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Updates in biological therapies for knee injuries: menisci

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Abstract The preservation of meniscal tissue is paramount for long-term joint function, especially in younger patients who are athletically active. Many studies have reported encouraging results following the repair of meniscus tears, including both simple longitudinal tears located in the periphery and complex multiplanar tears that extend into the central third avascular region. However, most types of meniscal lesions are managed with a partial meniscectomy. Options to restore the meniscus range from an allograft transplantation to the use of synthetic and biological technologies. Recent studies have demonstrated good long-term outcomes with meniscal allograft transplantation, although the indications and techniques continue to evolve, and the long-term chondroprotective potential of this approach has yet to be determined. Several synthetic implants, most of which are approved in the European market, have shown some promise for replacing part of or the entire meniscus, including collagen meniscal implants, hydrogels, and polymer scaffolds. Currently, there is no ideal implant generated by means of tissue engineering. However, meniscus tissue engineering is a fast developing field that promises to develop an implant that mimics the histologic and biomechanical properties of a native meniscus.

Keywords Meniscus · Meniscus repair · Replacement · Meniscal allograft · Meniscus transplantation · Review · Biological therapies · Knee injuries

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Introduction

The biomechanical importance of the meniscus has proven to be unquestionable as the follow-up of patients submitted to a total or partial meniscectomy increases. In addition, the increased life expectancy of the population, coupled with the growing interest in performing physical activities throughout life, increases the need for the preservation of joint health. In this context, and in view of the limited healing capacity of meniscal injuries, the preservation, repair, reconstitution, and replacement of meniscal tissues are essential. Several studies using different experimental designs have concluded that a meniscectomy is an important predisposing factor for knee osteoarthritis [1–5]. This predisposition occurs because the characteristics of the meniscus allow this tissue to perform the well-known functions that provide improved load distribution across the chondral surface, such as increased joint congruence. The meniscus is composed of not only proteoglycans and extracellular matrix [6] but also primarily fibrocartilage that is rich in type-3 collagen [7, 8], which forms networks predominantly oriented circumferentially and radially. Therefore, part of the load imposed on the knee joint during daily activities is dissipated, resulting in lower energy transmission to the chondral surface and consequently reduced biomechanical wear. Furthermore, both menisci, and particularly the medial meniscus, have an important role in knee joint stability, especially in knees with ligament injuries, and the absence of menisci can produce the negative outcomes inherent to unstable knees [9]. Finally, the meniscal injury itself triggers an inflammatory response that ultimately leads to degenerative processes in the affected knee [10••]. Despite the poor long-term results of meniscectomies, the postoperative relief of symptoms and the early return to normal activities are notable. Therefore, meniscal injuries and secondary symptoms should not be overlooked and have motivated researchers worldwide in the last 2 decades to find alternatives for the repair or replacement of meniscal tissues to maintain joint stability. The aim of this study is to investigate and critically analyze the procedures for meniscal preservation and replacement, with an emphasis on biological therapies.

Meniscal lesion treatment options

The physical therapy should be part of the arsenal of options and is an important part of the management of these lesions. The immediate treatment of a meniscal injury should consider the rest with load as tolerated, ice, compression, and elevation site; you can add the use of nonsteroidal anti-inflammatory drugs, analgesics, and physiotherapy for initial analgesia, range of motion, and proprioception exercises elongation for a period of 8 weeks. However, the success of physical therapy depends on some characteristics of the lesion. A satisfactory outcome is usually when the lesions are small (<1.0 cm), longitudinal, partial thickness, stable, in the vascular zone or degenerative lesions in patients older than 45 years. A recent multicenter, randomized, controlled trial involving symptomatic patients 45 years of age or older with a meniscal tear did not find significant differences between the groups in functional improvement 6 months after randomization; however, 30 % of the patients who were assigned to physical therapy alone underwent surgery within 6 months [11].

The primary surgical options include a partial meniscectomy or meniscal repair. Because of biological and technical issues, meniscal repair is typically limited to unstable, vertical, peripheral tears; therefore, most meniscal surgeries are partial meniscectomies. Arthroscopy for meniscal injuries is one of the most common orthopedic procedures and the most common procedure in sports medicine [11]. However, injuries with distinct characteristics should be addressed differently. Meniscal injuries can be classified by type (radial, horizontal, longitudinal, parrot beak, or complex), depth (type 1, 2, or 3), duration (acute or chronic), zone (red, red-white, or white zones), mechanism (traumatic or degenerative), and intraoperative findings (stable or unstable). Each of these classification criteria is associated with the others through a complex combinatorial analysis that prevents the design of an accurate flowchart for this type of treatment. Nevertheless, specific patient characteristics, including age, lower limb alignment, knee joint stability, associated injuries, weight, sports proficiency level, and the type of and expectations for the physical activity performed, directly influence the type of treatment for each patient. When a meniscectomy is performed, the meniscal tissue should be preserved as much as possible to avoid biomechanical consequences. Several options exist for restoring the deficient meniscus, from allograft transplantation to synthetic technologies. Synthetic implants have been developed to replace part of or the entire meniscus, including the collagen meniscal implant, hydrogels, and polymer scaffolds. These devices have shown some promise results in recent studies, although clinical experience with the use of synthetic implants is still limited.

Meniscal repair

Since the first reports of meniscal repair in 1980, special attention has been given to improving the surgical techniques, adapting the indications and contraindications, optimizing rehabilitation and adequately assessing the restoration of a functional joint. Previous studies have indicated that meniscal repair should ideally be performed in young patients with peripheral and longitudinal meniscal injuries [12, 13], and recent studies have reported satisfactory results after the repair of complex and multiplanar injuries, which extend into the avascular zone, and chronic injuries [14, 15]. A complex injury in more than 1 plane or in the central one-third zone has a rate of healing of approximately 50 %, given that a long rehabilitation program to protect the load on the knee joint for 6 weeks is required [15]. However, the failure rates of meniscal sutures have decreased over the years, and the reoperation rate has decreased from 23 % in 2003 to approximately 12.5 % currently. Nevertheless, the failure rates have varied from 9.0 % to 24.3 % depending on the study conducted and the preoperative criteria used [16••] because of the difficulty in standardizing the study groups relative to the type of injury and the need for concomitant surgery, which prevents an accurate analysis of the study results. In addition, some authors consider clinical success (when the patient becomes asymptomatic), whereas other authors consider biological success (when meniscal healing is observed). Regardless of the criteria, the success of meniscal repair involves stabilizing the articular cartilage and protecting it from degradation.

At present, some research groups are investigating how to improve meniscal fixation with safer devices and how to apply biological therapies direct to the site of injury (ie, growth factors) with the aim of increasing the healing rate after meniscal repair. However, not all meniscal injuries can be repaired, even with recent technological advancements. For this reason, experimental and clinical studies are being conducted with the goal of finding a safe substitute for irreparable injuries; these studies involve treatments with distinct procedures and have yielded different results.

Partial meniscal substitutes

Partial replacement procedures are effective in cases where they are indicated for the treatment of meniscal injuries. Meniscal replacement supposedly reduces the contact pressure across the articular surface. Therefore, it seems to be a logical approach for improving function, relieving pain and preventing joint degeneration. We should note that the FDA has not yet approved this type of procedure. However, it has been released in Europe, from where most studies addressing this technique originate [10••]. Previous studies on the treatment of injuries using partial replacement techniques have focused on a series of patient cases with specific indications and 2-year follow-up periods [17••, 18]. The indications for this type of procedure are still restricted to adult patients with the following profile: patients with postmeniscectomy symptoms, chondral injuries up to grade 2 according to the International Cartilage Repair Society (ICRS) criteria, stable knees or knees stabilized in the same procedure and a preserved meniscal rim and periphery [17••]. Patients not eligible for this type of treatment include those with a body mass index (BMI) greater than 35, a total meniscal loss or an unstable peripheral zone and those with multiple zones of meniscal wear, a misalignment or a chondral injury grade of≥3 [17••]. In addition, there is no scientific basis for the prophylactic indication of a partial meniscal replacement before the symptoms appear. The surgical strategy includes the following procedures: arthroscopic measurement of the space left by the meniscectomy, preparation of the synthetic and biodegradable graft and the placement and fixation of the graft in the selected location. This procedure promotes cell proliferation with the subsequent formation of tissue similar to the meniscal tissue within the structure of the graft [10••, 19]. The scaffolds available for clinical use to date can be classified into 2 types: collagen matrix (Menaflex, ReGen Biologics Inc.) and polyurethane noncollagen matrix (Actifit, Orteq Bioengineering, Ltd.) scaffolds (Table 1).

Collagen matrix scaffolds

The first studies that used collagen matrix scaffolds date from the late 80s and early 90s [20–22]. Although these studies were preliminary and mostly experimental, they helped define the parameters of the scaffolds used more recently. At that time, studies both in dogs [20] and rabbits [21] revealed significant histologic findings in the cartilage of the femoral condyles of the animals that were treated with unseeded small intestinal submucosa (SIS) during a period of 6–12 months following a partial medial meniscectomy compared with the animals that underwent a simple meniscectomy. However, a more recent study has contradicted these results [23].

With the development of tissue engineering techniques, the first collagen meniscus implant (CMI) for clinical use was developed in the United States. This biocompatible and degradable implant was designated Menaflex, and to date, this implant is only marketed in some European countries. The Menaflex implant comprises type I collagen fibers purified from bovine Achilles tendon [10••, 22]. In the late 90s, Stone et al initially reported the use of this technology, but with limited results because of the small number of cases and the short follow-up time. In addition, the procedure was only partially effective and had a reoperation rate of 22 % [24]. However, these studies demonstrated the safety of the technique [23]. Zaffagnini et al [25] published a study with 8 patients with a follow-up of 6–8 years and good clinical and radiological results. However, a second-look arthroscopic assessment and magnetic resonance imaging (MRI) revealed the deterioration of the implant over time, with a considerable reduction in size or the complete degradation of the implant. The same authors published a comparative, nonrandomized study [26••] with a 10-year follow-up that indicated good results using a CMI with various clinical outcomes. However, the faster degradation rate of this scaffold (6 months–2 years) may limit its clinical benefits. In a multicenter, randomized, controlled clinical study, 311 patients were divided into an experimental group comprising patients with scaffolds implanted after a partial meniscectomy and a control group that comprised patients submitted to a simple partial meniscectomy, and these groups were monitored for an average period of 59 months [27]. In addition, the patients were divided into acute and chronic cases prior to the randomization, and the results of these 2 groups were analyzed separately. The authors concluded that the clinical results of the chronic cases were more relevant than those of the acute cases. Indeed, for the acute cases, none of the measured parameters improved significantly compared with the controls. In contrast, among the parameters measured in the chronic patients, the Tegner score was significantly different and favored the CMI (P=0.04). Consequently, it can be inferred that Menaflex is an alternative to a partial meniscectomy. However, some important limitations are still unsolved, including the possibility of a reduction in the size or complete degradation of the implant. In addition, tissue growth inside the implant must be further studied in vivo because some authors argue that the implant tissue should exhibit the same biomechanical characteristics as those of native meniscal tissue [28].

Noncollagen matrix scaffolds

Another promising alternative for the treatment of irreparable injuries is Actifit®. Actifit® consists of a synthetic and bioabsorbable polyurethane scaffold that attaches to the

Table 1 Scaffolds available for meniscal replacement with its features of composition, indications, and type of studies (clinical phases)

	Characteristics	Indications	Side	Type of studies	Outcomes	Approval
Actifit	Polyurethane aliphatic, synthetic, biodegradable, acellular	Partial meniscal replacement	Lateral and medial	Phase I and II	Clinically and statistically improvements	Europe in process: USA (FDA), Brazil (ANVISA)
CMI	Achilles bovine tendon, bioresorbable,	Partial meniscal replacement	Lateral and medial	Phase I and II	Pain relief and functional improvement 10-year follow-up; MRI and histologic results are controversial	Europe
NuSurface	Synthetic, nonabsorbable	Total meniscal replacement	Medial	Phase I		Europe

vascular zone of the meniscus and enables the growth of similar meniscal tissue within the scaffold's porous [17••, 18]. The synthetic nature of this material may favor implant customization; Actifit is manufactured differently for the medial and lateral menisci. Moreover, this implant exhibits a porous surface that occupies up to 80 % of its structure, which facilitates the penetration of neomeniscal tissue; tissue integration occurs in 97.7 % of the patients. An experimental study confirmed that this type of polyurethane scaffold allows the penetration of tissue composed of extracellular matrix and blood vessels [29•, 30••]. In 12 cases involving surgery who were submitted to MRI and a second-look arthroscopic assessment, Verdonk et al found only 1 case in which meniscal tissue had not replaced the polyurethane scaffold [29•]. The implant itself does not assume the function of the meniscus, but the polyurethane scaffold is engulfed by macrophages and giant cells and allows the replacement of the meniscal tissue [31] in a process that takes approximately 5 years. Moreover, a prospective, multicenter clinical study by the same authors [17••] evaluated 52 patients (50 chronic and 2 acute cases) who underwent the implantation of an Actifit with a follow-up of 2 years. At the end of the study, a significant improvement was observed in all the clinical parameters evaluated [the Knee Injury and Osteoarthritis Outcome Score (KOOS), the International Knee Documentation Committee (IKDC) score, the Lysholm score and the visual analogue scale (VAS) for pain assessment] in addition to the stabilization or improvement of the ICRS score for cartilage in 92.5 % of the patients. Despite these good results, the adverse events and treatment failure rates were high (17.3 %), particularly in the lateral meniscus, where failure rates reached 33.3 %. Given that the study was a multiple-case study, it had methodological limitations, including the lack of randomization and the lack of a control group; these limitations must overcome for this technique to be compared with a traditional partial meniscectomy [17••].

Total meniscal substitutes

Despite the recent concept of preserving as much meniscal tissue as possible, orthopedic surgeons still perform surgical interventions on serious injuries for which a total meniscectomy is required. A few years following a meniscectomy procedure, nearly 50 % of the patients are symptomatic and consequently require meniscal replacement to reduce both pain and the progression to more advanced stages of osteoarthritis [10••]. In cases where the peripheral meniscal rim is absent, a total meniscal replacement should be prioritized. For many decades, the only option for symptomatic patients who had undergone a total meniscectomy was meniscal transplantation. However, despite encouraging results in the first 5 years, an assessment performed 20 years after the initiation of surgical interventions indicates a decrease in favorable clinical results [32••]. In addition, meniscal transplantation would ideally protect the knee joint from articular wear; however, there is insufficient evidence to support the chondroprotective ability of meniscal transplantations.

At present, meniscal transplantation is the best alternative therapy for symptomatic patients who have undergone a meniscectomy. However, problems related to graft availability, size differences between the donor and recipient grafts, the high cost, and the risk of disease transmission limit the use of this technique. Due to the difficulty of transplantation, a complete meniscal replacement with synthetic materials has been studied for decades. Recently, a synthetic and floating implant that lacks an anatomic shape and is used for the medial meniscus (NUsurface, Israel) is being tested in patients in a phase 1 clinical trial [10••]. Despite being considered a total replacement, the meniscal periphery together with the meniscal horns must be intact to accommodate the implant, which does not require fixation.

Meniscus allograft transplantation

Since the first meniscal transplantation in 1989, satisfactory results of meniscal transplantation have been reported in more than 30 clinical trials, and these results are primarily related to the improvement of pain and function. Even considering the different processing, sterilization, storage, surgical, and assessment procedures, the positive results in 85 % of the patients justify and encourage the performance of this type of transplantation in select cases [32••, 33]. The preoperative planning must be meticulous, starting with the indication, the graft size compatibility, and the surgical procedures to be used. In general, those patients who are relatively young, aged between 20 and 50 years, with a history of total or partial meniscectomy and persistent pain restricted to the operated region are considered the ideal candidates. The knee joint should be stable, with a normal alignment of the lower limbs, and the chondral injury should not exceed grade 2 (ICRS); however, if the injury grade exceeds 2, it should be a focal injury and would require concomitant treatment. Likewise, osteotomy and ligament reconstruction procedures must be performed during the same intervention with the goal of optimizing the longevity of the surgical results [34–37].

Several factors influence the clinical outcome following transplantation and are categorized into knee-specific factors (ie, chondral damage, ligamentous stability, axial alignment, prior surgery), graft-specific factors (ie, medial vs lateral side, the method of preservation, sterilization, the sizing method), surgeon-specific factors (ie, surgeon experience, the insertion method, graft fixation, concomitant procedures) and rehabilitation-specific factors (ie, the range of passive motion, weight bearing, continuous passive motion, return to activities) [36]. Undoubtedly, one of the most critical factors for the success of meniscal surgery is the preoperative measurement of the meniscus. In addition, the measurements of allografts must be made accurately and analyzed during processing, and only a 10 % measurement error is acceptable. However, no previous studies have compared the clinical outcomes with regard to graft size tolerance. The most reliable method to determine the width and length of the meniscus, and which professional is responsible for the measurement–the surgeon or nurse working in the tissue bank–have not yet been determined [36]. In our opinion, both professional categories should know which methods are available, and which methods would provide increased reliability, including an X-ray, MRI or a regression equation using anthropometric data, as proposed by Van Thiel et al [38]. MRI of the contralateral knee, when healthy, seems to be the best option for meniscus measurement, and if not available, an alternative technique that uses different calculations for the medial and lateral menisci can be employed. The method proposed by Pollard et al. [39] in 1995 is a good option for determining the length and width of the medial meniscus. For the lateral meniscus, the radiographic method proposed by Yoon et al [40] is a good option to determine length, whereas the anthropometric method [38] should be used to determine width.

The meniscal allograft can be cool (4 ° C), fresh-frozen (-80 ° C), cryopreserved or lyophilized (freeze-dried), and most surgeons use the prolonged fresh- or deep-frozen grafts because previous studies have indicated that donor cells are repopulated with recipient DNA [36], even without complete cell viability. Regarding surgery, various techniques have been reported, and it has been established that the fixation of the anterior and posterior horns is one of the essential steps in the technique. In addition, the proximity of the horns of the lateral meniscus is of special importance, which is why the most used method for the lateral meniscus is the construction of the bridge bone. In general, studies in the literature have a limited scope because of the absence of control groups. Nonetheless, the success of transplantation varies depending on the compartment involved. According to Verdonk et al success rates reached 72 % for the medial meniscus and 63 % for the lateral meniscus [41]. In contrast, Cole et al reported that patient satisfaction varied from 93 % for a lateral meniscal transplant to 68 % for a medial meniscal transplant [42]. Despite these encouraging results, some difficulties and risks of meniscal transplantation exist. The main concerns involve the low availability of grafts in tissue banks, high cost of the tissue graft, and precision of the surgical technique and the risk of bacterial contamination.

Research potential

In recent decades, regenerative medicine has made significant advancements, and many experimental studies have addressed the issue of meniscal regeneration. In particular, researchers are working on the development of regenerative solutions for different clinical scenarios that require distinct surgical interventions. These solutions involve the following: (1) improving biological adherence and the repair of injuries, (2) the partial regeneration of meniscal tissues to restore the tissue removed after a meniscectomy, and (3) total meniscal regeneration when total or partial meniscectomy is performed. The following sections describe the foundations of tissue engineering (cells, growth factors, and scaffolds) with respect to meniscal regeneration and experimental strategies that combine distinct techniques.

Cells

Mesenchymal stem cells are pluripotent cells found in various tissues, such as adipose tissue and bone marrow. The use of mesenchymal cells remains limited to scientific research for the treatment of meniscal injuries. Even in this context, the use of mesenchymal cells has had limited results and is not entirely reproducible. Another alternative to mesenchymal cells is bone marrow stromal cells (BMSCs), which suffer from the same limitations. In a clinical study, Vangsness et al compared the infiltration of mesenchymal cells using 2 cellular concentrations, in addition to a control group containing hyaluronic acid. According to the authors, an MRI examination indicated an increase in the meniscal volume in 24 % of the patients who

Table 2 Potential therapies for meniscal lesions

Types of therapy	Present	Future
Stem Cells	Mesenchymal stem cell-seeded scaffolds in animals,	Stem cell-based implants are still in investigative stage, preclinical studies in the near future; human trials are a distant prospect
Scaffold	Natural materials and synthetic polymers, cell-instructive, biomimetic, resilient and resistant, biocompatible, slowly biodegradable, easy to handle, high porosity	Custom-made shapes meniscal scaffold and hybrid material
Platelet rich plasma	Increased cell viability and the glycosaminoglycan concentration in animal study	Promising therapy, particularly for meniscal injuries that compromise poorly vascularized regions
Growth factors	Isolate the main factors for matrix synthesis enhancement and metalloproteinase inhibition	TGF- β1: enhance cell proliferation, collagen and proteoglycans synthesis IGF-1: anabolic factor of cartilage, stimulate cell migration
Hydrogels	Possible solution to meniscal replacement in small animals; in a large animal model demonstrated increase in cartilage damage	Improve material properties No clinical studies to date of hydrogels used for meniscal replacement

received 50 x 10^6 allogeneic mesenchymal stem cells [43••]. This increase was higher than that found in the other experimental groups. Zelner et al created injuries in the avascular zone of the meniscus in rabbits and treated these injuries with a noncellular matrix of hyaluronan-collagen in 1 group. A second group was supplemented with platelet-rich plasma (PRP); a third group was supplemented with autologous bone marrow; a fourth group comprised mesenchymal cells cultured for 14 days; in addition, there was an untreated control group. The mesenchymal cells group differed from the other groups with the appearance of a repair tissue resembling fibrocartilage, although this tissue was not yet fully integrated into the native meniscal tissue. The authors believe that, experimentally, mesenchymal cells exhibit the biological potential to repair injuries in the avascular zones [44, 45]. However, according to some authors, cells from the resected meniscal fragment are considered ideal because these cells exhibit less morbidity and can be seeded into biological scaffolds. In addition to meniscal and mesenchymal cells and BMSCs, other cell types can be used for meniscal regeneration, including synoviocytes, articular chondrocytes, ear chondrocytes, nose chondrocytes, and rib chondrocytes.

Platelet rich plasma (PRP)

From the early 90s, PRP has been used to increase the healing potential of different tissues, particularly in dentistry and maxillofacial surgery. In general, PRP consists of an autologous source of platelets at a supraphysiological concentration, in addition to growth factors, and can be used in distinct forms for tissue healing. Studies in this area have focused on the treatment of muscle injuries due to the mechanism of action of PRP, but it seems logical to use PRP in the treatment of knee injuries, either by itself or as a repair adjuvant. Although promising, the few studies conducted to date failed to prove the efficacy of PRP [46, 47]. Ishida et al [46] studied the potential of PRP to heal meniscal tissue both in vitro and in vivo. These authors initially compared PRP and platelet-poor plasma and found that PRP increased cell viability and the glycosaminoglycan concentration. Subsequently, these same authors studied the effects of PRP on injuries in the avascular zone of the meniscus in rabbits and compared the results with the control groups. The animals were sacrificed after 3, 6, and 12 weeks. After the last follow-up, Ishida et al found increased concentrations of fibrochondrocytes and extracellular matrix in the animals that underwent PRP therapy [46]. These results suggest that PRP may be a promising therapy, particularly for meniscal injuries that compromise poorly vascularized regions.

Growth factors and gene therapy

Currently, one of the most promising topics in all of medicine is gene therapy. Few studies have investigated this type of treatment in orthopedics and in the treatment of meniscal injuries. However, some relevant studies have been conducted. Goto et al [48] infected a monolayer culture of canine and human meniscal cells with retroviruses carrying either the transforming growth factor-beta (TGF-beta) cDNA gene or marker genes. The cell cultures infected with the TGF-beta-carrying viruses contained much higher concentrations of TGF-beta, collagen, and proteoglycans compared with the control group. Similarly, Hidaka et al [49] proposed to improve the conditions for meniscal vascularization via gene therapy, which in theory could improve the prognosis of meniscal healing and repair. By using adenoviruses as vectors for the hepatocyte growth factor gene to induce neovascularization in the bovine meniscus, the authors obtained encouraging results. After 2 weeks (P=0.02) and 8 weeks (P=0.001), microscopic examination revealed increased vascularization in the experimental groups compared with the control group. These authors concluded that gene therapy is feasible for the treatment of meniscal injuries and, therefore, warrants further investigation.

In addition, the effects of growth factors on increasing matrix synthesis and inhibiting matrix metalloproteinases have been studied. In particular, TGF-β had significant effects on the proliferation of cells in monolayer cultures and on the increased synthesis of proteoglycan and collagen [50, 51]. In a recent study, great importance was attributed to platelet-derived growth factor (PDGF), which was found in higher concentrations in the knee joint after reconstruction of the anterior cruciate ligament (ACL) compared with the concentration found after a meniscectomy. Therefore, the release of PDGF during ACL reconstruction may be one of the factors that explain the enhanced meniscal repair that occurs when a meniscectomy is performed concomitantly with knee stabilization surgery [50, 52•]. The rapid cellular proliferation following growth factor stimulation is a complex mechanism in the tissue engineering process (Table 2).

Scaffold

Scaffolds are synthetic or biological structures that exhibit the following characteristics that are important for tissue engineering: (1) biocompatibility; (2) a shape similar to the normal meniscus or the ability to adjust the shape during implantation; (3) a porous structure that promotes cell growth; (4) resistance and resilience to withstand the mechanical forces acting on the knee joint while cellular integration occurs; (5) slow biodegradability, which promotes the gradual deposition of newly synthesized tissue; (6) permeability to macromolecules; and (7) cell-instructive structures that promote cellular differentiation, proliferation or migration [45, 50]. At present, scaffolds are divided into collagen and noncollagen matrix scaffolds. Notably, polymeric scaffolds eliminate the problems of tissue availability, graft size adjustments, and disease transmission.

Conclusions

The unsatisfactory results of a meniscectomy over the long term and the preservation of meniscal tissue in physically active subjects are good reasons to surgically repair meniscal injuries, preserving most of the tissue whenever is possible. The repair technique had the most reliable results, but when a partial meniscal replacement is indicated, the desired scaffold should be a tissue that allows an orderly mesenchymal cell invasion with little inflammatory response. Clinically, the implant should be chondroprotective, restore the biomechanical features of the normal meniscal kinematics of the knee joint and promote pain relief.

Patients who underwent total a meniscectomy and later presented with pain and functional limitations can benefit from meniscal transplantation. However, the long-term effects of this procedure in protecting the articular cartilage have not been fully elucidated. In addition to the unavailability of allografts in some countries, the long-term results of meniscal prostheses and replacements are not yet available. To date, a few scaffolds that allow a 3-dimensional reconstruction of the meniscal structure have been constructed and made available for use. However, none of these scaffolds has achieved the histologic and biomechanical properties of the native meniscus. In this respect, improved scaffolds, cellular matrices, growth factors, and cell culture protocols should be investigated to improve the current treatment of meniscal injuries.

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Compliance with Ethics Guidelines

Conflict of Interest Camila Cohen Kaleka, Pedro Debieux, Diego da Costa Astur, Gustavo Gonçalves Arliani, and Moisés Cohen declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Englund M, Roos EM, Roos HP, Lohmander LS. Patient-relevant outcomes fourteen years after meniscectomy: influence of type of meniscal tear and size of resection. Rheumatology (Oxford). 2001;40:631–9.
2. Fairbank TJ. Knee joint changes after meniscectomy. J Bone Joint Surg (Br). 1948;30B:664–70.
3. Lanzer WL, Komenda G. Changes in articular cartilage after meniscectomy. Clin Orthop Relat Res. 1990;252:41–8.
4. Noble J. Clinical features of the degenerate meniscus with the results of meniscectomy. Br J Surg. 1975;62:977–81.
5. Roos H, Lauren M, Adalberth T, Roos EM, Jonsson K, Lohmander LS. Knee osteoarthritis after meniscectomy: prevalence of radiographic changes after twenty-one years, compared with matched controls. Arthritis Rheum. 1998;41:687–93.
6. McDevitt CA, Webber RJ. The ultrastructure and biochemistry of meniscal cartilage. Clin Orthop Relat Res. 1990;252:8–18.

7. Thompson WO, Thaete FL, Fu FH, Dye SF. Tibial meniscal dynamics using three-dimensional reconstruction of magnetic resonance images. Am J Sports Med. 1991;19:210–5.
8. Saamanen AM, Tammi M, Kiviranta I, Helminen HJ. Running exercise as a modulator of proteoglycan matrix in the articular cartilage of young rabbits. Int J Sports Med. 1988;9:127–33.
9. Helfet AJ. Mechanism of derangements of the medial semilunar cartilage and their management. J Bone Joint Surg (Br). 1959;41-B: 319–36.
10.•• Vrancken ACT, Buma P, van Tienen TG. Synthetic meniscus replacement: a review. Int Orthop. 2013;37:291–9. *This study consists of a literature review that points to interesting topics and is focused on the treatment of irreparable meniscal tears with synthetic menisci*.
11. Sihvonen R, Paavola M, Malmivaara A, Itälä A, Joukainen A, Nurmi H, et al. Finnish Degenerative Meniscal Lesion Study (FIDELITY) Group. Arthroscopic partial meniscectomy vs sham surgery for a degenerative meniscal tear. N Engl J Med. 2013;26: 2515–24.
12. Rubman MH, Noyes FR, Barber-Westin S. Arthroscopic repair of meniscal tears that extend into the avascular zone. A review of 198 single and complex tears. Am J Sports Med. 1998;26:87–95.
13. Ahn JH, Lee YS, Yoo JC, et al. Clinical and second-look arthroscopic evaluation of repaired medial meniscus in anterior cruciate ligament-reconstructed knees. Am J Sports Med. 2010;38:472–7.
14. Noyes FR, Barber-Westin SD. Meniscus tears: diagnosis, repair techniques, clinical outcomes. In: Noyes FR, editor. Noyes' knee disorders: surgery, rehabilitation, clinical outcomes. Philadelphia: Saunders; 2009. p. 733–71.
15. Noyes FR, Heckmann TP, Barber-Westin SD. Meniscus repair and transplantation: a comprehensive update. J Orthop Sports Phys Ther. 2012;42:274–90.
16.•• Nepple JJ, Dunn WR, Wright RW. Meniscal repair outcomes at greater than five years: a systematic literature review and meta-analysis. J Bone Joint Surg Am. 2012;94:2222–7. *A systematic review of the outcomes of meniscal repair from 13 studies demonstrated very similar rates of meniscal failure for all the techniques investigated*.
17.•• Verdonk P, Beaufils P, Bellemans J, Djian P, Heinrichs EL, Huysse, et al. Successful treatment of painful irreparable partial meniscal defects with a polyurethane scaffold two-year safety and clinical outcomes. Am J Sports Med. 2012;40:844–53. *This study is important because it presents the outcomes of a new option for the treatment of irreparable meniscal injuries. The study consists of a multicenter series of cases, with 52 patients treated with a new polyurethane scaffold exhibiting good results in a 2-year follow-up*.
18. Kon E, Filardo G, Zaffagnini S, Di Martino A, Di Matteo B, Muccioli GMM, et al. Biodegradable polyurethane meniscal scaffold for isolated partial lesions or as combined procedure for knees with multiple comorbidities: clinical results at 2 years. Knee Surg Sports Traumatol Arthrosc. 2014;22:128–34.
19. Mouzopoulos G, Siebold R. Partial meniscus substitution with tissue-engineered scaffold: an overview. Clin Sports Med. 2012;31:167–81.
20. Silver FH, Pins G. Cell growth on collagen: a review of tissue engineering using scaffolds containing extracellular matrix. J Long-Term Eff Med Implants. 1992;2:67–80.
21. Gastel JA, Muirhead WR, Lifrak JT, Fadale PD, Hulstyn MJ, Labrador DP. Meniscal tissue regeneration using a collagenous biomaterial derived from porcine small intestine submucosa. Arthroscopy. 2001;17:151–9.
22. Steadman JR, Rodkey WG, Li S-T. The collagen meniscus implant. Development of a prosthetic meniscal replacement. In: Mow VC, Arnoczky SP, Jackson DJ, editors. Knee meniscus: basic and clinical foundation. New York: Raven Press; 1992. p. 165–73.
23. Welch JA, Montgomery RD, Lenz SD, Plouhar P, Shelton WR. Evaluation of small-intestinal submucosa implants for repair of meniscal defects in dogs. Am J Vet Res. 2002;63:427–31.
24. Stone KR, Steadman JR, Rodkey WG, et al. Regeneration of meniscal cartilage with use of a collagen scaffold. Analysis of preliminary data. J Bone Joint Surg Am. 1997;79:1770–7.
25. Zaffagnini S, Giordano G, Vascellari A, Bruni D, Neri MP, Iacono F, et al. Arthroscopic collagen meniscus implant results at 6 to 8 years follow up. Knee Surg Sports Traumatol Arthrosc. 2007;15:175–83.
26.•• Zaffagnini S, Marcheggiani Muccioli GM, Lopomo N, et al. Prospective long-term outcomes of the medial collagen meniscus implant vs partial medial meniscectomy: a minimum 10-year follow-up study. Am J Sports Med. 2011;39:977–85. *This study consists of a prospective cohort of 33 patients treated with CMI for irreparable meniscal lesions demonstrating good outcomes after a 10-year follow-up*.
27. Rodkey WG, DeHaven KE, Montgomery III WH, Baker Jr CL, Beck Jr CL, Hormel SE, et al. Comparison of the collagen meniscus implant with partial meniscectomy. A prospective randomized trial. J Bone Joint Surg Am. 2008;90:1413–26.
28. Spencer SJ, Saithna A, Carmont MR, et al. Meniscal scaffolds: early experience and review of the literature. Knee. 2012;19:760–5.
29.• Verdonk R, Verdonk P, Huysse W, Forsyth R, Heinrichs E. Tissue ingrowth after implantation of a novel, biodegradable polyurethane scaffold for treatment of partial meniscal lesions. Am J Sports Med. 2011;39:774–82. *This study consists of a case series of 52 patients, which shows the proper integration of the polyurethane scaffold with the native meniscal tissue, as well as tissue ingrowth within this scaffold*.
30.•• De Coninck T, Huysse W, Willemot L, Verdonk R, Verstraete K, Verdonk P. Two-year follow-up study on clinical and radiological outcomes of polyurethane meniscal scaffolds. Am J Sports Med. 2013;41:64–72. *This is the first study to correlate the radial displacement of the scaffold measured via MRI with clinical outcomes, and it concludes that there is no correlation between the scaffold displacement and the clinical outcome score, either pre- or postoperatively*.
31. Zuidema J, van Minnen B, Span MM, Hissink CE, van Kooten TG, Bos RR. In vitro degradation of a biodegradable polyurethane foam, based on 1,4-butanediisocyanate: a three-year study at physiological and elevated temperature. J Biomed Mater Res A. 2009;90:920–30.
32.•• Elattar M, Dhollander A, Verdonk R, et al. Twenty-six years of meniscal allograft transplantation: is it still experimental? A meta-analysis of 44 trials. Knee Surg Sports Traumatol Arthrosc. 2011;19:147–57. *This meta-analysis demonstrates satisfactory outcomes after meniscal allograft transplantation; the procedure was considered safe and reliable for the treatment of refractory postmeniscectomy symptoms in selected patients*.
33. Lee AS, Kang RW, Kroin E, Verma NN, Cole BJ. Allograft meniscus transplantation. Sports Med Arthrosc Rev. 2012;20:106–14.
34. Packer JD, Rodeo SA. Meniscal allograft transplantation. Clin Sports Med. 2009;28:259–83.
35. Lee SR, Kim JG, Nam SW. The tips and pitfalls of meniscus allograft transplantation. Knee Surg Relat Res. 2012;24:137–45.
36. Brophy R, Matava MJ. Surgical options for meniscal replacement. J Am Acad Orthop Surg. 2012;20:265–72.
37. Lubowitz JH, Verdonk PC, Reid III JB, Verdonk R. Meniscus allograft transplantation: a current concepts review. Knee Surg Sports Traumatol Arthrosc. 2007;15:476–92.
38. Van Thiel GS, Verma N, Yanke A, Basu S, Farr J, Cole B. Meniscal allograft size can be predicted by height, weight, and gender. Arthroscopy. 2009;25:722–7.
39. Pollard ME, Kang Q, Berg EE. Radiographic sizing for meniscal transplantation. Arthroscopy. 1995;11:684–7.

40. Yoon JR, Kim TS, Lim HC, Lim HT, Yang JH. Is radiographic measurement of bony landmarks reliable for lateral meniscal sizing? Am J Sports Med. 2011;39:582–9.
41. Verdonk PC, Demurie A, Almqvist KF, Veys EM, Verbruggen G, Verdonk R. Transplantation of viable meniscal allografts: survivorship analysis and clinical outcome of one hundred cases. J Bone Joint Surg Am. 2005;87:715–24.
42. Cole BJ, Dennis MG, Lee SJ, et al. Prospective evaluation of allograft meniscus transplantation: a minimum 2-year follow-up. Am J Sports Med. 2006;34:919–27.
43.•• Vangsness Jr CT, Farr II J, Boyd J, Dellaero DT, Mills CR, LeRoux-Williams M. Adult human mesenchymal stem cells delivered via intra-articular injection to the knee following partial medial meniscectomy: a randomized, double-blind, controlled study. J Bone Joint Surg Am. 2014;96:90–8. *A multicenter study evaluating 55 patients who underwent a partial meniscectomy; patients treated with mesenchymal stem cells were compared with a control group. Although not definitive, the study presents a good outcome over time.*
44. Zellner J, Mueller M, Berner A, Dienstknecht T, Kujat R, Nerlich M, et al. Role of mesenchymal stem cells in tissue engineering of meniscus. J Biomed Mater Res A. 2010;94:1150–61.
45. Liu C, Toma IC, Mastrogiacomo M, Krettek C, von Lewinski G, Jagodzinski M. Meniscus reconstruction: today's achievements and premises for the future. Arch Orthop Trauma Surg. 2013;133:95–109.
46. Ishida K, Kuroda R, Miwa M, et al. The regenerative effects of platelet-rich plasma on meniscal cells in vitro and its in vivo application with biodegradable gelatin hydrogel. Tissue Eng. 2007;13:1103–12.
47. Braun HJ, Wasterlain AS, Dragoo JL. The use of PRP in ligament and meniscal healing. Sports Med Arthrosc. 2013;21:206–12.
48. Goto H, Shuler FD, Niyibizi C, Fu FH, Robbins PD, Evans CH. Gene therapy for meniscal injury: enhanced synthesis of proteoglycan and collagen by meniscal cells transduced with a TGFbeta (1) gene. Osteoarthr Cartil. 2000;8:266–71.
49. Hidaka C, Ibarra C, Hannafin JA, Torzilli PA, Quitoriano M, Jen SS, et al. Formation of vascularized meniscal tissue by combining gene therapy with tissue engineering. Tissue Eng. 2002;8:93–105.
50. Scotti C, Hirschmann MT, Antinolfi P, Martin I, Peretti GM. Meniscus repair and regeneration: review on current methods and research potential. Eur Cell Mater. 2013;26:150–70.
51. de Mulder EL, Hannink G, Giele M, Verdonschot N, Buma P. Proliferation of meniscal fibrochondrocytes cultured on a new polyurethane scaffold is stimulated by TGF-β. J Biomater Appl. 2013;27:617–26.
52.• de Girolamo L, Galliera E, Volpi P, Denti M, Dogliotti G, Quaglia A, et al. Why menisci show higher healing rate when repaired during ACL reconstruction? Growth factors release can be the explanation. Knee Surg Sports Traumatol Arthrosc. 2013; [Epub ahead of print]. *The authors try to find a difference between the concentration of the growth factors in the knee joint, with and without ACL reconstruction, to find out why meniscus repair has better outcomes with this concomitant surgery.*