Treatment of Chondral Lesions in the Knee

Tratamento das lesões condrais no joelho

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Abstract

Articular cartilage injuries are common and lead to early joint deterioration and osteoarthritis. Articular cartilage repair techniques aim at forming a cartilaginous neo-tissue to support the articular load and prevent progressive degeneration. Several techniques are available for this purpose, such as microfracture and chondrocyte transplantation. However, the procedural outcome is often fibrocartilage, which does not have the same mechanical resistance as cartilaginous tissue. Procedures with autologous osteochondral graft have a morbidity risk, and tissue availability limits their use. As such, larger lesions undergo osteochondral transplantation using fresh or frozen grafts. New techniques using minced or particulate cartilage fragments or mesenchymal stem cells are promising. This paper aims to update the procedures for treating chondral lesions of the knee.

Keywords
- cell transplantation
- cartilage, articular
- knee injuries
- microfracture
- chondrocytes

Resumo

As lesões da cartilagem articular são comuns e levam à deterioração precoce da articulação e ao desenvolvimento da osteoartrite. As técnicas de reparo da cartilagem articular visam a formação de um neo-tecido cartilaginoso capaz de suportar carga articular e evitar a progressão da degeneração. Há várias técnicas disponíveis para esse fim, como a microfratura e o transplante de condrócitos. Entretanto muitas vezes o desfecho do procedimento é a formação de fibrocartilagem, que não possui a mesma resistência mecânica do tecido cartilaginoso. Em outros procedimentos, nos quais é realizado enxerto osteocondral autólogo, há risco de morbidade associada ao procedimento, além da disponibilidade limitada de tecido. Por esse motivo, o transplante osteocondral, utilizando enxertos a fresco ou congelados tem sido utilizado para lesões de maior volume. Por fim, novas técnicas utilizando fragmentos de cartilagem picada ou particulada, assim como o uso de células tronco mesenquimais se apresentam como promissores. O objetivo desse artigo é realizar uma atualização dos procedimentos para tratamento das lesões condrais do joelho.

Palavras-chave
- transplantes de células
- cartilagem articular
- traumatismos do joelho
- microfratura
- condrócitos

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Introduction

Articular cartilage is a specialized avascular, non-neural tissue covering the bony ends in synovial joints. It provides a surface for frictionless gliding, absorbing and supporting mechanical loads.[1] It consists of chondrocytes, which contribute to about 1 to 2% of tissue volume, embedded in a highly-organized dense extracellular matrix of collagen and proteoglycans.[2–4] Type II collagen is the main collagen fiber of mature articular cartilage, constituting about 90 to 95% of the total collagen weight and 10% of the dry cartilage weight.[2]

Studies on case series of knee arthroscopies show that the incidence of these injuries ranges from 19%[5] to 66%.[6] The treatment of articular cartilage injuries is difficult because of their limited intrinsic repair ability, generating high economic and social impacts.[7] The major concern is the progression of osteochondral defects to osteoarthritis.[8]

Diagnosis

The first assessment step involves a thorough history and physical examination to investigate when the injury occurred and the symptoms present. Common symptoms of articular cartilage damage include joint swelling, activity-related pain, lameness, and joint locking or an instability sensation. However, these symptoms are not specific.[9]

Screening for several clinical conditions is required before the specific treatment of chondral lesions of the knee, such as the evaluation of the cruciate and collateral ligaments, the patellofemoral joint, and the menisci. One also needs to investigate previous treatments, including surgery.[9,10] Ligament reconstruction should occur before or during the treatment of the articular cartilage lesion. Lower limb alignment evaluation rules out dynamic varus or valgus overload in the orthostatic position. All patients must undergo panoramic radiographs of the lower limbs to assess the need for corrective osteotomy. The menisci must undergo magnetic resonance imaging (MRI) and arthroscopic examination; in addition, the menisci should be preserved as much as possible. Patellofemoral joint assessment involves careful physical examination, radiographs, MRI, and, sometimes, computed tomography (CT). This allows the surgical treatment of any anatomical abnormality placing the patient at risk of recurrent dislocation or increased stress on the patellar facets.[9–11]

The investigation of variables specific to the chondral defect, including location, size, depth, defect geometry and number, subchondral bone quality, surrounding cartilage quality, and degree of defect containment, is critical before choosing a surgical procedure.[9,12] Outerbridge[13,14] classified the macroscopic alterations of the articular cartilage (►**Table 1**). However, the use of the International Cartilage Regeneration and Joint Preservation Society (ICRS) classification[15] in studies on chondral lesion treatment became more frequent (►**Table 2**).

Table 1 Outerbridge classification

Grade	Description
Grade 0	Normal
Grade I	Cartilage softening
Grade II	Fragmentation and fissure $\leq$ 0.5 inch in diameter
Grade III	Fragmentation and fissure $>$ 0.5 inch in diameter
Grade IV	Cartilage erosion with subchondral bone exposure

Table 2 International Cartilage Regeneration and Joint Preservation Society (ICRS) classification

Normal	Grade 0
Almost normal	Grade 1a – Superficial lesions/softening Grade 1b - Superficial lesions/softening and/or fissures or artificial gaps
Abnormal	Grade 2–Extension $<$ 50% thickness
Severe lesion	Grade 3a – Extension $>$ 50% thickness Grade 3b – Up to the calcified layer Grade 3c – Up to the subchondral bone surface (with no penetration) Grade 3d – Includes cartilage bulging around the lesion
Very severe lesion	Grade 4a – Subchondral bone penetration but not in the total diameter of the defect Grade 4b – Penetration in the whole diameter of the defect

Treatment

Recently, some authors suggested an algorithm to divide surgical strategies for treating joint cartilage injuries into three "Rs": repair, restoration, and regeneration.[1] Cartilage repair techniques aim to induce tissue formation at the chondral or osteochondral defect site by stimulating local cells and/or implanting cells, biological agents, and/or scaffolds in the defect. The most common among these techniques are microfracture and autologous chondrocyte transplantation.[1] Restoration techniques replace a chondral or osteochondral defect with functional hyaline cartilage and subchondral bone, such as autologous osteochondral grafting and allogeneic osteochondral transplantation.[1] Regeneration techniques comprise intervention methods resulting in the recapitulation of functional hyaline cartilage and subchondral bone.[1]

Cartilage repair techniques

Microfracture

Microfracture is a bone marrow stimulation technique introduced in the late 1980s and indicated for small Outerbridge III to IV chondral defects ($<$ 2 to 4 cm^2). It consists of subchondral bone perforations to allow the migration of mesenchymal progenitor cells and growth factors from the bone marrow. These elements form a cell-rich clot that proliferates and differentiates, originating a repair tissue to fill the chondral defect.[16–18] It demands checking the

outflow of blood and fat through the perforations with a deflated tourniquet to ensure sufficient penetration of the subchondral surface. This check must occur at the end of the procedure to not impair the arthroscopic view and allow clot formation at the cartilage defect site.[10]

Microfracture is the first line of treatment for small defects of the articular cartilage of the knee, improving function and providing medium-term pain.[19] However, it often results in a fibrocartilaginous tissue biomechanically and biochemically inferior to hyaline cartilage, vulnerable to mechanical trauma, and deteriorating 18 to 24 months after the procedure.[7,18]

A recently published systematic review reports that patients with the best prognosis after microfracture are young, present preoperative symptoms for a short time, and have a non-degenerative mechanism of injury, with small injuries or a single lesion.[20] On the other hand, subjects with a high body mass index ($> 30\,kg/m^2$), a defect bigger than 2 to $4\,cm^2$, located in the patellofemoral compartment or tibial plateau, and aged over 40 years have a worse prognosis.[21] Contraindications to microfracture include deviation of the lower limb axis, partial-thickness defects, uncontained cartilage defects, osteoarthritis, immune-mediated systemic arthritis, and inability to comply with the postoperative rehabilitation protocol.[22]

The main complications include incomplete defect filling, when the clot fills or adheres to only a portion of the lesion, bone overgrowth due to the formation of an intralesional osteophyte or elevation of the subchondral bone plate, and deterioration over time.[23]

Autologous chondrocyte implantation

Autologous chondrocyte implantation (ACI) is a recommended procedure for defects larger than 3 or $4\,cm^2$. ACI occurs in two stages.[17,18] The first stage consists of a diagnostic arthroscopic procedure and biopsy to obtain a cartilage fragment for in vitro culture and expansion for 4 to 6 weeks. The second stage is the implantation of the differentiated cells in the defect and its coverage with a periosteal flap.[9] However, it has the disadvantages of requiring two surgeries and having high costs.[18] In addition, ACI requires a longer recovery period for neotissue maturation, ranging from 6 to 12 months.[7]

Over time, ACI underwent modifications, and there are four generations of ACI to date. The first generation (P-ACI) consisted of a chondrocyte suspension injection under a periosteal flap. The second generation (C-ACI) injected a chondrocyte suspension under a collagen membrane. In the third generation, chondrocyte culture used a carrier surface or a porous matrix/scaffold. In the fourth generation, chondrocytes implant occurred in a one-step procedure.[24]

The third ACI was called MACI (matrix-assisted chondrocyte implantation) and used a type I/III collagen membrane for chondrocyte culture, followed by cell implantation in the defect.[25,26] The membrane acts as a cell carrier, distributing them at a density of 500,000 to 1,000,000 cells per cm^2, and it is easy to implant.[10] Other products have been developed and are commercially available, such as Hyalograft® C (Fidia Advanced Biopolymers, Abano Terme, Italy), which uses hyaluronic acid as a scaffold, ChondroGide (Geistlich Biomaterials, Wolhusen, Switzerland), a porcine collagen I/III membrane, and NeoCart® (Histogenics Corporation, Waltham, United States), a type I collagen scaffold.[27,28]

An observational case series analyzed outcomes from 15 patients treated with autologous matrix-induced chondrogenesis (AMIC) based on a porcine membrane of type I/III collagens. AMIC had a greater benefit in patients with larger chondral lesions evaluated per subjective clinical scores and magnetic resonance observation of cartilage repair tissue (MOCART).[29] Another study with 56 patients presenting single chondral or osteochondral lesions demonstrated that chondrocyte culture in fibrin could provide a favorable microenvironment for matrix synthesis, improving their clinical condition and activity after 1 year of follow-up.[30]

The most common complications of ACI are graft hypertrophy, commonly associated with the periosteal flap, with an incidence of 28% to 36%; insufficient cartilage regeneration, more frequent in repairs with periosteum coverage (3.8%) and using matrix (3.7%); delamination, i.e., the separation of cartilage from the underlying bone, occurring in 22.1% of cases; and inadequate/insufficient fusion, when the graft fails to incorporate itself into the adjacent cartilage, which occurs in approximately 23.1% of cases.[23]

Cartilage restoration techniques

Autologous osteochondral graft

An autologous osteochondral graft transfers osteochondral cylinders containing the patient's mature cartilage and bone from regions with relatively lower loads to those with higher joint loads. The procedure can occur through an open or arthroscopic approach.[26] It is indicated for full-thickness cartilage or larger ($> 3\,cm^2$) osteochondral defects.[17]

The retrieved cylinders must be contoured to fit the lesion site and have 6 to 10 mm in diameter. Numerous cylinders can form a mosaic to treat larger defects ($>3\,cm^2$).[10,31,32] However, using more than two large cylinders is not recommended due to morbidity at the donor site.[26] The retrieved cylinder must have 10 to 15 mm deep; this measurement requires confirmation after extraction.[26]

Cylinder fixation uses press-fit, not requiring materials. Fixation must be careful to maintain perpendicularity to the receptor site and reproduce the articular surface curvature.[9,10,26]

Its main advantages include being a single-stage procedure, cheaper than osteochondral grafting, capable of treating lesions with subchondral involvement,[10] and the lack of risk of disease transmission.[24] Its disadvantages are the self-limiting tissue amount and the morbidity at the donor site. This is why it is indicated for smaller lesions ($< 2\,cm^2$).[9,18] In addition, there is concern about fibrocartilage formation between the cylinders, resulting in mixed repair outcomes.[33] One study stated that when properly used, the mosaicplasty technique can produce excellent outcomes with good durability and functional impact, low morbidity rates, and low costs.[34]

A recently published technique described harvesting an osteochondral graft from the proximal tibiofibular joint.[35]

Osteochondral transplantation

Osteochondral transplantation involves the transplantation of a cadaver graft with viable articular cartilage and its underlying subchondral bone. It is a treatment option for lesions larger than 2.5 cm^2. It may provide a hyaline cartilage surface for deep chondral defects and fill any associated bone defects.[12]

Osteochondral transplantation is indicated for patients with symptomatic, large ($\geq 2\ cm^2$) cartilage defects secondary to trauma, intra-articular fractures, osteonecrosis, osteochondritis dissecans, and revision of previously failed cartilage procedures.[36,37] It may consist of osteochondral cylinders such as those used in mosaicplasty or larger grafts with surgical instrumentation to ascertain size compatibility to the recipient's defect.[26]

The graft storage method (e.g., frozen, cryopreserved, fresh) plays a decisive role in chondrocyte viability and immunogenicity, and time for transplantation.[38–40] Typical storage uses a specific medium between 4 °C and 37 °C.[36] Fresh grafts have the highest degree of cell viability. However, this viability starts to decrease after 14 days under 4 °C,[38] reaching 70% of viable chondrocytes up to 28 days.[41] Viability is deleterious after this period.[37]

The size compatibility between the donor and the recipient is also critical to guarantee the optimal superficial congruence, curvature, and shape to minimize the formation of joint step, load on the edge of the graft, and risk of graft failure.[37]

Its advantages include the possibility of performance in a single procedure,[9] achieving precise joint architecture, and treating large defects without morbidity to the donor site.[42] However, its disadvantages are the more difficult operative learning curve, the high cost of materials, the high rate of early reoperation (30% in two years), the availability of knee grafts with similar dimensions, and chondrocyte death by excessive handling.[36]

The technique demonstrates favorable outcomes, with radiographic consolidation in 86% of cases and good to excellent outcomes in 86 to 89% of the patients 2 years after the procedure. However, patients aged over 30 who underwent three or more previous procedures have worse outcomes.[33] In Brazil, one study reported that osteochondral transplantation was a safe procedure, resulting in short and medium-term good clinical outcomes for treating osteochondral lesions of the knee ($> 4\ cm^2$).[43] However, another study warned that lesions caused by corticosteroids, bipolar lesions, and degenerative disease present inferior long-term outcomes when using fresh grafts.[44]

Treatment perspectives

Minced or particulate cartilage

The principle of using minced or particulate autologous cartilage ("minced cartilage," "particulate cartilage," or "cartilage chips") is based on cutting healthy, viable hyaline cartilage into pieces as small as possible ($< 1\ mm^3$) until obtaining a pasty appearance. Next, the cartilage is directly implanted into the chondral or osteochondral lesion.[45,46]

Fragmentation induces repair by activating chondrocytes in migration, proliferation, and differentiation.[46] It must be performed quickly, with precise cuts (using a scalpel, shaver, or perforator), avoiding cartilage crushing, which would reduce cell viability.[45,46] The smaller the fragment, the greater the potential for chondrocyte proliferation and differentiation.[46]

The procedure, either open[47] or arthroscopically,[48] is indicated for all types of lesions (contained, isolated and unipolar), including osteochondral injuries. The fixation techniques described involve platelet-rich plasma, fibrin glue, membranes, or a combination of them.[46] Its advantages are a one-stage procedure for chondrocyte and extracellular matrix transplantation and the possibility of arthroscopy, which is quick and economically attractive. However, its limitation is the defect size.[48]

A recently described technique uses intact allogeneic juvenile joint cartilage, particulate, with fragments adhesion to the defect with fibrin adhesive. The advantage of juvenile cartilage (<13 years) is the higher chondrogenic potential compared with adult cartilage. Moreover, in laboratory conditions, it forms hyaline-like cartilage with cell viability of 40 to 45 days from collection and grafting.[49]

In the United States of America, minced autologous cartilage (Cartilage Autograft Implantation System [CAIS; DePuy/Mitek]) and allogeneic particulate juvenile cartilage (DeNovo Natural Tissue [NT]; Zimmer Inc, Warsaw, United States) techniques have been described. For CAIS, the hyaline cartilage is arthroscopically removed from an area under little load (lateral wall of the intercondylar node or trochlear margin) with an instrument that chops it into 1 to 2 mm fragments and then disperses the chopped cartilage in a biodegradable scaffold. The DeNovo NT graft implant occurs after defect preparation and dimension determination (one package for 2.5 cm^2 of defect size). Both procedures are promising, but studies suggest that further research is required to define their indications and contraindications.[17,50]

Wodzig et al.[51] had promising results when treating 18 patients with CAIS, reporting a significant improvement in joint function, quality of life, and pain in a 12-month follow-up. In addition, the radiological evaluation showed good cartilage quality in the same period per the MOCART score.

Bone marrow aspirate and bone marrow aspirate concentrate

Bone marrow aspirate is a complex mixture of cellular components, including platelets, white cells, red cells, hematopoietic precursors, and non-hematopoietic precursors.[52,53] Bone marrow aspirate concentrate (BMAC) is a mixture of bone marrow elements with mesenchymal stem cells isolated from the bone marrow obtained by one or multiple centrifugations of a bone marrow aspirate.[52,53] BMAC was investigated alone or associated with cartilage repair procedures with good clinical efficacy. However, some questions remain regarding its use, including cell source, expansion requirements, treatment timing, and amount.[53]

Microfragmented adipose tissue aspirate

The micro-fragmented adipose tissue aspirate is an innovative and safe procedure[54] deemed simple, sustainable,

minimally invasive, fast, and requiring a single stage.[55] Available methods in Brazil include Lipogems®, a non-enzymatic process using mechanical force. In this method, adipose tissue from abdominal or flank fat undergoes washing, emulsification, and microfragmention, removing blood and residues without jeopardizing the integrity of the vascular stromal niche.[56]

Expanded mesenchymal stem cells

Expanded mesenchymal stem cells in the clinical setting may be safe since there are no short and medium-term reports of major adverse events related to the treatment or the cell-retrieving process. In addition, clinical improvement and positive histological and imaging findings from some studies indicate its effectiveness.[57] However, the path may be long due to chondrogenesis and joint cartilage repair complexity.[58]

Final considerations

The treatment of articular cartilage injuries is difficult due to their limited repair capacity. Several techniques are available for treatment, ranging from bone marrow stimulation to osteochondral cylinder transplantation. All present inherent advantages and disadvantages. New procedures, including cell therapy, have shown promising potential. However, we advise caution as some methods still require further studies and approval by regulatory agencies for use in the country.

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Conflict of Interests
The authors declare no conflict of interest.

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