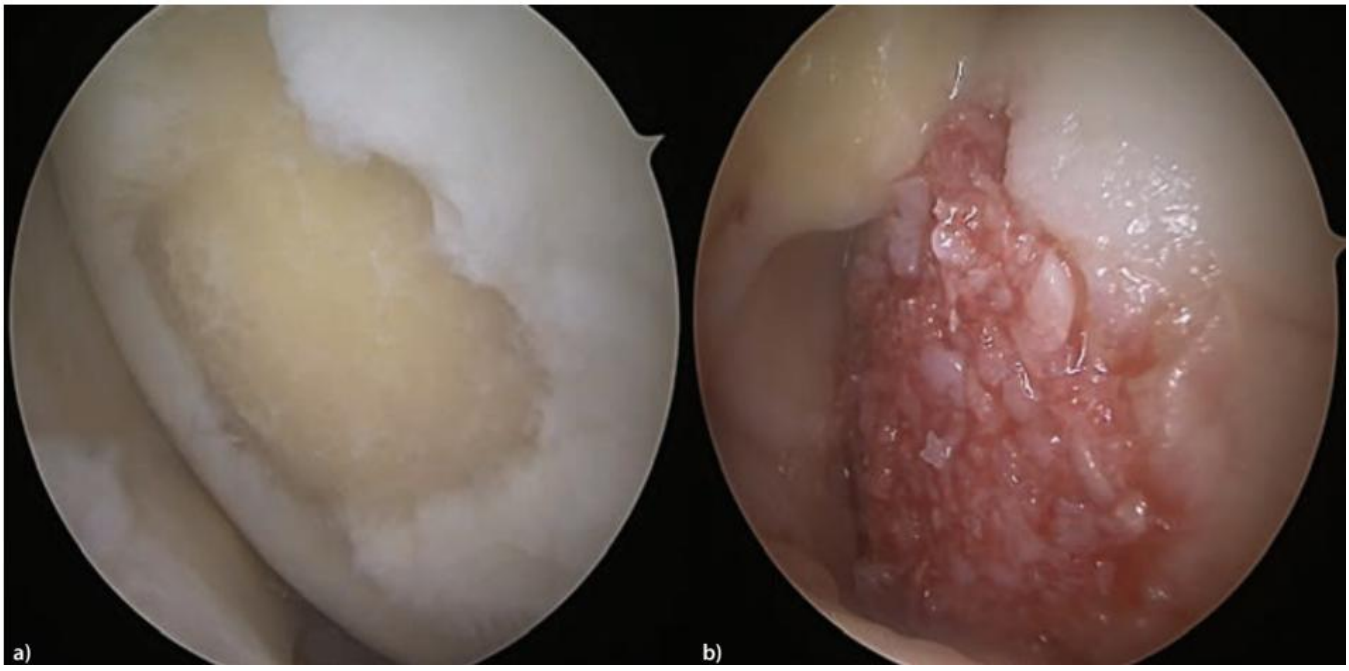

Figure 8. Implantation of minced autologous cartilage: a) arthroscopically visible cartilage lesion of the femoral condyle, b) cartilage lesion filled with a mixture of minced cartilage, PRP and autologous thrombin (4)

Osteochondral transplantation

Osteochondral transplantation is a surgical technique in which cylindrical autologous osteochondral grafts are harvested from non-weight-bearing areas of the joint and implanted into the cartilage defect (Figure 9). The goal of this method is to cover the lesion with native hyaline cartilage along with healthy subchondral bone, thereby ensuring functional and biomechanical restoration of the defect. The concept of transplantation is based on filling the defect with one or more osteochondral cylinders taken from low-load regions, where the bone part provides stable integration while the cartilaginous surface ensures optimal biomechanical properties of the reconstructed joint surface. Indications for this technique include small to medium-sized defects ranging from 1 to 4 cm^2, although for larger defects, up to 13 cm^2, multiple cylinders can be used. The method is particularly suitable for younger, active patients with isolated lesions and without significant malalignment or ligamentous instability. Grafts are most commonly harvested from the peripheral zones of the femoral condyles and are placed into the defect in a mosaic-like pattern to best reconstruct the natural contour of the articular surface.

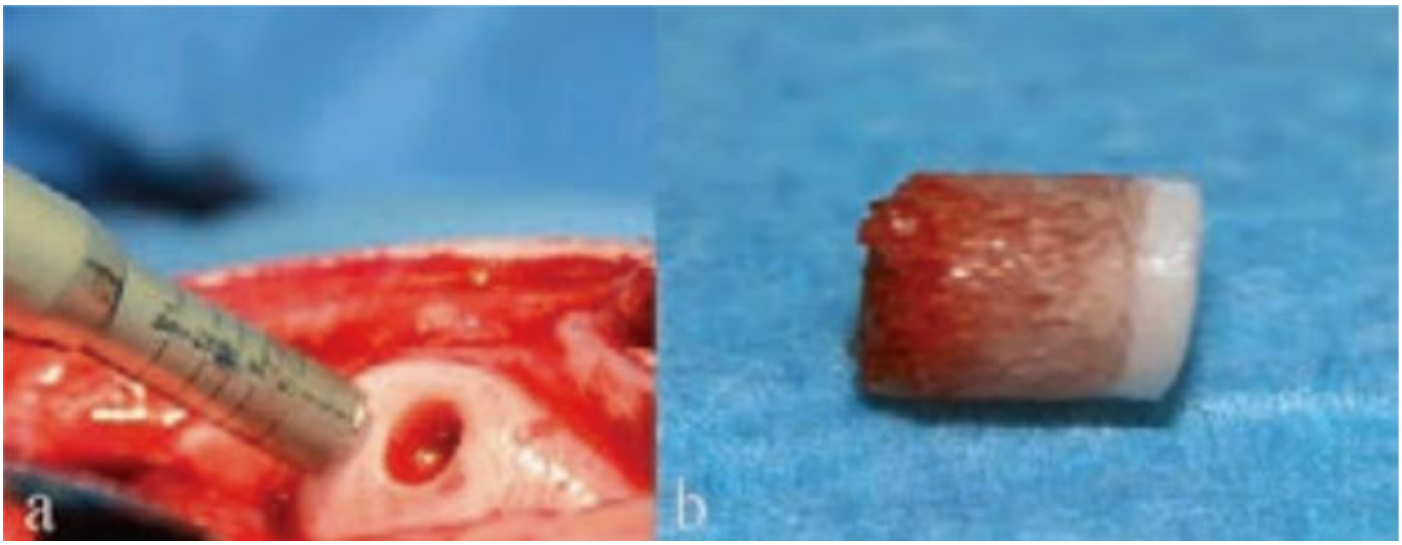

Figure 9. Prepared bone-cartilage cylinder for transplantation into the damaged part of the cartilage (13)

Despite its many advantages, osteochondral transplantation also has certain limitations, including the risk of surface irregularities if the grafts are not perfectly aligned, a limited volume of available healthy donor tissue, and potential morbidity at the donor site. Although the reported incidence of donor site complications varies among studies, occurrences of pain, hemarthrosis, and loss of function have been described, particularly when larger graft volumes are harvested. Given that this method utilizes native hyaline cartilage, osteochondral transplantation provides very good clinical outcomes, with an average ten-year graft survival rate of approximately 90% for autologous and about 80% for allogeneic transplants. Osteochondral transplantation remains a valuable option for the treatment of focal cartilage defects in active individuals, offering a high rate of functional recovery and return to sports activities. (13,58–63)

Osteochondral allografts

In cases of large osteochondral defects where biological methods and autologous transplantations are limited by tissue size and availability, osteochondral allografts are used. This technique allows for the reconstruction of extensive segments of the articular surface using cadaveric donor tissue that includes both hyaline cartilage and the corresponding subchondral bone.
Clinical studies have shown that fresh allografts retain high chondrocyte viability and can provide long-term improvements in function and pain relief, with success rates of approximately 60–75% over a period of five to ten years. The success of the procedure depends on precise graft fitting, minimal storage time, and anatomical compatibility between the donor and recipient. (2,29,61,64)

Corrective osteotomies around the knee joint, most commonly performed in the proximal part of the tibia, are used to realign the load-bearing axis of the joint and may be carried out either as standalone procedures or in combination with other intra-articular interventions. The goal of a corrective osteotomy is to offload the area of damaged articular cartilage within the joint. For example, in cases of cartilage defects of the medial femoral condyle, minced articular cartilage may be applied to the defect site, followed by an open wedge valgus-producing osteotomy of the proximal tibia. (4) (Figure 10.)

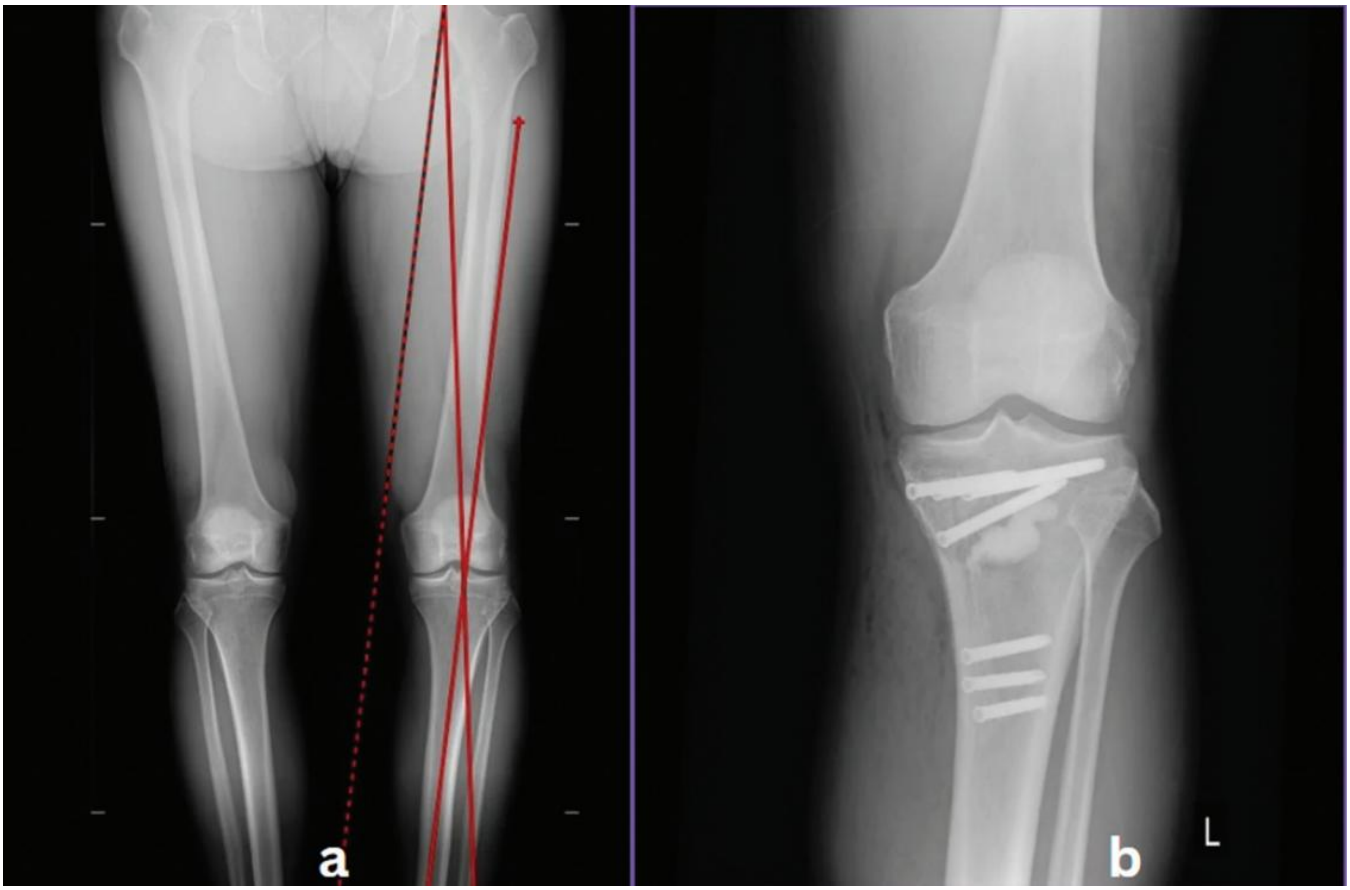

Figure 10. a) Preoperative x-ray demonstrating a varus deformity of the knee; b) postoperative x-ray following an open-wedge high tibial valgus osteotomy of the proximal tibia. (4)

Individualized metal implants

A new therapeutic option in the treatment of focal cartilage lesions of the knee is the use of individualized metal implants (Figure 11). These implants are designed based on an MRI-derived 3D model of the joint, allowing for optimal adaptation to the patient's cartilage morphology and minimal disruption of surrounding tissue. The implant is made of a cobalt-chromium alloy with a surface layer of titanium and hydroxyapatite, which enables biological integration with the bone. Clinical studies in humans have demonstrated significant pain reduction and improvement in knee function within the first twelve months after surgery, with a very low revision rate (2–7%). This method represents a valuable alternative between biological-regenerative and conventional surgical approaches, particularly for middle-aged patients in whom biological techniques are less effective and total knee arthroplasty is not yet indicated. Individualized implants provide targeted and functional joint preservation, allowing for faster recovery and delaying the need for more extensive surgical procedures. (65,66)

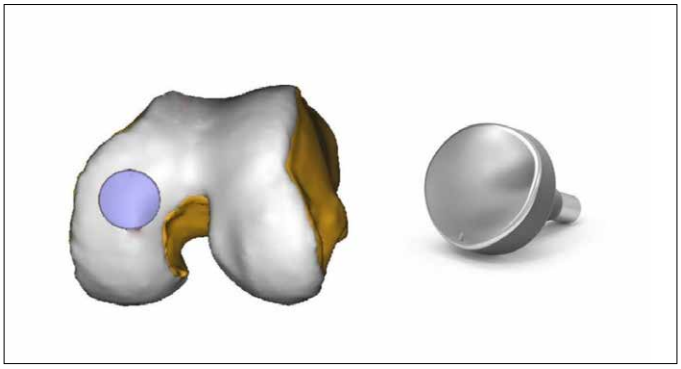

Figure 11. Patient-specific metal implant for focal chondral and osteochondral lesion (65)

Biological and Regenerative Approach – Orthobiologics

Cartilage and osteochondral lesions usually develop because of an imbalance between mechanical load and the natural ability of the tissue to heal. While surgical treatment aims mainly to reduce pain and improve joint function, modern regenerative therapies focus on restoring the balance between cartilage wear and tissue repair. These approaches are especially relevant in sports injuries and overload-related conditions. Their goal is not only to relieve symptoms but also to restore joint function in the long term. In recent decades, the development of biological and regenerative treatments has greatly changed the understanding and management of cartilage injuries. Regenerative medicine and tissue engineering have introduced new options that use the body's own healing mechanisms to create new tissue and speed up repair processes. Unlike traditional surgical techniques, these methods offer a more holistic and minimally invasive way to restore the structure and function of joints as part of the musculoskeletal system.

Mesenchymal Stem Cell Therapy

Musculoskeletal tissues, especially articular cartilage and tendons, have a limited ability to regenerate because of poor vascularization and a low number of native cells. To overcome this biological limitation, several biological approaches have been developed, including replacement therapy, which uses mature differentiated cells such as chondrocytes and tenocytes to stimulate the synthesis of new extracellular matrix (ECM). Since all tissues of interest in orthopedics and sports medicine, such as cartilage, bone, tendons, and ligaments, originate from mesenchymal stem cells (MSCs), these cells have become a major focus of regenerative research. Their advantage lies in the ability to be isolated from multiple sources, including bone marrow, adipose tissue, synovium, muscle, periosteum, umbilical cord, and dental pulp. Although it was initially believed that the differentiation of transplanted MSCs would directly lead to tissue repair, current evidence suggests that their greatest therapeutic value lies in their secretion of bioactive molecules. These molecules have immunomodulatory and anti catabolic effects and promote the regeneration of native cells, a process known as the trophic effect. For this reason, some authors propose redefining the term MSC as Mesenchymal Secreting Cells to emphasize their paracrine role. In sports regenerative medicine, MSC therapy is primarily focused on intralesional application, which has shown greater efficacy compared to intraarticular injection, especially in cartilage lesions. Although bone marrow was traditionally the main source for MSC isolation, the invasiveness of the procedure has led to increased use of alternative sources such as adipose and muscle tissue. Today, bone marrow and adipose tissue are the most common sources of MSCs used in clinical practice (Figure 12). It is important to note that samples obtained from these tissues contain a relatively low concentration of MSCs, which is why laboratory enrichment techniques are being developed to increase their yield and therapeutic effectiveness. (13,21,67–71)

Platelet-Rich Plasma – PRP

In the 21st century, the treatment of cartilage injuries has undergone a transformation with the introduction of blood-derived therapies, among which platelet-rich plasma (PRP) has gained particular prominence (Figure 12). This method quickly became popular, especially among professional athletes, due to its potential to accelerate tissue regeneration at the biological level. The main mechanism of action of PRP is based on the high concentration of cytokines and growth factors released by activated platelets, creating a pro-regenerative microenvironment that promotes healing of the damaged tissue. It is believed that the synergistic action of these bioactive molecules plays a key role in stimulating cell proliferation, angiogenesis, and extracellular matrix synthesis. A review of recent literature confirms that platelet-rich plasma is an effective therapeutic option in many orthopedic indications, with an increasing number of high-quality studies demonstrating its clinical benefits. (72) For knee osteoarthritis, a meta-analysis of 24 randomized controlled trials including 1,344 patients showed a significant improvement on the visual analogue scale (VAS) for pain in patients with osteoarthritis of the knee, hip, and ankle compared to control groups. (73) The results for knee osteoarthritis were impressive, with a mean difference of -1.03 (95% CI [-1.16, -0.9], $p < 0.05$). (72) A key factor determining the therapeutic success of PRP lies in the optimal platelet dose. The minimum effective threshold is considered to be around five billion platelets, while a pivotal study by Himanshu Bansal (74) and colleagues indicated that the ideal substrate should contain more than ten billion platelets to achieve a lasting clinical effect. Studies using less than five billion platelets show minimal or no improvement compared to controls, while those using between five and ten billion demonstrate moderate benefit. The best results are achieved with doses exceeding ten billion platelets. It is also essential to ensure proper standardization and characterization of the PRP substrate.

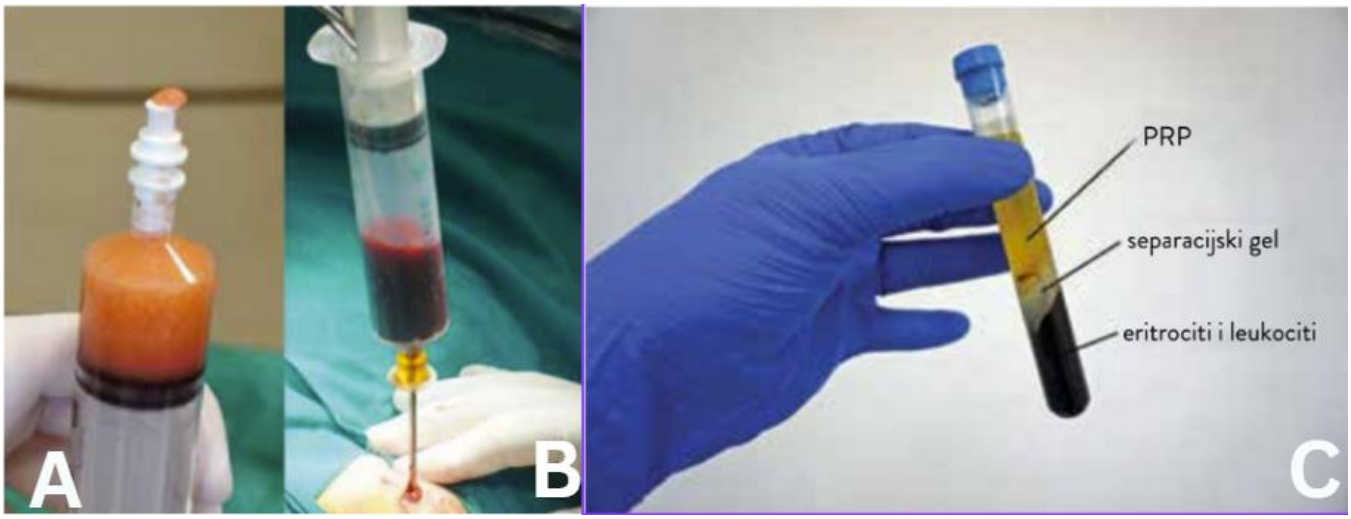

Figure 12. Samples of A) adipose tissue and B) bone marrow for the isolation of mesenchymal stem cells, C) the fraction rich in platelets (PRP) is separated from the whole blood by the centrifugation process (13)

The analysis of each PRP preparation must include precise reporting of platelet count, total dose, and platelet capture efficiency to allow for comparison of results and standardization of treatment protocols. Various factors, such as the volume of blood collected, centrifugation time and speed, and the number of rotations, significantly influence the final composition of PRP. (75) Recent studies increasingly emphasize the complex role of leukocytes in the therapeutic effects of PRP. Detailed analyses show that leukocyte-rich PRP (LR PRP) consists predominantly of lymphocytes, followed by neutrophils. This composition differs markedly from that of whole blood, in which neutrophils outnumber lymphocytes. (76) Results indicate that PRP with an optimal platelet dose (≥10 billion) and controlled leukocyte content—rich in monocytes and lymphocytes but low in neutrophils—represents the most effective formulation for orthopedic applications. These findings call for a revision of current commercial kits, which typically rely on smaller blood volumes and produce only 3–4 mL of low-dose PRP. (77) Future clinical protocols must include standardized PRP characterization, with mandatory reporting of the absolute platelet count, leukocyte composition, and platelet recovery rate. (13,50,78)

Gene Therapy

Although the direct application of bioactive molecules such as proteins and growth factors shows certain therapeutic potential, limitations such as a short half-life and difficulty maintaining therapeutic concentrations at the injury site significantly reduce their clinical effectiveness. For this reason, gene therapy has gained increasing interest as an advanced strategy that enables long-term local expression of bioactive molecules directly within the tissue. Gene therapy involves the transfer of specific genes into host cells with the aim of altering their expression and function. Depending on the type of vector used, the transfer process can occur through transduction (using viral vectors) or transfection (using non-viral methods). In the treatment of cartilage lesions, gene therapy can be applied either as *in vivo* gene therapy, where the vector carrying the therapeutic gene is delivered directly into the affected joint, or as *ex vivo* gene therapy, where cells are first isolated from the patient, genetically modified in laboratory conditions with the desired gene, and then reimplanted into the site of injury.

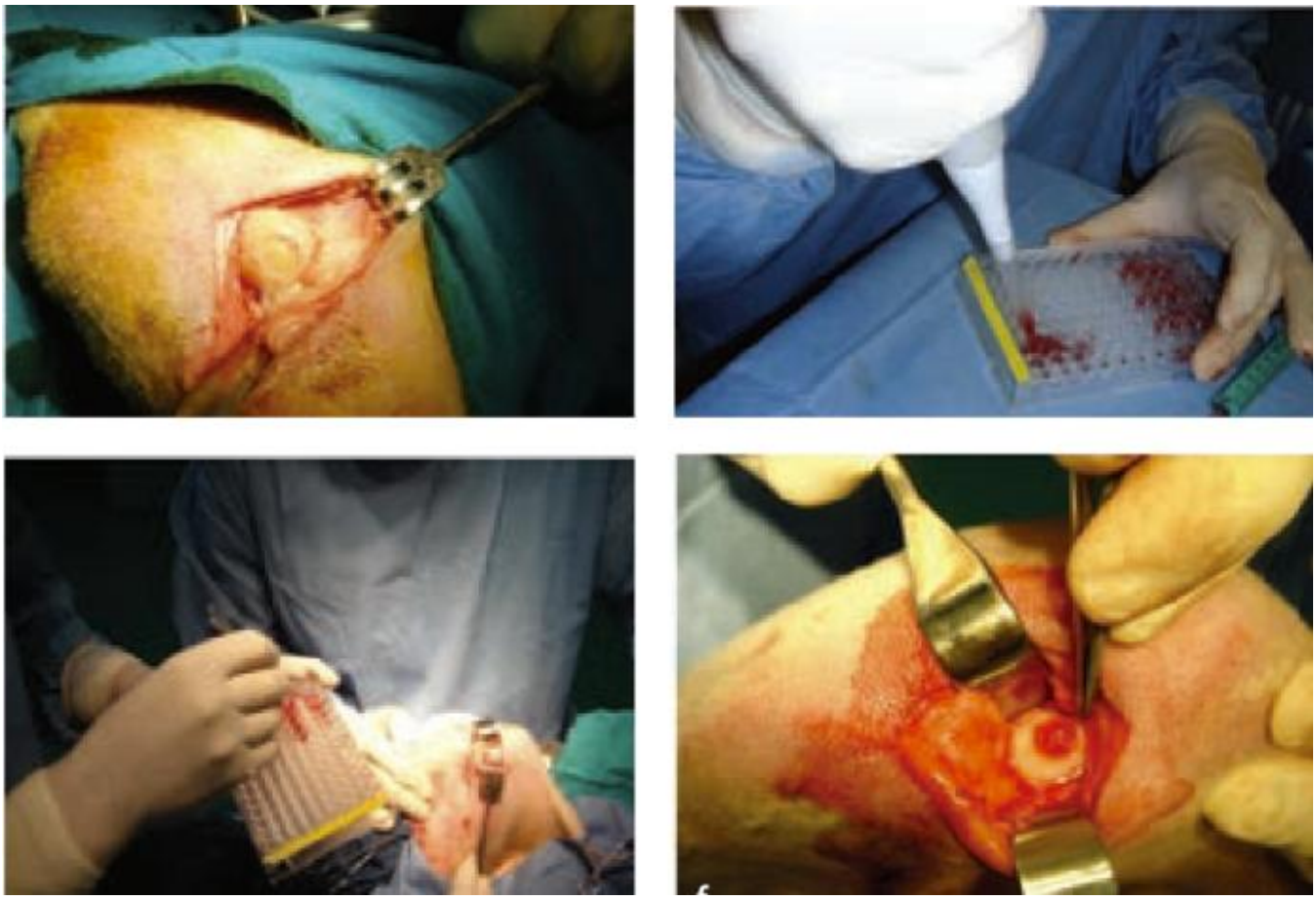

Figure 13. Ex vivo method of transplanting a genetically modified autologous bone marrow clot on an animal model of a sheep (13).

The direct method is technically simpler but often less precise due to the low rate of gene transfer into target cartilage cells, as the transduced cells are most commonly synoviocytes. In contrast, the indirect method allows better control over the type of cells used, verification of the desired protein expression before transplantation, and removal of excess viral particles to reduce the immune response. It is ex vivo gene therapy that has achieved the most significant results in experimental models and is considered the preferred method in most studies. Among innovative approaches, the so-called gene plug technique stands out, which involves intraoperative implantation of bone marrow clots that have been genetically modified beforehand, and it has shown promising results in large animal models (Figure 13). Gene therapy is also being actively investigated for the treatment of rheumatoid arthritis, with several clinical trials already underway. Although further research and long-term evaluation are needed, current findings confirm the great potential of gene therapy in orthopedics, particularly in the regeneration of articular cartilage. (3,69,79–83)

Bone Morphogenetic Proteins – BMP-s

Cartilage regeneration requires a complex and finely regulated biological response involving various signaling molecules responsible for cell activation, migration, and differentiation, as well as for the synthesis and remodeling of the extracellular matrix (ECM). In the context of cartilage repair, several growth factors and transcription factors have been identified as potentially beneficial for promoting chondrogenic differentiation and cell proliferation. These include transforming growth factors TGF-β1 and TGF-β2, which stimulate chondrogenesis of mesenchymal stem cells (MSC), fibroblast growth factor FGF-2 and insulin-like growth factor IGF-1, which enhance cell proliferation, as well as BMP-7 and cartilage-derived morphogenetic protein (CDMP), which are essential for extracellular matrix synthesis. Additionally, transcription factors such as Sox9, Runx2, Cart1, and Ets, along with signaling pathways including Wnt and Hedgehog, have been identified as key regulators of gene expression involved in the synthesis of structural components of cartilage, such as type II collagen and aggrecan. Another important strategy in

cartilage preservation and regeneration focuses on inhibiting the catabolic activity of pro-inflammatory cytokines, such as IL-1, TNF-α, and IL-17, which contribute to matrix degradation and progression of cartilage lesions under pathological conditions. (6,8,85,86)

Conclusion

Articular cartilage injuries represent a complex and increasingly common clinical challenge, particularly among young, active individuals and athletes. Due to the limited regenerative capacity of cartilage tissue, treatment approaches must be carefully individualized and based on the anatomical, biomechanical, and pathophysiological characteristics of the lesion. Conservative methods often provide symptomatic relief but do not result in structural restoration. In contrast, surgical and biological techniques, including microfracture, ACI/MACI, osteochondral transplantation, mesenchymal stem cell therapy, and PRP, show promising outcomes in functional recovery and slowing lesion progression, although their long-term efficacy and protocol standardization remain subjects of ongoing research. Ultimately, a multidisciplinary and personalized approach that integrates biomechanical correction, biological stimulation, and targeted rehabilitation is essential for achieving optimal treatment results and preserving joint function.

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